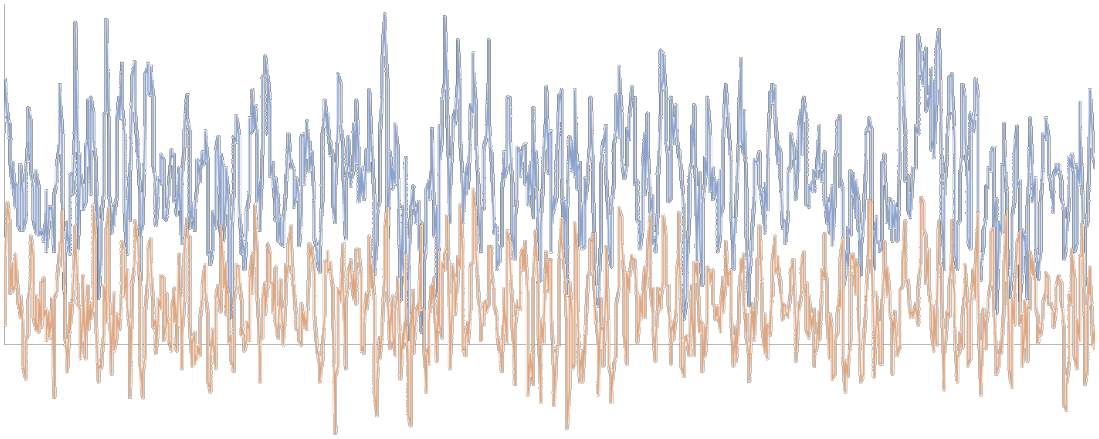
The Architecture and Limbic Activity Characteristics of Rapid Eye Movement Sleep as Symptomatic and Prognostic Factors in an Animal Model of Post-Traumatic Stress Disorder



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ERKLÄRUNG
Hiermit versichere ich ehrenwörtlich, dass meine Dissertation selbständig und ohne unerlaubte Hilfsmittel angefertigt worden ist. Die vorliegende Dissertation wurde weder ganz, noch teilweise bei einer anderen Prüfungskommission vorgelegt.
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Munich, 29th of April 2014

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Für Opa

„Nie verzagen, Opa fragen.“

ABSTRACT

Sleep disturbances, particularly disturbed architecture of Rapid Eye Movement Sleep (REMS), constitute a hallmark of Post-Traumatic Stress Disorder (PTSD), a fear-disorder characterized by recurrent and intrusive memories of a traumatic experience of horror and helplessness during wakefulness (flashbacks) and while being asleep (nightmares). Recent clinical observations suggest that REMS disturbances in PTSD patients not only correlate with the PTSD symptom severity, but also might represent a risk factor for developing the disorder. Over the last decades, a plethora of neuroanatomical and -functional correlates of PTSD have been described in humans and animal models, however their roles in the etiopathogenesis of PTSD and individual resilience towards developing the disease are still not well understood. The latter is of particular importance, as only a proportion (10-15 %) of people, who have experienced a traumatic event, develop PTSD in the later course. Clinical and animal studies have proposed that in affected subjects, memory consolidation processes, especially emotional mnemonic processing, might be disturbed, although, so far, no consensus has been reached whether these subjects suffer from hyper-consolidation of traumatic memories, or from failure of fear memory extinction. Sleep in general is well known as a crucial determinant of successful memory consolidation.

Within the scope of the present work, we examined this strong interconnection between sleep-related consolidation of traumatic fear memories and architectural, as well as limbic activation features of REMS in an animal model of PTSD. We hypothesized that in mice, similar to the clinical situation, **(I)** sleep (especially REMS) architecture might be altered in the aftermath of a trauma-resembling event. **(II)** REMS characteristics prior to the aversive situation might predict later severity of the developed PTSD-like phenotype. **(III)** Distinct activity patterns in relevant brain areas that are displayed upon re-exposure to the traumatic context, spontaneously re-occur during REMS in the aftermath of the event, and thus might represent correlates of ill-consolidation of traumatic memories during sleep.

To this end, we performed longitudinal monitoring of circadian sleep-wake behavior combined with field potential recordings from fear memory-related limbic structures (dorsal hippocampus and basolateral amygdala (BLA)) in C57BL/6N mice. Behavioral and electrophysiological endpoints were obtained before (baseline) and up to 2 months after exposure to a trauma-resembling contextual fear-conditioning protocol, with an electric foot shock (1.5 mA, 2s) serving as the aversive unconditioned stimulus.

We show that in response to the aversive fear conditioning, shocked animals spent an increased amount of time in REMS, an effect which was observed in the early aftermath of the traumatic event and was sustained even 2 months later. This increase was visible when comparing REMS amounts to the individual baseline, as

well as in inter-group comparison to non-shocked controls. In addition, we report that the degree of REMS fragmentation under basal (*pre* shock) conditions positively correlated with the later observed individual PTSD-like hyperarousal phenotype.

Strikingly in terms of fear-related behavior, animals in the experimental group that received the shock showed a distribution into two sub-groups: a majority (60%) displayed strong freezing behavior when re-exposed to the shock context, while the remaining animals (40%) were classified as low responders. Behavioral divergence in these two subgroups was accompanied by inter-group dissimilarities of electrophysiological patterns during re-exposure to the shock context, but also during REMS after the fear conditioning. High fear responders showed increased theta 2 activity in the BLA and spend more time in distinct REMS episodes where limbic activity patterns resembled those of the re-exposure condition during wakefulness. In particular, these REMS episodes were characterized by increased coupling between hippocampus and amygdala in the theta 2 frequency band, which is implicated in fear and anxiety-related behaviors. In contrast, low-fear responders failed to show increased theta 2 power in the BLA, nor did they display the above described REMS alterations. A retrospective analysis of electrophysiological recordings during novelty exposure and basal sleep periods, several days before the animals underwent the fear conditioning, revealed the above described subdivision of the animals according to electrophysiological read-outs already *pre* shock.

These findings suggest that REMS alterations not only mark early-onset effects of a trauma-like experience in mice, but also represent a long-term symptom-like phenotype in the model. In addition, upon re-exposure to the shock context, alterations of neuronal activity patterns in limbic brain areas resemble neurofunctional findings related to emotional hyper-activity in PTSD patients. In the present study, similar alterations are also observed during a proportion of REMS episodes, which are entered more frequently by mice with a strong fear phenotype. It remains obscure, whether low fear responding animals, which share the same genetic background as high responders, represent a more resilient subgroup or rather show deficits in learning. However, the stringent divergence of the two subgroups according to electrophysiological readouts during wakefulness and REMS already prior to the shock suggests that determinants of limbic activity might constitute important risk factors for the development of PTSD-like behavior.

Taken together, the data presented in this work highlight that baseline characteristics as well as early-onset changes in REMS architecture, quality and limbic activity characteristics may constitute prognostic, but also diagnostic markers of PTSD-like symptoms in mice.

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List of Abbreviations

ACC	Anterior Cingulate Cortex
ANOVA	Analysis of Variance
ASR	Acoustic Startle Response
AUC	Area Under the Curve
BDNF	Brain-Derived Neurotrophic Factor
BLA	Basolateral Amygdala
BOLD	Blood-Oxygen-Level-Dependent
CA	Cornu Ammonis
dACC	Dorsal Anterior Cingulate Cortex
DFT	Discrete Fourier Transformation
dHPC	Dorsal Hippocampus
DSM-V	Diagnostic and Statistical Manual of Mental Disorders V
EEG	Electroencephalogram
EOG	Electrooculogram
EMG	Electromyogram
FFT	Fast Fourier Transformation
fMRI	Functional Magnetic Resonance Imaging
FT	Fourier Transformation
GABA	Gamma-Aminobutyric Acid
HPA	Hypothalamus-Pituitary-Adrenal (axis)
HT	Hilbert Transformation
LA	Lateral Amygdala
LFP	Local Field Potentials
LTP	Long-Term Potentiation
MA	Microarousal
mPFC	Medial Prefrontal Cortex
NAC	Nucleus Accumbens
NREMS	Non-Rapid Eye Movement Sleep
PFC	Prefrontal Cortex
PGO	Ponto-Geniculo-Occipital (waves)
P-wave	Pontine wave
PSD	Power Spectral Density
PTSD	Post-Traumatic Stress Disorder
REMS	Rapid Eye Movement Sleep
SEM	Standard Error of Mean
SSRI	Selective Serotonin Reuptake Inhibitor
SWS	Slow Wave Sleep

vHPC	Ventral Hippocampus
VTA	Ventral Tegmental Area
vmPFC	Ventromedial Prefrontal Cortex
WAKE	Wakefulness

Chapter 1 | You lack the season of all natures, sleep.

William Shakespeare, Macbeth, act 3, scene 4

Night-time
Terror
Since
Ever
Remembered
Night-time
No peace
Insomnia
Presides
This being
Her norm

Ultimately
Exhaustion
Brings sleep
Memories
Terror
Return
Haunting
Her dreams
Night
Upon
Night

Awakening
Violently
Fear and dread
Crushing her body
The memory
So real
Detail vivid
Eyes
Cheeks
Clothes
Damp

Barley able
To breathe
Disorientated
Fearful
Confused
But slowly
Awareness
Of darkness
Night-time
Flashbacks

Once
Breathing
Controlled
Tears
Subside
Remembering
Distraction
She fumbles
In darkness

The TV
Her need
The light
Provides
Reassurance
Of where
Who
She is
Now

As she begins
To calm
Wipes
away tears
Distraction
Mindfulness
Her aid
Her focus
Now
Her presence
Now
Her safety
Is
Now

Night-time
Terror
Ended
Until
The next
Always
Another
Is coming
Always

Relentless
Terror
Her past
Always
Her present

Poem about PTSD Nightmares
Posted on November 11, 2013
by Healing From Complex Trauma & PTSD/CPTSD
http://healingfromcomplextraumaandptsd.wordpress.com/

POST-TRAUMATIC SLEEP DISORDER?

Nightmares, distressing dreams that primarily arise during Rapid Eye Movement Sleep (REMS) in the second half of the night (HASLER AND GERMAIN, 2009), constitute very common complaints of patients suffering from Post-Traumatic Stress Disorder (PTSD) (ROSS ET AL., 1989; SCHREUDER ET AL., 2000; LAVIE, 2001; SPOORMAKER ET AL., 2006; SPOORMAKER AND MONTGOMERY, 2008). In the general population, about 2–6 % of adults report weekly nightmares independently of the cultural background (BIXLER ET AL., 1979; BELICKI AND BELICKI, 1982; JANSON ET AL., 1995; OHAYON ET AL., 1997; STEPANSKY ET AL., 1998). Nightmares occur with the highest prevalence during childhood and young adulthood and decline with age (LEVIN AND NIELSEN, 2007). In patients with PTSD, traumatic nightmares, i.e. disturbing dreams with some degree of resemblance to the actual traumatic event, occur in up to 90 % of cases (HASLER AND GERMAIN, 2009) and as frequently as six nights per week (KRAKOW ET AL., 2002B). Together with flashbacks and intrusive memories, nightmares force patients to re-live or re-experience the traumatic situation for months and even up to 40-50 years after the original trauma (GUERRERO AND CROCQ, 1994; KAUP ET AL., 1994; SCHREUDER ET AL., 2000).

Diagnostic Criteria for PTSD

Nightmares, as well as the most commonly reported nightmare associated emotion, fear, belong to two out of four symptom clusters of the diagnostic criteria for PTSD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, (AMERICAN PSYCHIATRY ASSOCIATION, 2013)). PTSD belongs to the class of "trauma and stressor-related disorders" and therefore requires the diagnostic criterion of a direct or indirect exposure to a traumatic situation. Patients diagnosed with PTSD express **(I) INTRUSION SYMPTOMS** (intrusive memories, flashbacks, traumatic nightmares, distress, physiological reactivity), **(II) AVOIDANCE SYMPTOMS** (avoidance of trauma-related thoughts/feelings and external reminders), **(III) NEGATIVE ALTERATIONS IN MOOD AND COGNITION** (inability to recall key features of the traumatic event, negative trauma-related emotions, e.g. fear) and **(IV) ALTERATIONS IN AROUSAL AND REACTIVITY** (exaggerated startle response, hypervigilance, sleep disturbances), persisting for more than one month.

As can be deduced from these diagnostic criteria, difficulties with sleep are listed twice as diagnostic symptoms in DSM-V (nightmares, sleep disturbances) and play a major role in the disease, also because of their high negative impact on daily quality of life (KRAKOW ET AL., 2002A). It has been proposed that disturbed sleep is more than just a consequence or a secondary symptom of PTSD and has a central role in the origin and persistence of the illness (ROSS ET AL., 1989; SPOORMAKER AND

Montgomery, 2008; Babson and Feldner, 2010; Germain, 2013). Amongst others, patients undergoing behavioral or pharmacological treatment for PTSD display mixed and inconsistent therapeutic effects on sleep disturbances and nightmares (Galovski et al., 2009), whereas specific treatments for nightmares and insomnia not only ameliorate dyssomnia and parasomina but also reduce PTSD symptom severity (for review see (Maher et al., 2006; Germain et al., 2008; Spoormaker and Montgomery, 2008; Fraser, 2009; Aurora et al., 2010; Germain, 2013)).

Sleep Disturbances in PTSD

Sleep disturbances in PTSD patients most frequently manifest in sleep-onset insomnia, sleep-maintenance insomnia, and nightmares (Harvey et al., 2003). Although nightmares are primarily a REMS-phenomenon, in patients suffering from PTSD (but also healthy individuals) nightmares can occur during both, non-rapid eye movement sleep (NREMS) and REMS (van der Kolk et al., 1984; Wittmann et al., 2007). Also, not all awakenings from sleep in PTSD are triggered by traumatic nightmares. Bad dreams unrelated to the trauma (idiopathic nightmares; (Germain and Nielsen, 2003b)) as well as disruptive behaviors (e.g. acting-out dreams) and sleep-disordered breathing (Kessler et al., 1995; Neylan et al., 1998) are also more likely to arouse from REMS (Germain and Nielsen, 2003b; Germain, 2013). However, awakenings from NREMS probably result in insomnia and also include panic attacks and sleep terrors (Freed et al., 1999; Germain et al., 2005). Therefore, clinical observations in PTSD patients point toward disturbances of sleep during both, NREMS and REMS.

Similarly, polysomnographic studies (recordings of electroencephalogram (EEG) electromyogram (EMG) and electrooculogram (EOG)) yield rather inconsistent findings regarding the presence and form of REMS abnormalities and seem to be partially controversial (Wittmann et al., 2007; Germain, 2013). Increased (Ross et al., 1994a, 1994b; Mellman et al., 1995b; Engdahl et al., 2000) as well as decreased (Schlosberg and Benjamin, 1978; Lavie et al., 1979; Glaubman et al., 1990), but also unchanged REMS amounts (Lavie et al., 1979; Dow et al., 1996; Mellman et al., 1997) have been reported. Moreover, NREMS disturbances (Brown and Boudewyns, 1996; Germain and Nielsen, 2003b; Capaldi et al., 2011) as well as lack of NREMS alterations have been observed (Hurwitz et al., 1998; Engdahl et al., 2000; Klein et al., 2003). A meta-analysis of polysomnographic findings in PTSD (Kobayashi et al., 2007) reports more light NREMS (stage I), less deep NREMS (slow wave sleep (SWS), stage III and IV) and a greater REMS density (i.e. an increased amount of the characteristic rapid eye movements during REMS) in PTSD patients. The described increase of REMS density (Ross et al., 1994a, 1994b, 1999; Mellman et al., 1995b, 1997; Dow et al., 1996; Kobayashi et al., 2007) has also been related to the severity of PTSD symptoms (Mellman et al., 1995a). Additionally, several studies

indicate REMS fragmentation (short, but frequent REMS episodes) as a major characteristic of disturbed sleep in PTSD patients (GLAUBMAN ET AL., 1990; MELLMAN ET AL., 1995B, 2002, 2007; HABUKAWA ET AL., 2007; INSANA ET AL., 2012). The fragmented pattern of REMS involves more brief arousals from REMS (MELLMAN ET AL., 1995B; BRESLAU ET AL., 2004; HABUKAWA ET AL., 2007) and has been shown to be associated with the severity of trauma-related nightmare complaints (HABUKAWA ET AL., 2007). Furthermore, REMS disturbances are associated with an elevated risk to develop PTSD (MELLMAN ET AL., 2004, 2007) and are even considered predictive of PTSD severity (MELLMAN ET AL., 2002). Similarly, early life trauma-related REMS fragmentation has been suggested to increase the vulnerability to psychopathologies in adulthood (INSANA ET AL., 2012).

However, not only REMS fragmentation seems to be of symptomatic and prognostic significance in PTSD. Poor sleep and nightmares early after the trauma seem similarly to be related to the onset and persistence of PTSD, but also other stress-related disorders (FORD AND KAMEROW, 1989; BRESLAU ET AL., 1996; BRYANT ET AL., 2000, 2010; KOREN ET AL., 2002; WRIGHT ET AL., 2011). Persistent post-traumatic nightmares occurring in the early aftermath of a traumatic incident were not only associated with sleep disturbances, but also predicted later sleep difficulties (KOBAYASHI ET AL., 2008) as well as later PTSD symptom severity (FOA ET AL., 1995). Furthermore, nightmares and disturbed sleep, due to nightmares occurring before the experience of a trauma, have been associated with an increased risk for the development of PTSD symptoms (VAN LIEMPT, 2012; VAN LIEMPT ET AL., 2013) and PTSD severity (MELLMAN ET AL., 1995A). PTSD in turn involves sleep disturbances and nightmares, suggesting that *"disturbed sleep is a precipitating and perpetuating factor in PTSD symptomatology, creating a perpetual circle"* (VAN LIEMPT, 2012).

One possible explanation of the prognostic value of REMS disturbances and nightmares could be the observation that frequent nightmare sufferers (with a resultant fragmented sleep pattern) tend to be emotionally more sensitive and therefore more susceptible to emotionally arousing triggers in their internal and external environments (HARTMANN, 1984; HARTMANN ET AL., 1987). Numerous studies, which are discussed in the following paragraphs, draw the conclusion that REMS is likely particularly related to emotions and emotional memory processing. The findings are outlined in detail below and can be summarized as follows: **(I)** Dreams of highly emotional content occur mainly during REMS. **(II)** Emotional and reward circuits are activated during sleep and dreaming. **(III)** Emotional regulation processes occur during sleep, with more intense negative emotions and aggressiveness during REMS. **(IV)** Memory consolidation constitutes one possible function of sleep, however, depending on the nature of the memory, differentiations between emotional memory processing during REMS and declarative or procedural memory processing during NREMS are likely.

Emotions during REMS and Dreaming

REMS (ASERINSKY AND KLEITMAN, 1953; DEMENT AND KLEITMAN, 1957), also referred to as paradoxical sleep (JOUVET, 1962), is characterized by high cortical activity (high frequency/ low amplitude electroencephalographic activity), rapid eye movements, muscle atonia and prominent theta oscillations in the hippocampus and cortex (in contrast to muscle activity and slow wave activity during NREMS) and accounts for approximately 5-20 % of adult mammalian sleep (HORNE, 2013). Although dreams can occur during both, NREMS and REMS, regardless of time during the night reports of dreaming are longest and most bizarre following awakenings from REMS (ASERINSKY AND KLEITMAN, 1953; HOBSON ET AL., 2000; HOBSON, 2009). Rather than being assigned to a certain sleep stage, dreaming might be a continuous phenomenon along sleep, from thought-like dreaming during NREMS to vivid dreams during REMS (DE KONINCK AND KOULACK, 1975; CAVALLERO ET AL., 1992; FOSSE ET AL., 2001; DESSEILLES ET AL., 2011). Also, after awakening from REMS about 80 % of persons are able to remember a dream, whereas awakening from other sleep stages only results in a dream report in 10-20 % of the cases (ASERINSKY AND KLEITMAN, 1953). Particularly during phasic REMS, when rapid eye movements are frequent (as opposed to tonic REMS where rapid eye movements are rare), dream reports are prevalent (WEHRLE ET AL., 2007). REMS dreams show features of primary consciousness, i.e. the awareness of perception and emotions, without self-reflection or abstract thinking which are characteristics of secondary consciousness present during wakefulness (WAKE) and lucid dreaming (HOBSON, 2009). That is, perception and emotions, as well as the conscious awareness of them, are present during dreaming and produced by the brain without external stimulation. However, the dreamer remains unaware of being in a dream and perceives the dream as a real life experience (the only exception constitutes lucid dreaming). Interestingly, it has been proposed that also Theory of Mind, i.e. the ability to attribute mental states to oneself and others and to understand that others have beliefs, desires, and intentions that are different from one's own (PREMACK AND WOODRUFF, 1978), may at least partly be preserved during dreaming (KAHN AND HOBSON, 2005; MCNAMARA ET AL., 2005; PACE-SCHOTT, 2007). Therefore, not only is the dreamer confronted with his own emotions but also with the emotions of other dream characters (PEROGAMVROS ET AL., 2013). However, whereas friendly interactions and actual wakening events are more characteristic of NREMS dream reports, aggressive social interactions are more prevalent during REMS dreams (MCNAMARA ET AL., 2005). Also, REMS dream reports contain less integration between self-referential and social cognitive reasoning with auto-biographical memory (PACE-SCHOTT, 2013). Instead, emotionality, in particular instinctual

emotions and behaviors (like aggressiveness and fear), is a more frequent characteristic of dreams during REMS than during NREMS (CARTWRIGHT ET AL., 1998; SCHREDL AND DOLL, 1998; SMITH ET AL., 2004; WAMSLEY ET AL., 2007). Dream content thus seems to vary depending on sleep stage and/or time of night (PAYNE AND NADEL, 2004).

Emotion Regulation – a Function of REMS and Dreaming?

Dating back to the clinical observations of Siegmund Freud (FREUD, 1900), the proposition was born that dreams as well as the dream-rich sleep stage of REMS are responsible for the processing of emotions and emotional memories (reviewed by (PERLIS AND NIELSEN, 1993; WALKER, 2009; WALKER AND VAN DER HELM, 2009; DESSEILLES ET AL., 2011; PEROGAMVROS ET AL., 2013; RASCH AND BORN, 2013)). However, studies investigating the processing of the affect (or emotional "tag") of memories revealed contradictory findings. Whereas one prominent hypothesis ("Sleep to Forget – Sleep to Remember") declares that REMS and dreaming during REMS re-normalizes or stabilizes the reactivity of the emotional system (WALKER, 2009, 2010; GOLDSTEIN AND WALKER, 2014), others found the emotional component of memories being unaffected by REMS (BARAN ET AL., 2012; GROCH ET AL., 2012). The following paragraph describes hypotheses about the possible functions of REMS and dreaming concerning emotional processing, and summarizes findings about positive and negative influence of REMS and dreaming on emotionality.

First theories about the function of REMS dreaming are based on the assumption that dreaming is a random by-product of REMS (HOBSON AND MCCARLEY, 1977) and speculate that REMS might involve unlearning processes to prevent the brain from overload (CRICK AND MITCHISON, 1983, 1995). Hypotheses from more recent years assume dreams being re-activations of previous experiences during WAKE and thus strengthening the consolidation of "replayed" memories (STICKGOLD ET AL., 2001; CIPOLLI ET AL., 2004; SCHWARTZ, 2010; WAMSLEY ET AL., 2010A). Although in healthy people dream contents only rarely involve parts of a past waking experience (only 1-2 %) and usually constitute novel constructions (SCHWARTZ, 2003), about 50 % of PTSD patients report their dreams to be exact replications of the traumatic event (WITTMANN ET AL., 2007), with a tendency of this traumatic dream to repeat (SCHREUDER ET AL., 1998). Studies about memory consolidation and re-activation processes during REMS, however, are rare as compared to reports examining NREMS (see **SELECTIVE RE-ACTIVATION DURING REMS, P.27 FF.**; (RASCH AND BORN, 2013)). Nevertheless, theories about emotion regulation during REMS and dreaming seem to be more consistent. An evolutional perspective, stating that especially presentations of fear and anxiety in dreams might function as a simulation of threat and a practice for threat recognition and adaptation of emotional responses to it in real life ("Threat Stimulation Theory"; (REVONSUO, 2000;

Valli et al., 2005)), is in accordance with the psychological view of dreams serving as an emotion regulator due to internal activation of emotions during dreaming (Cartwright et al., 1998; Mancia, 2004; Nielsen and Levin, 2007). In the same vein, it was suggested that REMS might serve as a "virtual rehearsal mechanism" from which particularly newborns and infants (there is a preponderance of REMS during early life (Roffwarg et al., 1966) also in non-human mammals (Jouvet-Mounier et al., 1970)) might benefit due to the experience of a diversified and vivid environment during dreaming (Franklin and Zyphur, 2005).

Studies investigating the effect of dreaming or the impact of REMS on mood and emotions both point towards a "re-setting" of emotional affect after sleep. While dreaming was proposed to resolve emotional conflicts and reduce negative emotions and mood the next day (Greenberg et al., 1970; Cartwright et al., 1998, 2006), REMS after an emotional experience strengthens the content but simultaneously reduces the emotional tone of the memory (Walker, 2009, 2010; Gujar et al., 2011a); that is, recently learned memories are released from their emotional context (Deliens et al., 2013a). According to this hypothesis, in depressed patients, who show an increased amount of REMS, memories with a negative content would be particularly strengthened while the REMS-associated attenuation of the emotional tone of memories seems to be disturbed (Walker, 2010). Similarly and as described above, repetitive nightmares in PTSD patients seem not to lead to forgetting of the traumatic experience. They rather might reflect a failure of fear memory extinction or of adaption to or recovery from the trauma, and the attenuation of associated emotions during REMS might fail here as well (Hartmann, 1984; Greenberg et al., 1992; Stickgold, 2002; Levin and Nielsen, 2007; Nielsen and Levin, 2007).

In general, emotional memories are remembered better than neutral ones (Cahill and McGaugh, 1998; Wagner et al., 2001; McGaugh, 2004; Holland and Lewis, 2007; Walker, 2009; Paz and Paré, 2013), an effect probably involving the activation of the beta-adrenergic system (Cahill et al., 1994). From an evolutionary perspective it is clear that the remembering of emotional situations and experiences is favorable (Roozendaal and McGaugh, 2011). Thus it is not surprising that memories of positive as well as negative experience are learned faster (e.g. after a single occurrence), are remembered better, are transferred more precisely into long-term storage and are more resistant to disruption (Cahill and McGaugh, 1998; McGaugh, 2004; Adolphs et al., 2005; Dirnberger et al., 2012; Dudai, 2012; Paz and Paré, 2013).

Even one year after encoding, emotional pictures are remembered better than neutral ones, and successful remembering is associated with enhanced activity in the amygdala and the hippocampus (Dolcos et al., 2005). Furthermore, emotional memories are particularly strengthened across sleep (Wagner et al., 2001, 2006, 2007; Hu et al., 2006; Holland and Lewis, 2007; Payne et al., 2008; Nishida et al., 2009; Walker and van der Helm, 2009; Payne and Kensinger, 2010; Lewis et al., 2011), especially when hippocampus-dependent (Wagner et al., 2001, 2006; Sterpenich et al., 2007, 2009) and particularly during REMS (Grieser et al., 1972;

Cartwright et al., 1975; Greenberg et al., 1983; Horne, 2000, 2013; Wagner et al., 2001, 2006; Nishida et al., 2009; Menz et al., 2013). Enhanced functional connectivity between the amygdala and the medial prefrontal cortex (mPFC) during REMS induces long-lasting consolidation of emotional memories (Sterpenich et al., 2009; Payne and Kensinger, 2011). Also, stronger anxiety ratings and autonomous nervous system responses have been found to be paired with increased activation of the basolateral amygdala (BLA) and to be correlated with the time spent in REMS (Menz et al., 2013). In support of the hypothesis that REMS re-normalizes the emotionality of a memory (Gujar et al., 2011a), the amygdala, a key structure related to fear and anxiety processes (Vuilleumier, 2005), is highly active during REMS (Maquet et al., 1996; Braun, 1997). Amygdalar activity de-potentiates after a night of sleep in response to previous emotional experiences (Sterpenich et al., 2007; van der Helm et al., 2011) and this reduced activation, as well as reduced next-day subjective emotionality, have been shown to be correlated with overnight REMS architecture (van der Helm et al., 2011).

Sleep as well as selective REMS deprivation studies have revealed negative consequences on emotional functions, regarding behavioral (Dinges et al., 1997; Zohar et al., 2005; Kahn-Greene et al., 2006; Killgore et al., 2006, 2008; Banks and Dinges, 2007; McKenna et al., 2007; Huck et al., 2008; Killgore and Weber, 2014) as well as neurophysiological aspects (Yoo et al., 2007; Gujar et al., 2011b; Menz et al., 2012; Rosales-Lagarde et al., 2012; Motomura et al., 2013). Disturbances emerging from sleep deprivation include, for example, **(i)** negative mood (Dinges et al., 1997; Zohar et al., 2005), **(ii)** an altered response to frustration (Kahn-Greene et al., 2006) and loss, paired with reduced activation of the insular and orbitofrontal cortices (Venkatraman et al., 2007), **(iii)** compromised decision making under uncertainty (Killgore et al., 2006; McKenna et al., 2007), **(iv)** faster responses in a conflict situation with high risk, paired with attenuated signals in the midbrain, parietal cortex, and ventromedial prefrontal cortex (vmPFC) (Menz et al., 2012), **(v)** hyper-activation of the amygdala in response to negative emotional stimuli, associated with decreased functional connectivity with the mPFC, suggesting a failure of top-down control (Yoo et al., 2007), **(vi)** increasing number of emotional stimuli judged as pleasant, correlated with the activity in mesolimbic regions (Gujar et al., 2011b) and **(vii)** elevated behavioral and amygdalar responses to the facial expression of fear, associated with a decrease in the functional connectivity between the amygdala and the ventral anterior cingulate cortex (ACC) (Motomura et al., 2013).

Selective REMS deprivation studies also support the idea of emotional "reset" during REMS, as the lack of REMS is associated with enhanced emotional reactivity at behavioral and neural levels (Rosales-Lagarde et al., 2012). Subjects deprived from REMS are irritable and anxious (Dement and Fisher, 1963), confused, suspicious, lack emotional intelligence and empathy and show deteriorated interpersonal relationships (Agnew et al., 1967) as well as impaired adaptation to anxiety-provoking stimuli (Greenberg et al., 1972). Similarly, animal studies have found enhanced responses to emotional stimuli after selective REMS deprivation (Morden

ET AL., 1968; HICKS AND MOORE, 1979; MARTINEZ-GONZALEZ ET AL., 2004). Also, neonatal selective REMS suppression by the administration of antidepressant drugs leads to enhanced anxiety, decreased sexual activity, sleep disturbances and depressive-like behavior in rats (VOGEL ET AL., 1990; MIRMIRAN AND ARIAGNO, 2003). Interestingly, while the prevalence for hypomania-like mood changes in humans increases after sleep deprivation (WEHR ET AL., 1982; COLOMBO ET AL., 1999), REMS-non-suppressing antidepressants display the lowest risk to induce hypomanic/manic symptoms in depressed subjects (LEVERICH ET AL., 2006), thus strengthening the hypothesis that antidepressants and sleep deprivation may produce a hypomanic/manic phase by REMS suppression (SALVADORE ET AL., 2010; PEROGAMVROS ET AL., 2013).

Although the theory of REMS being responsible for re-setting emotionality and strengthening the consolidation of emotional memories seems plausible and has found wide acceptance and affirmation, there are also contradicting findings. Results encompass conclusions suggesting reduced dependency of memories with negative emotional tone on sleep (STERPENICH ET AL., 2007; ATIENZA AND CANTERO, 2008) or rather on NREMS than REMS (TALAMINI ET AL., 2013), exaggerated (WAGNER, 2002; LARA-CARRASCO ET AL., 2009) or reserved emotional reactivity *post* REMS-rich sleep (BARAN ET AL., 2012; GROCH ET AL., 2012), increased amygdalar activity and limbic connectivity after sleep (PAYNE AND KENSINGER, 2011), and predominant importance of adrenergic activity during NREMS, rather than REMS, for the consolidation of emotional memory (GROCH ET AL., 2011). Investigating the unbinding of memories from their emotional context during sleep lead to the suggestion that several cycles passing NREMS and REMS might be necessary in order to reach emotional "untagging" (DELIENS ET AL., 2013A, 2013B). However, another recent study exploring the bidirectional interactions between emotional experience, sleep architecture and emotional processing during sleep, found subpopulations differing in their baseline sleep characteristics, emotional responsiveness and both subjective and electrophysiological sleep responses to emotional distress (TALAMINI ET AL., 2013). These findings suggest a coupling of certain emotion and sleep traits into distinct emotional sleep types (TALAMINI ET AL., 2013). Therefore, contradicting results might not only be explained by the diversity of the used emotionally arousing stimuli and paradigms. It may also be the case that people vary in their ability to cope with emotionally distressing experience, which might also be depending on certain sleep traits (TALAMINI ET AL., 2013).

Prospective studies revealing possible prognostic markers for the development of PTSD, like nightmares and REMS fragmentation (see **SLEEP DISTURBANCES IN PTSD, P.4 FF.**), also point towards REMS-related vulnerability traits: individual differences regarding certain REMS features may cause different effects of stress or a traumatic experience between individuals (see also (GERMAIN, 2013)). Unfortunately, so far, no study has directly related brain activation during sleep with emotions experienced during dreaming (DESSEILLES ET AL., 2011). However, there is some evidence that REMS and dreaming may be implicated in different dimensions of adaptation to negative emotions (LARA-CARRASCO ET AL., 2009).

Regionally Specific and Transient Brain Activity during Sleep

Consistent with the observations described above, emotional and reward networks are activated during sleep in both, humans and animals (for review see (Vandekerckhove and Cluydts, 2010; Perogamvros et al., 2013)). Early (Maquet et al., 1996; Braun, 1997) and recent (Massimini et al., 2005, 2010; Dang-Vu et al., 2008; Koike et al., 2011) neuroimaging studies in humans have revealed that brain activation is inhomogeneous across sleep stages: NREMS is characterized by a general decrease in activation, whereas REMS shows an unchanged or even increased activation pattern as compared to WAKE. However, brain activation patterns related to phasic events within specific sleep stages have been identified, showing that also during NREMS brain activity is increased as compared to WAKE, in a region-specific and transient manner (for review see (Dang-Vu et al., 2010)). That is, associated with specific oscillations during NREMS (sleep spindles, slow waves) and REMS (ponto-geniculo-occipital (PGO) waves), brain activity was found to be elevated (Wehrle et al., 2005; Schabus et al., 2007; Dang-Vu et al., 2008; Miyauchi et al., 2009). In summary it can be concluded that during both, REMS and NREMS, key structures of the reward- and emotion-related circuits are activated, as described in detail below.

Although brain activity decrements during NREMS, as compared to WAKE, were located in subcortical (brainstem, thalamus, basal ganglia, basal forebrain) and cortical (prefrontal cortex (PFC), ACC, and precuneus) regions (Braun, 1997; Maquet et al., 1997; Maquet, 2000), when adjusting for the overall decrease in activation of the whole brain, metabolism in the ventral striatum, ACC, and regions of the medial temporal lobe, including the amygdala and hippocampus, increase compared to WAKE (Nofzinger et al., 2002). Furthermore, during NREMS spindles (spontaneous brain oscillations in the ~10-15 Hz frequency range brought about by thalamo-corticothalamic loops (Steriade and Deschenes, 1984)), the lateral and posterior thalamus, as well as emotion-related regions such as the ACC, insula and superior temporal gyrus display increased blood-oxygen-level-dependent (BOLD) responses (Schabus et al., 2007). Also, fast spindles (~13-15 Hz) are associated with increased activity in the mPFC and the hippocampus (Schabus et al., 2007). BOLD responses during NREMS slow waves (cortically generated rhythm in the 0.5-4 Hz frequency range shaped by the thalamus (Timofeev and Steriade, 1996; Steriade and Timofeev, 2003)) on the other hand are elevated within the inferior frontal gyrus, brainstem, parahippocampal gyrus, precuneus and posterior cingulate cortex (Dang-Vu et al., 2008).

During REMS, in addition to brainstem activation involved in REMS generation (Fort et al., 2009; Brown et al., 2012; Horne, 2013; Luppi et al., 2013), particularly emotion-related circuits are activated as compared to WAKE, i.e. the hippocampus, amygdala, and ACC (Maquet et al., 1996; Braun, 1997; Nofzinger et al., 1997; Lövblad et al., 1999; Maquet, 2000). In contrast, structures implicated in executive and attentional functions during WAKE, including the dorsolateral PFC, orbitofrontal

cortex, precuneus, and the inferior parietal cortex, are significantly less activated during REMS (Maquet et al., 1996; Braun, 1997; Nofzinger et al., 1997; Maquet, 2000). Similarly, the connectivity within the dorsomedial prefrontal system is diminished during REMS (Koike et al., 2011), in contrast to the elevated activation of the mPFC (Maquet et al., 1996). PGO waves during REMS (phasic oscillations generated by the activation of a group of glutamatergic cells in the pons (Datta et al., 1992, 1998; Datta, 1997)) have been associated with activity in the putamen, ACC, parahippocampal gyrus, and amygdala (Miyauchi et al., 2009). Particularly during dream-rich phasic REMS, limbic areas show elevated activation (Wehrle et al., 2007). Also, in accordance with diverse dream characteristics during REMS and NREMS, the amygdala and other limbic structures undergo substantially stronger activation during REMS as compared to NREMS (Payne and Nadel, 2004; Vandekerckhove and Cluydts, 2010). Thus, activation of emotion-related circuits during REMS could explain the preponderance of emotions, predominantly negative ones like anxiety and fear (Valli and Revonsuo, 2009), whereas deactivation of higher cortical control function may be responsible for disorientation, illogical thinking, reduced cognitive control, and impaired working memory during REMS dreaming (Schwartz and Maquet, 2002; Hobson, 2009).

Some recent investigations on dreaming also outline the activation of emotion-related limbic structures during NREMS, as well as REMS, dreams (De Gennaro et al., 2012). In a study of patients with cerebral lesions, repetitive nightmares have been found to emerge in the presence of temporal-limbic seizure activity (Solms, 1997). Intracranial recordings in epileptic patients disclosed that enhanced rhinal-hippocampal, as well as intrahippocampal, connectivity, mediating memory formation in the waking state (Fell et al., 2001), was associated with a successful dream recall after awakening from REMS (Fell et al., 2006). Consistently, subjects capable to report a dream upon awakening from REMS showed a strong bilateral amygdala activation (Maquet, 2000). A recent microstructural imaging analysis of the hippocampus and the amygdala further revealed direct association of these limbic structures with the emotional load of dreams (De Gennaro et al., 2011); especially volume and integrity of the left amygdala were correlated with a high emotional character of dreams.

Although the translation and comparability of animals studies to the above findings observed in humans are skewed by the difficulties of neuroimaging in experimental animals, several studies have documented specific activation of limbic and reward structures during both, NREMS and REMS. Ventral tegmental area (VTA) activity has been shown to be low during NREMS but elevated during REMS in rats (Dahan et al., 2007) and to result in a strong dopaminergic release in the nucleus accumbens (NAC) shell (Maloney et al., 2002; Dahan et al., 2007), comparable to activation patterns during awake emotional- and reward-related behavior like feeding, punishment and sex (Dahan et al., 2007). Also, dopaminergic levels in the NAC have been found to be elevated during REMS, which might facilitate the replay of emotional memories during sleep (Léna et al., 2005). Further,

neural firing patterns occurring during reward-seeking behavior in the VTA were spontaneously re-activated during NREMS the following night (Pennartz et al., 2004; Lansink et al., 2008). It was proposed that this offline hippocampal-driven re-activation might designate the memory trace with an emotional value during sleep and function as a mechanism for the consolidation of motivational memories (Lansink et al., 2009; Singer and Frank, 2009; Pennartz et al., 2011). Similarly, orexin (hypocretin) neurons in the hypothalamus, whose projections to the VTA, as well as to the amygdala and to the NAC have been related to emotional processing and motivated behaviors (Harris et al., 2005; Thompson and Borgland, 2011), display occasional discharges during REMS (Mileykovskiy et al., 2005; Takahashi et al., 2008). Like in humans, amygdalar activation is increased during sleep in cats (Pelletier et al., 2005). Electrical activity in the amygdala, and its modulation and synchronization with hippocampal activity, have been shown to be strongly affected during REMS in rats (Karashima et al., 2010). Also, synchronous activity in the amygdala and connected areas during REMS has been reported to support the consolidation of conditioned fear (Popa et al., 2010). Furthermore, PGO-waves during REMS, the characteristic cortical oscillations during REMS linked to dreaming and learning, have been found to increase upon electrical stimulation of the amygdala during REMS, but rather to decrease upon stimulation during NREMS (Datta, 2000).

Taken together, activation patterns of reward- and emotion-related circuits during sleep might imply a specific re-processing and consolidation of memories that are of a high emotional and motivational importance for the organism (see also "Reward Activation Model" proposed by (Perogamvros and Schwartz, 2012)). Although limbic circuits seem to be activated especially during REMS, it seems that both, NREMS and REMS, contribute to the consolidation of emotionally relevant memories. As can be reasoned also from the above-described sleep deprivation studies, sleep supports the update of cognition and emotion required for the later performance in the waking state. Especially REMS may have a crucial role in the maintenance of the integrity of emotional networks and, therefore, emotionality. Furthermore, dreaming might represent an offline replaying state where experiences gathered during waking (like emotions and learning) are re-processed, although, due to lack of data in this domain, the latter interrelation remains hypothetical (Perogamvros et al., 2013). However, since negative emotions and aggression rather characterize dreams occurring during REMS (Cartwright et al., 1998; Schredl and Doll, 1998; Smith et al., 2004; Wamsley et al., 2007), it seems conceivable that different types of emotional experiences might predominate different sleep stages.

The prevalence of dreaming, particularly emotional dreaming and nightmares, in patients suffering from PTSD, leads to the assumption that particularly the activation of areas involved in emotions during REMS is pathologically enhanced in the disease. The amygdala and its connections with the hippocampus and the PFC might therefore play a major role (Hull, 2002; Liberzon and Sripada, 2008). Indeed, neuroimaging studies in PTSD patients have revealed lower volumes of the hippocampus (Kitayama et al., 2005; Smith, 2005; Karl et al., 2006; Bonne et al., 2008; Schuff et al., 2008; Karl and Werner, 2010)but see (De Bellis et al., 2001) as well as of the vmPFC (Kasai et al., 2008), a putative homologue to the infralimbic cortex in rodents implicated in the extinction of fear (Milad and Quirk, 2012), and the dorsal ACC (dACC) (Kitayama et al., 2006), a putative homologue to the prelimbic cortex in rodents implicated in the expression of fear (Milad and Quirk, 2012). These structural variations favor the theory of reduced cortical inhibition of fear and hippocampal failure to signal safety in PTSD (Pitman et al., 2012). Whether hippocampal as well as cortical volume differences might constitute pre-existing features in PTSD, and thus might serve as risk factors for the development of PTSD, remains under discussion ((Bremner, 2001; Gilbertson et al., 2002; Kasai et al., 2008; Woon et al., 2010; Sekiguchi et al., 2013); see also **chapter 4 We are what we dream?, p. 129 ff.**). A recent study has furthermore identified a decreased volume of the amygdala as a potential vulnerability marker in PTSD (Morey et al., 2012), although earlier meta-analyses yielded inconsistent results (Karl et al., 2006; Woon and Hedges, 2009). Also, aberrant white matter integrity has been found in PTSD patients in the cingulum bundle which connects the ACC with the amygdala (Kim et al., 2006). This finding could again explain impaired inhibitory cortical control of the amygdala in PTSD, which is further affirmed by functional neuroimaging studies described in the following paragraph.

Amygdala activity towards trauma-related (Liberzon et al., 1999b; Fonzo et al., 2010), but also generic stimuli (Etkin and Wager, 2007), is abnormally elevated in PTSD patients. During the acquisition of conditioned fear, PTSD patients show increased levels of amygdalar activation (Bremner et al., 2005). Additionally, impaired extinction learning in PTSD patients, particularly impaired recall of the extinction learning (Milad et al., 2009), has been linked to greater amygdala activation, as the BLA has been shown to be critical for reinstating the fear response to a previously extinguished fear memory (Laurent and Westbrook, 2010). Two prospective studies in healthy soldiers moreover have found that hyper-activation of the amygdala in response to negative stimuli is predictive of the amount of developed PTSD symptoms after the experience of a traumatic event (Admon et al., 2009, 2013a). Similarly, activation of the dACC in PTSD patients is increased upon fear conditioning (Rougemont-Bücking et al., 2011), recall of fear extinction (Milad et al., 2009; Rougemont-Bücking et al., 2011), exposure to novel stimuli (Bryant et al., 2005; Pannu et al., 2009) and even at rest (Shin et al., 2009), indicating that dACC

activity might represent a risk factor for PTSD (Shin et al., 2011). Activity of the dACC is positively associated with PTSD symptom severity (Fonzo et al., 2010) and shows elevated levels even in healthy identical twins of patients with PTSD (Shin et al., 2009, 2011). Interestingly, genetic imaging studies, examining dopamine and serotonin signaling-associated genetic polymorphisms in PTSD patients, indicate that structural/activity changes in the amygdala and/or the dACC might already be evident at birth (Morey et al., 2011; Schulz-Heik et al., 2011).

In contrast, activation of the vmPFC and the rostral ACC is decreased in subjects with PTSD upon confrontation with trauma-related (Shin et al., 1999) as well as unrelated stimuli (Felmingham et al., 2010; Gold et al., 2011), during extinction memory recall (Milad et al., 2009) and during emotional cognitive interference tasks (Shin et al., 2001). Also, vmPFC activation is negatively correlated with PTSD symptom severity (Shin et al., 2004; Felmingham et al., 2007). Prefrontal activation has also been shown to be negatively correlated with amygdalar activation, as well as the response to fearful stimuli in PTSD (Shin et al., 2005b). Whereas studies exploring hippocampal activation in PTSD patients have revealed inconsistent results (Bremner et al., 2003; Milad et al., 2009; Shin and Liberzon, 2010), activity of the insular cortex is elevated in subjects with PTSD (Simmons et al., 2008; Strigo et al., 2010; Aupperle et al., 2012). However, although positively correlated with PTSD symptom severity (Simmons et al., 2008), insular hyper-activation does not seem to be specific to PTSD, as it can be found in several anxiety disorders (Etkin and Wager, 2007). Taken together, whereas the amygdala and the dACC constitute hyper-activated regions in PTSD, rostral ACC and vmPFC are pathologically hypo-activated in the disease (Hayes et al., 2012a).

Combining the findings of individual brain area hyper- and hypo-activation patterns in PTSD patients, neurocircuitry studies have found altered amygdala connectivity (Rabinak et al., 2011; Sripada et al., 2012a), specifically decreased connectivity of the BLA with its prefrontal cortical targets (Brown et al., 2014), in PTSD patients as compared to trauma-exposed controls. Rather, PTSD patients showed stronger functional connectivity of BLA with the ACC, and the dorsomedial PFC. Accordingly, abnormal activation (hypo-connectivity) in PTSD patients has also been found in the default-mode network (Bluhm et al., 2009; Yin et al., 2011; Sripada et al., 2012b). The default network idea arose from experiments showing that the brain is constantly active with a high level of activity, even when a person is at rest without performing mental work (Raichle et al., 2001; Raichle and Snyder, 2007; Raichle, 2010). It encompasses a network of brain regions that are active when the individual is not focused on the outside world and engaged in internally focused tasks (autobiographical memory retrieval, envisioning the future, conceiving the perspectives of others). This network includes the medial temporal lobe, the mPFC and the posterior cingulate cortex (Buckner et al., 2008). Recently, this specific activation of brain regions at rest has been also demonstrated in rats (Lu et al., 2012). As argued by Brown and colleagues (Brown et al., 2014), stronger coupling between the BLA and regions of the default mode network in PTSD

patients, indicating a strong involvement of amygdalar activity in internal monitoring and self-referential thoughts, might explain the preponderance of emotional thoughts, re-processing of the traumatic event and an increased anxiety level in PTSD patients, even at rest.

In summary, similarly as during sleep in healthy subjects, an increased activation of the amygdala and the dACC, paired with a low activation of prefrontal cortical areas involved in the regulation and top-down control of the amygdala (Sotres-Bayon et al., 2004; Sotres-Bayon and Quirk, 2010), can be found in PTSD patients, potentially leading to or sustaining an increased affective processing (Vandekerckhove and Cluydts, 2010; Pitman et al., 2012). A failure of the PFC to exert inhibitory control of the amygdala might lead to increased fear responses, impaired extinction and recall of extinction memory, deficits in emotion regulation, as well as an attentional bias toward threatening stimuli (Jovanovic and Norrholm, 2011; Hayes et al., 2012b; Pitman et al., 2012). On the other hand, hyper-activation of the dACC might even promote fear expression, which possibly is even strengthened by elevated insular activation, which probably reflects heightened awareness of bodily arousal. Hippocampal deficits further might underlie cognitive impairments (e.g. of spatial cognition; for review see (Samuelson, 2011)), and the inability of PTSD patients to reliably recognize a safe context (Jovanovic et al., 2012). Thus, PTSD might involve a "brain-state shift" from higher cortical- and hippocampal-dependent cognitive processing to a lower amygdala-dependent association processing, of course under regulation and modulation by neuroendocrine, genetic and epigenetic mechanisms (Pitman et al., 2012). Furthermore, whereas abnormal structure and activation of amygdala and dACC might represent risk factors for developing PTSD after the exposure to a trauma, reduced volume and connectivity between prefrontal cortical areas and the hippocampus might be acquired after the traumatic experience (Admon et al., 2013b).

Neuroanatomical Effects in Animal Models

In order to identify possible underlying causes, mechanisms and affected brain regions in the human disease, basic research studies make use of animal models of PTSD (for an extensive overview see **Animal Models of PTSD, p.37 ff.**). Many of these models imply the method of classical fear conditioning as resemblance of the traumatic event. Classical (Pavlovian) fear conditioning is referred to as the temporal pairing of a neutral stimulus, the conditioned stimulus (e.g. tone, light, odor, environment), with an aversive event, the unconditioned stimulus (e.g. foot shock), eliciting a fear response, the unconditioned response (e.g. freezing, increased skin conductance) (LeDoux, 2000; Wotjak, 2005; Milad et al., 2011). Repetition of this pairing causes the conditioned stimulus to elicit the fear response without the occurrence of the unconditioned stimulus, now referred to

as the conditioned response. Cued fear conditioning constitutes the pairing of the unconditioned stimulus with a specific cue (e.g. a tone), whereas contextual conditioning uses the context or environment *per se* as a conditioned stimulus. Fear extinction on the other hand describes the opposite learning effect, i.e. the loss of the conditioned response by repeated presentation of the conditioned stimulus alone. Pathways and mechanism of this frequently used paradigm have been studied and described in detail (for review see (Pape and Paré, 2010; Johansen et al., 2011; Paré and Duvarci, 2012; Wotjak and Pape, 2013)). Most importantly for this work, the BLA was found to receive convergent information about context and shock during learning of a contextual fear conditioning, whereas this concurrence of stimuli during learning was not observed in the dorsal hippocampus (Barot et al., 2009). Also, bilateral activation of the BLA seems to be necessary for the expression of contextual, but not cued fear (Flavell and Lee, 2012).

Without any doubt, it is neither possible to adequately "rebuild" any human mental disease in animals, nor does any fear conditioning or stress paradigm imply the broad physical and psychological features of a trauma, as it is experienced by a human. However, these models allow for investigation of very specific reactions of the body and the brain to the stressful situation, be it at behavioral, endocrine or neuronal level. Adequate physiological reactions to stress are absolutely essential for survival. The perception of psychological stressors is, however, highly subjective, as are behavioral and endocrine responses to stress, mostly dependent on previous experience and cognitive processing (Sousa and Almeida, 2012; Lucassen et al., 2014). Accordingly, emotional as well as cognitive neural circuits are involved in the control of the stress response and thus affected by stressful events (Jankord and Herman, 2008; Roozendaal et al., 2009; Sousa and Almeida, 2012). As mentioned before, the variety of stress and PTSD models is enormous, and interpretations and conclusions have to be drawn with high caution when comparing between them. Prolonged stress, for example, can have distinctly different effects on cognition, emotion, and nervous system activity and morphology than acute stress (Patchev and Patchev, 2006). Nevertheless, indirect consequences for the possible changes and effects in PTSD might also be imported from experimental findings in these fields.

High levels of circulating stress hormones lead to differential structural reshaping (in terms of volume and/or morphology) of specific regions in the brain which are known to be involved in emotional and cognitive processes (Joëls and Baram, 2009; Roozendaal et al., 2009; Ulrich-Lai and Herman, 2009; McEwen, 2012; Sousa and Almeida, 2012; Goswami et al., 2013) as well as to be affected in PTSD, as detailed above (**Functional Neuroanatomy in PTSD, p.14 ff.**). In the hippocampus, stress leads to cellular atrophy, inhibition of neurogenesis and activity-dependent synaptic plasticity (McEwen, 1999; Pavlides et al., 2002; Pawlak et al., 2005). Similarly, stress reduces proliferation and induces dendritic shrinkage and spine loss in the mPFC (Radley et al., 2004, 2008; Banasr et al., 2007). In contrast, opposite effects (hypertrophy, synaptic strengthening, spine growth) can be found in the amygdala,

specifically the BLA (Vyas et al., 2002; Mitra et al., 2005; Roozendaal et al., 2009). Also, the orbitofrontal cortex shows hypertrophy in response to stress (Liston et al., 2006). Stress and treatment with stress hormones further result in reduced volume of the mPFC and ACC (Cerqueira et al., 2005; Perez-Cruz et al., 2007, 2009).

Structural imaging in mice which underwent the fear conditioning paradigm used in the present experiments revealed a volume loss in both, left hippocampus and right central amygdala, paralleled by the development of a PTSD-like phenotype (Golub et al., 2011). Moreover, in the same model diminished left hippocampal levels of N-acetyl-aspartate, a marker of neuronal integrity (Demougeot et al., 2001) that is expressed at lower levels in the hippocampus of PTSD patients (Gilbertson et al., 2002; Karl et al., 2006), predicts the development of PTSD-like symptoms (Siegmund et al., 2009b).

Consistent with the evidence of hippocampal atrophy and volume loss, many animal models of PTSD are also associated with signs of hippocampal dysfunction, e.g. impairments in spatial memory, novel object recognition and hippocampus-dependent working memory (Richter-Levin, 1998; Diamond et al., 1999; Wang et al., 2000, 2012; Woodson et al., 2003; Park et al., 2008; Zoladz et al., 2008; Andero et al., 2012; Goswami et al., 2012). Furthermore, connectivity between emotional and cognitive circuits is affected by stress, as exemplified by decreased synaptic plasticity and synchronous activity between the hippocampus and the mPFC (Cerqueira et al., 2007; Lee et al., 2011). Amygdalar influence on hippocampal activity, in contrast, has been shown to increase with stress (Ghosh et al., 2013).

Another indirect evidence for altered brain activation after a trauma-like experience in animals, comes from studies on the brain-derived neurotrophic factor (BDNF) (Binder and Scharfman, 2004). BDNF constitutes a growth factor acting on neurons of the peripheral and central nervous system, e.g. in the hippocampus, cortex, and basal forebrain, and supports the survival, growth and differentiation of neurons and synapses in these regions (Huang and Reichardt, 2001). Thus, it has also been implicated in learning and memory processes (Yamada and Nabeshima, 2003). Consistent with the implication of BDNF in neurobiological mechanisms underlying the clinical manifestations of PTSD, reduced levels of BDNF are found in the cerebrospinal fluid of PTSD patients (Berger et al., 2010; Hauck et al., 2010). Similarly, trauma-like stressors suppress BDNF in the dorsal hippocampus of rodents (Kozlovsky et al., 2007; Roth et al., 2011), in contrast to long-lasting increases of BDNF levels in the BLA (Lakshminarasimhan and Chattarji, 2012). Amygdalar BDNF signaling has been shown to be critical for both, the initial learning of a conditioned fear memory, as well as its extinction (Chhatwal et al., 2006; Andero et al., 2011; Mahan and Ressler, 2011; Andero and Ressler, 2012), whereas prelimbic cortical BDNF seems to be required for the learning of the fear association, only (Choi et al., 2010). Deletion of the BDNF gene in the dorsal hippocampus results in poor spatial memory and impaired extinction of conditioned fear, while fear conditioning and inherent anxiety remains unaffected, a phenotype similar to what is found in PTSD patients (Heldt et al., 2007).

Furthermore, deficient extinction learning in rats has been associated with reduced BDNF in hippocampal projections to the mPFC, while augmenting BDNF in this pathway prevented extinction failure (PETERS ET AL., 2010).

In summary, stressor-induced changes in brain structure and function in animal models of stress and PTSD resemble findings of functional neuroanatomical alterations reported in PTSD patients. The affected emotional and cognitive brain circuits seem also to be responsible for the particular strengthening of emotionally salient and engraving memories during sleep. Theories describing how memories might be consolidated during sleep, which brain areas are implicated in the sleep-dependent consolidating processes and how the communication between these brain areas might proceed, are discussed in the following paragraph.

Replay and Memory Consolidation during Sleep

"Practice, practice, and all is coming"

Sri K. Pattabhi Jois

The one and only function and immanent importance of sleep remains elusive, as sleep contributes to several basic physiological functions (energy saving, energy restoration, hormonal regulation, immunity, thermoregulation, ontogenesis, metabolism) (Roth et al., 2010; Rattenborg et al., 2012). However, the null hypothesis (e.g. no sleep is required) can be rejected, since **(i)** all animals studied so far show some sort of sleep or sleep-like resting state (Cirelli and Tononi, 2008; Siegel, 2008; Roth et al., 2010), **(ii)** loss of sleep is accompanied by elevated sleep pressure and a recovering rebound sleep period (Cirelli and Tononi, 2008; Rattenborg et al., 2012), and **(iii)** persistent sleep deprivation has severe consequences for health and well-being of the organism and can result even in death (Rechtschaffen et al., 1989; Rechtschaffen and Bergmann, 1995, 2002; Shaw et al., 2002; Stephenson et al., 2007; Cirelli and Tononi, 2008). Nevertheless, it is the brain that seems to suffer the most from sleep deprivation, and cognitive and emotional disturbances are the most prominent and immediate effects of sleep loss (for review see (Killgore, 2010; Vandekerckhove and Cluydts, 2010; Brown, 2012; Killgore and Weber, 2014)). That is, sleep seems to be mainly "for the brain" (Hobson, 2005).

Besides the involvement of sleep in emotional regulation, detailed above (**Emotion Regulation, p.7 ff.**), one prominent hypothesized function of sleep is memory consolidation (for review see (Born et al., 2006; Diekelmann et al., 2009; Diekelmann and Born, 2010; Inostroza and Born, 2013; Rasch and Born, 2013)). The latter has been described as a perpetual process by which new memories are progressively re-structured, temporarily stored into a labile short-term memory at the level of the hippocampus, and finally incorporated into pre-existing memories of the stable cortical long-term memory network (Diekelmann et al., 2009; Wang and Morris, 2010; Rasch and Born, 2013). Also REMS has been proposed to be involved in this process (Poe et al., 2010), even though evidence is rather scarce as compared to the role of NREMS (Ackermann and Rasch, 2014).

For any organism, the formation of memories is essential in order to be able to adapt to changes in the environment and adequately respond to daily life situations. Newly encoded memories are fragile and need to be consolidated over time (MÜLLER AND PILZECKER, 1900; LECHNER ET AL., 1999), possibly involving several consolidating runs for long-term storage (MCGAUGH, 2000) and re-consolidating processes upon retrieval of the memory (NADER AND HARDT, 2009). The classical **TWO-STAGE MEMORY FORMATION** theory (MARR, 1971) states that retrieved memories are initially encoded into a fast learning system (e.g. the hippocampus for declarative memories) and are then gradually stored into long-term storing, slow learning, cortical structures, thus become progressively independent of the hippocampus (ALVAREZ AND SQUIRE, 1994; MCGAUGH, 2000; FRANKLAND AND BONTEMPI, 2005). According to this hypothesis, strengthening of new memories and their incorporation into the long-term storage are presumably achieved by repeated re-activation of new memory traces during off-line periods, like sleep. Regardless of the type of memory, declarative or non-declarative (SQUIRE AND ZOLA, 1996), the transfer of recent memories from a temporary store to a permanent store might be a general feature of long-term memory formation, and the sleeping brain provides optimal conditions for these consolidating processes (RASCH AND BORN, 2013). For example, it has been demonstrated that successful recall of an (emotional) memory 3 days after encoding following normal sleep was paralleled by increased activation of the hippocampus and cortical areas (STERPENICH ET AL., 2007), whereas 6 months later recollection was associated with responses in cortical areas, but not the hippocampus (GAIS ET AL., 2007; STERPENICH ET AL., 2009). Similarly, labeling of neurons, activated during a fear conditioning task in mice, has shown that the retrieval of a recent memory re-activated the same neuronal networks in the amygdala, hippocampus and cortex, while retrieving of remote memory content resulted in altered re-activation in the hippocampus and amygdala, but not in the cortex (TAYLER ET AL., 2013). These findings support the assumption of reorganization of memories within cerebral networks over time. It was also suggested, that consolidation of emotional memories might involve separate portions of the amygdala, depending on the various temporal-functional stages of memory consolidation (STERPENICH ET AL., 2009).

Numerous studies have proven the beneficial effect of sleep on memory consolidation and successful memory retention (reviewed extensively by (AMBROSINI AND GIUDITTA, 2001; MAQUET, 2001; STICKGOLD ET AL., 2001; BLISSITT, 2001; WAGNER ET AL., 2004; WALKER AND STICKGOLD, 2004, 2006; STICKGOLD, 2005; STICKGOLD AND WALKER, 2005, 2007; BORN ET AL., 2006; ELLENBOGEN ET AL., 2006; AXMACHER ET AL., 2009; WALKER, 2009; PAYNE AND KENSINGER, 2010; BORN, 2010; DIEKELMANN AND BORN, 2010; RIBEIRO, 2012; SALETIN AND WALKER, 2012; BORN AND WILHELM, 2012; ABEL ET AL., 2013; RASCH AND BORN, 2013; INOSTROZA AND BORN, 2013)) at retrieval times from hours to days and even months after memory encoding (GAIS ET AL., 2007; DIEKELMANN ET AL., 2009). Experimental studies have provided congruent evidence that REMS is essential for

memory consolidating processes, as REMS amounts have been found to increase after learning, and selective REMS deprivation has been shown to result in impaired memory of specifically complex tasks, whereas simpler tasks were less affected (VOGEL, 1975; FISHBEIN AND GUTWEIN, 1977; MCGRATH AND COHEN, 1978; PEARLMAN, 1979; SMITH, 1985, 1996, 2003, 2011; POE ET AL., 2010). In contrast, human studies investigating the impact of REMS on memory consolidation are rather inconsistent. Most of them report no effect of REMS deprivation on the retention of declarative memories (CHERNIK, 1972; LEWIN AND GLAUBMAN, 1975; TILLEY, 1981; SMITH, 1995), only of more complex ones (EMPSON AND CLARKE, 1970; TILLEY AND EMPSON, 1978). Consolidation of procedural memories, on the other hand, has been described as being sensitive to REMS deprivation (SMITH, 1993, 1995; KARNI ET AL., 1994; SMITH AND SMITH, 2003) and learning of procedural tasks was accompanied by subsequent elevation of REMS amount (VERSCHOOR AND HOLDSTOCK, 1984; DE KONINCK ET AL., 1989, 1990; MANDAI ET AL., 1989; BUCHEGGER ET AL., 1991; FISCHER ET AL., 2002). In this context it was proposed that REMS is essential for the consolidation of procedural (non-declarative) memories, while being insignificant for declarative memory processing (SMITH, 1995, 2001). Although these discrepant findings could also be explained by the rather stressful procedures of REMS deprivation in animals and thus by the effect of stress, rather than lack of REMS, on memory consolidation, also in humans (BORN AND GAIS, 2000; DE QUERVAIN, 2006), the importance of REMS for the consolidation of emotional memories is indisputable (see **EMOTION REGULATION, P.7 FF.**).

Consistently with the apparent differential effect of REMS on declarative and non-declarative memories, the **DUAL PROCESS HYPOTHESIS** (MAQUET, 2001; SMITH, 2001; GAIS AND BORN, 2004; RAUCHS ET AL., 2005; BORN ET AL., 2006) states that different types of memories are consolidated during different sleep stages. It has been proposed that declarative memories are strengthened particularly by deep NREMS (SWS), whereas non-declarative memories benefit from REMS. Comparing SWS-rich sleep periods (early half of the night) with REMS-rich sleep periods (late half of the night) in humans, it has been shown that the retention of a neutral declarative memory improves after a sleep period rich of SWS, but not REMS, whereas REMS-rich sleep selectively supports procedural, implicit and emotional declarative memories (YAROUSH ET AL., 1971; BARRETT AND EKSTRAND, 1972; FOWLER ET AL., 1973; PLIHAL AND BORN, 1997, 1999; WAGNER ET AL., 2001, 2003; WAGNER, 2002; VERLEGER ET AL., 2008). Negative emotional (fear) memory, as well as its extinction, benefit from sleep (PACE-SCHOTT ET AL., 2009). REMS might play a crucial role specifically in the extinction of fear memories, which by itself is a learning process (SPOORMAKER ET AL., 2010). In animals, where sleep is only sub-classified into NREMS and REMS without a further differentiation of SWS, contextual fear conditioning, a hippocampus-dependent task, was impaired by sleep deprivation before (RUSKIN ET AL., 2004), as well as after training (GRAVES ET AL., 2003; HAGEWOUD ET AL., 2011). Also, REMS deprivation was shown to impair the extinction of cued fear (SILVESTRI, 2005). Direct examination of synaptic plasticity by the electrophysiological measure of long-term-potentiation

(LTP) in the hippocampus and cortex has revealed a negative effect of sleep deprivation (Campbell et al., 2002; Romcy-Pereira and Pavlides, 2004; Marks and Wayner, 2005; Vecsey et al., 2009; Alkadhi et al., 2013), selective REMS deprivation (Shaffery et al., 2002; Davis et al., 2003; McDermott et al., 2003; Romcy-Pereira and Pavlides, 2004; Lopez et al., 2008) and sleep fragmentation (Tartar et al., 2006; Arrigoni et al., 2009). Similarly, hippocampal neurogenesis was found to be reduced after sleep disruptions (Guzman-Marin et al., 2003, 2005, 2007; Hairston et al., 2005).

Another possible explanation for the differential effects of early and late sleep periods on memory consolidation might be the different cyclic organization of sleep during these phases, rather than the preponderance of NREMS *vs.* REMS (Ficca and Salzarulo, 2004; Rasch and Born, 2013). That is, the cyclic succession of sleep stages, with NREMS and REMS exerting differential functions, might be crucial for successful memory consolidation. This **SEQUENTIAL HYPOTHESIS** (Giuditta et al., 1995; Ambrosini and Giuditta, 2001) assigns the strengthening and weakening of memories as a potential function of NREMS, whereas subsequent REMS possibly integrates and stores new memories into the preexisting memory storage. The importance of succeeding NREMS and REMS cycles for memory consolidation has been supported by several reports of experiments in rats (Ambrosini et al., 1988a, 1988b, 1992, 1995; Langella et al., 1992; Giuditta et al., 1995) and humans (Mazzoni et al., 1999; Ficca et al., 2000; Gais et al., 2000; Stickgold et al., 2000; Mednick et al., 2003). Furthermore, transitional sleep between NREMS and REMS, showing mixed EEG characteristics of both sleep stages (Piscopo et al., 2001), has been found to be predictive of successful memory consolidation (Ambrosini et al., 1993; Stickgold et al., 1999; Ambrosini and Giuditta, 2001), also for aversively conditioned avoidance learning (Datta, 2000; Mandile et al., 2000).

The combination of the previously described **DUAL PROCESS** and **SEQUENTIAL HYPOTHESES**, led to the proposition of the **ACTIVE SYSTEM CONSOLIDATION HYPOTHESIS** (for review see (Ribeiro and Nicolelis, 2004; Ellenbogen et al., 2007; Rasch and Born, 2007, 2008, 2013; Diekelmann and Born, 2010; Walker, 2010; Wang et al., 2011; Lewis and Durrant, 2011; Mölle and Born, 2011; Born and Wilhelm, 2012; Ribeiro, 2012; Inostroza and Born, 2013)). It states that repeated re-activations of new memory traces during SWS lead to redistribution and integration of these memories from temporary storages into long-term storage sites. During SWS, neocortical slow wave oscillations hereby drive the re-activation of still hippocampus-dependent memory traces during hippocampal sharp wave ripples (i.e. hippocampal events consisting of large negative "sharp waves" in the hippocampal Cornu Amonis 1 (CA1) stratum radiatum and transient fast "ripple oscillations" (150-250 Hz) in the CA1 pyramidal layer (Buzsáki, 1986)). Simultaneously, neocortical slow wave oscillations drive thalamo-cortical spindles, thus facilitating transformation (system consolidation) of the new memories into cortical areas by coordinated activity in the hippocampo-thalamo-cortical network. The following strengthening of this transfer (synaptic consolidation) is thought to occur during subsequent REMS (Dudai, 2012). Accordingly, during REMS several hours after a novel experience in rats, plasticity has been found up-regulated in the cortex, but not in the

hippocampus, possibly explaining hippocampal mnemonic disengagement over time (RIBEIRO ET AL., 2007).

In summary, by definition of the **ACTIVE SYSTEM CONSOLIDATION HYPOTHESIS**, memory consolidation constitutes a completely active process. Thus, rather than supporting only passively or incidentally, by providing a status of reduced interference (WIXTED, 2004; MEDNICK ET AL., 2011), sleep actively promotes memory consolidation. Active replay of memory traces during SWS and REMS is postulated to initiate memory consolidation and long-term storage. Several re-activation studies in animals and in humans substantiate this view, as outlined in the next paragraphs. Although replay occurs also during WAKE (for review see (CARR ET AL., 2011; RASCH AND BORN, 2013)), re-activations during sleep and WAKE possibly have differential effects on memory consolidating processes (DIEKELMANN ET AL., 2011).

Selective Re-activation during SWS

Replay of neural traces during sleep, i.e. re-activation of long temporal sequences of patterned multi-neural activity, coding for newly acquired information during wakefulness, have first been described in the hippocampus by multi-unit recording of place cells in rats (PAVLIDES AND WINSON, 1989). These hippocampal cells code for a particular position (place) in space, thus leading to a specific cell firing sequence when the animal is, e.g., running along a track to receive a food reward (WILSON AND MCNAUGHTON, 1993; BURGESS ET AL., 1998, 2011). This firing pattern re-occurs during SWS after the awake performance (PAVLIDES AND WINSON, 1989; SHEN ET AL., 1998), but not before (WILSON AND MCNAUGHTON, 1994), preserving the same temporal order of spiking of the cell assembly (SKAGGS AND MCNAUGHTON, 1996; KUDRIMOTI ET AL., 1999), albeit in a time-compressed manner (10-20 times faster) (NÁDASDY ET AL., 1999; LEE AND WILSON, 2002, 2004). Further, replay during sleep has been found after natural exploratory behavior (O'NEILL ET AL., 2006, 2008), for more than 24 hours (RIBEIRO ET AL., 2004), and in conjunction with sharp wave ripples ((KUDRIMOTI ET AL., 1999; O'NEILL ET AL., 2008; NAKASHIBA ET AL., 2009); for detailed review see (SUTHERLAND AND MCNAUGHTON, 2000; O'NEILL ET AL., 2010)). Re-activation of activity patterns, however, has been observed not only in the hippocampus, which is in consistence with the **ACTIVE SYSTEM CONSOLIDATION HYPOTHESIS**, which assumes a hippocampal disengagement form memory processing with time. In animals, replay has also been reported for the parietal (QIN ET AL., 1997) and the visual cortex (JI AND WILSON, 2007), the mPFC (EUSTON ET AL., 2007; PEYRACHE ET AL., 2009; JOHNSON ET AL., 2010) and the striatum (PENNARTZ ET AL., 2004; LANSINK ET AL., 2008, 2009), again in close association with sleep spindles and sharp wave ripples (PENNARTZ ET AL., 2004; PEYRACHE ET AL., 2009; JOHNSON ET AL., 2010). The hippocampus hereby seems to have a guiding role, as hippocampal replay precedes replay in cortical and striatal regions (LANSINK ET AL., 2008, 2009; PEYRACHE

ET AL., 2009), supporting the view of a hippocampal transfer of memories to long-term storage sites.

In humans, demonstrations of spontaneous replay during sleep are limited. However, similarly to the described replay studies in rodents, hippocampal areas, which are relevant for the acquisition of a virtual navigation task, have been shown to be re-activated during subsequent SWS, but not REMS (PEIGNEUX ET AL., 2004). This re-activation was associated with the improvement in task performance the next day. Moreover, increased EEG coherence during learning of word pairs was correspondingly observed during following SWS, in association with slow wave oscillations (MÖLLE ET AL., 2004). Also, learning of a texture discrimination task was followed by an increased BOLD signal in the trained region of the visual cortex, predicting the improvement in task performance at re-test (YOTSUMOTO ET AL., 2009). Learning of a face-scene association, on the other hand, resulted in re-activation of hippocampo-cortical areas, particularly during the occurrence of sleep spindles (BERGMANN ET AL., 2012) when connectivity between hippocampus and cortex is generally elevated (ANDRADE ET AL., 2011). In addition, trained motor sequences are replayed in form of overt behavior in patients with parasomnia (OUDIETTE ET AL., 2011). A recent study, using multivariate pattern classification analysis of simultaneous EEG and functional magnetic resonance imaging (fMRI) signals, provides direct evidence that specific pattern activity is spontaneously replayed during post-learning sleep also in humans. Here, subjects had to learn an item-spatial-location-association during which stimulus-specific activation patterns were identified. Consecutive re-activation of these activity patterns during periods of awake rest or sleep predicted the memory for individual items upon re-testing (DEUKER ET AL., 2013). Thus, congruent results from murine and human studies support the notion of spontaneous re-activation of learning-associated activity patterns during post-learning sleep.

The question, whether replay during SWS is indeed relevant for a successful consolidation of memories and whether lack of replay results in the impairment of memory, has not yet been tested by direct disruption of memory re-activations (RASCH AND BORN, 2013). More indirect evidence comes from studies in old rats, where no signs of replay during sleep have been detected, and this lack has been associated with the rats' reduced performance in a spatial memory task (GERRARD ET AL., 2001, 2008). Genetic blockage of the output from the CA3 region of the hippocampus, resulted in reduced sharp wave ripple events and pattern re-activation during sleep after a contextual fear conditioning task (NAKASHIBA ET AL., 2009). Interestingly, the presentation of an auditory cue that had been entrained to be associated with a specific spatial location (left or right), during NREMS resulted in a biased re-activation of hippocampal place cells that had been active in the corresponding side of the track during the task acquisition (BENDOR AND WILSON, 2012). Most importantly, in a recent study in mice it has been shown that not only spatial, but also fear memories can be influenced by triggered replay during NREMS. Whereas the presentation of a foot shock-associated odor during

NREMS resulted in an elevated fear response on the next day, injecting a protein synthesis inhibitor into the BLA before cueing during sleep reduced fear expression to the odor, indicating the blockage of memory strengthening processes activated by the cue during NREMS (Rolls et al., 2013).

Similar findings have been reported in humans and the connection of the two studies and their clinical projections have been discussed extensively (Welberg, 2013; Oudiette et al., 2014). Human subjects underwent a contextual fear conditioning, where face images (conditioned stimuli) had been paired with a mild electrical shock (unconditioned stimulus), while an odor was present in the background (conditioned context). Presentation of the odor during a subsequent nap (SWS) reduced fear responses, as well as hippocampal, amygdalar and ACC activity to the corresponding faces during later testing (Hauner et al., 2013). Further analysis revealed distinctly distributed pattern activity in the left amygdala during testing *post* sleep. Also, monitoring of fear responses (skin conductance) following the odor presentation during sleep showed a decay of fear (i.e. extinction) over sleeping time. Further replay studies in humans support the memory strengthening effect of cued re-activations during SWS. Re-exposure to an olfactory or auditory stimulus that had been paired with the learning of card-pair locations (Rasch et al., 2007), object locations (Rudoy et al., 2009), melodies played on a piano (Antony et al., 2012), finger tapping sequences (Schönauer et al., 2014) or a problem solving task (Ritter et al., 2012), during post-learning SWS, consistently improved performance upon re-testing. It was further demonstrated that the memory improving effect was stimulus-specific (Rihm et al., 2014; Schönauer et al., 2014) and associated with changes in slow wave delta (1.5 - 4.5 Hz) and sleep spindle (13 - 15 Hz) power (Rihm et al., 2014), as well as increased connectivity in parahippocampal-mPFC networks (van Dongen et al., 2012). Memories that had been rewarded with a low value and thus retained to a lesser extent than highly rewarded memories, were rescued from forgetting by cued replay during SWS (Oudiette et al., 2013). The dependency of this replay phenomenon on the hippocampus has been underlined by a study in patients with temporal lobe epilepsy and unilateral or bilateral hippocampal sclerosis. The authors report a strengthening effect of triggered re-activation of memories only in control subjects and patients with unilateral hippocampal damage (Fuentemilla et al., 2013). The degree of the mnemonic benefit was predicted by the volume of spared hippocampus, as well as the density of sleep spindles during SWS (Breton and Robertson, 2013; Fuentemilla et al., 2013). Interestingly, after learning a virtual navigation task, imagery of the task during dreams in a following afternoon nap, but not during WAKE, improved the performance at re-test the next day (Wamsley et al., 2010b).

Studies, investigating the potential re-activation of neuronal activity during REMS, are rare. The classic study by Pavlides and Winson in rats (Pavlides and Winson, 1989) reports that replay of place cell firing also occurs during REMS. In a more recent study, it has been found that, with the rat becoming familiar with parts of a running track, place cells show reversed firing phases relative to local theta oscillations during REMS (Poe et al., 2000). In contrast, no replay was observed after experience on a novel part of the track. The authors conclude that REMS might selectively contribute to the strengthening of recently acquired memories, while weakening more remote ones, when they become familiar. Others found no pattern re-activation during REMS (Kudrimoti et al., 1999), while modeling approaches strongly suggest the presence of REMS-associated replay (Booth and Poe, 2006; Hasselmo, 2008). Only one study, up to now, has examined the replay of hippocampal neuronal ensemble activity on the basis of recordings of local field potentials (LFP). The authors report a replay of firing patterns corresponding to a previously learned behavior-specific activity (track running task) during REMS at a timescale similar to that during WAKE, i.e. tens of seconds to minutes, which is much longer than observed re-activations during NREMS (Louie and Wilson, 2001). Similarly, re-activation of brain activity and changes in connectivity patterns during post-learning REMS, linked to the formation of a procedural memory, have been described in humans (Maquet et al., 2000; Laureys et al., 2001; Peigneux et al., 2003).

Support for the functional relevance of re-activation during REMS has been provided by cueing experiments during REMS. In humans, the replicated presentation of a learned Morse code specifically during phasic REMS, as opposed to tonic REMS or no presentation, increased performance the next day (Guerrien et al., 1989). Equivalently, re-delivery of a ticking sound, that had been present in the process of learning of complex rules, during subsequent phasic REMS improved memory performance tested 1 week later (Smith and Weeden, 1990). Similar findings have been reported in rodent studies. After learning of an association between a mild ear shock (conditioned stimulus) and a strong foot shock (unconditioned stimulus), the mild ear shock was re-delivered to the animals during subsequent periods of REMS. The procedure resulted in a stronger fear memory upon recall and an increased amount of REMS (Hars et al., 1985). By contrast, cueing during SWS (Hars and Hennevin, 1987) or cueing of remote memories (Hars and Hennevin, 1990) reduced the fear memory. Simultaneous single-cell recordings in the hippocampus confirmed the re-activation of activity patterns during REMS upon delivery of the cue (Maho et al., 1991). Elevated neuronal responses upon presentation of an auditory cue after cued fear conditioning has also been observed in the lateral amygdala (LA) and the medial geniculate body of the auditory thalamus during REMS (Hennevin et al., 1993, 1998; Maho and Hennevin, 2002), but not during NREMS (Hennevin and Maho, 2005). These results are consistent with the notion that REMS is specifically important for the

processing of emotional memories. Direct evidence for spontaneous replay of particularly emotional memory during REMS has, nevertheless, not been provided, yet.

Indications for REMS-related memory consolidation processes have, however, been added by work of Datta and coworkers, who found that activation of the phasic pontine-wave (P-wave, PGO-like phasic potential in the rat (DATTA ET AL., 1998)) generator in the dorsolateral pons facilitates learning and memory of hippocampus-dependent tasks (DATTA, 2000; MAVANJI AND DATTA, 2003; DATTA ET AL., 2005, 2008). Also, this activation can prevent learning impairment induced by REMS deprivation (DATTA ET AL., 2004), whereas its disruption impairs successful learning (MAVANJI ET AL., 2004). A recent study by the same group shows that particularly an increase in P-wave activity during post-training REMS is crucial for the successful consolidation of a fear extinction memory (DATTA AND O'MALLEY, 2013). Another recent molecular study revealed that immuno-reactivity of certain enzymes, which are strongly involved in signaling cascades controlling neuronal activity, plasticity and memory consolidation, is elevated in the CA1 hippocampal region of animals sacrificed in REMS, as compared to WAKE and NREMS (LUO ET AL., 2013). It has been suggested that REMS constitutes a well-suited state for the processing of especially emotional experiences, particularly because of its characteristic oscillatory properties (WALKER AND VAN DER HELM, 2009). That is, REMS is accompanied by rather slow oscillations between 4-12 Hz, the so-called theta oscillations, which in turn by their long-ranging properties facilitate large-scale communication between distant brain structures, especially between limbic and paralimbic structures including the hippocampus and the amygdala (for review see (PIGNATELLI ET AL., 2012; COLGIN, 2013)).

Theta Oscillations – a Temporal Code for Learning?

In order to perform complex cognitive functions, neuronal activity within different brain areas needs to be coordinated. Brain oscillations (i.e. oscillations of bioelectric discharges in the brain) are a potential mechanism by which the brain achieves this task of activity linking between neuronal ensembles. Oscillations within the frequency range of 4-12 Hz, with a nearly sinusoidal regularity, have been identified to particularly support this brain-wide communication (VARELA, 2001; COLGIN, 2013).

Theta rhythms, first described in rabbits (JUNG AND KORNMÜLLER, 1938), occur predominantly during awake locomotion, attention and cognition, and during REMS (VANDERWOLF, 1969; BUZSÁKI, 2002) and seem to be related to distinct behaviors in different species (WINSON, 1972). They are assumed to constitute a temporal code for superimposed cell firing, e.g. in gamma frequency ranges (≈30-150 Hz) (SCHEFFZÜK ET AL., 2011), and thereby to facilitate memory consolidation and

plasticity (Buzsáki and Draguhn, 2004; Kahana, 2006; Jutras and Buffalo, 2010). Already early experiments exploring theta oscillations, as recorded by epidural electrodes (resembling EEG recording conditions), have revealed that these very regular rhythms support memory consolidation. It was shown that the amount of theta in the EEG signal, after a fear conditioning in rats, was related to the strength of the formed fear memory (Landfield et al., 1972). Many subsequent reports support the notion of theta oscillations being important for learning and memory processes (Berry and Thompson, 1978; Winson, 1978; Macrides et al., 1982; Mitchell et al., 1982; Mizumori et al., 1990; M'Harzi and Jarrard, 1992; Robbe and Buzsáki, 2009) and synaptic plasticity (Larson et al., 1986; Staubli and Lynch, 1987; Greenstein et al., 1988; Pavlides et al., 1988; Orr et al., 2001; Hyman et al., 2003), also in primates (Liebe et al., 2012) and humans (Klimesch et al., 1996; Osipova et al., 2006; Rutishauser et al., 2010). Theta rhythm has additionally been shown to facilitate inter-regional communication and to promote the formation of all types of memory (Seidenbecher et al., 2003; Jones and Wilson, 2005; Kay, 2005; DeCoteau et al., 2007; Paz et al., 2008; Tort et al., 2008; Benchenane et al., 2010; Hyman et al., 2010; Kim et al., 2011; Liebe et al., 2012).

Theta oscillations have accordingly been considered a probable mechanism of the organization of synaptic pathways of conditioned fear (Paré et al., 2002; Pape et al., 2005). The functional role of theta synchrony in neuronal networks for fear memory consolidation has been verified repeatedly (Seidenbecher et al., 2003; Pape et al., 2005; Narayanan et al., 2007a, 2007b; Lesting et al., 2011). In detail, synchronous activity between the LA and the CA1 region of the dorsal hippocampus has been shown to increase upon recall of conditioned fear (Seidenbecher et al., 2003). The observed theta synchronization was associated with the behavioral fear response of the animals during recall of long-term, but not short-term (Pape et al., 2005) or remote fear memories (Narayanan et al., 2007a). Both, re-exposure to the conditioned context or to the conditioned cue (tone), were sufficient to elicit limbic synchrony, also after re-consolidation (Narayanan et al., 2007b). Furthermore, fear extinction processes have been shown to be dependent on mPFC activation via Gamma-Aminobutyric Acid (GABA)-ergic signaling, possibly by projections to the amygdala (Sangha et al., 2009), as theta synchrony between LA and CA1 decreased upon extinction training (Sangha et al., 2009; Lesting et al., 2011), whereas CA1-mPFC and LA-mPFC synchrony increased during extinction memory recall (Lesting et al., 2011). Theta activity and synchronization between amygdala and hippocampus have been found to be enhanced in relation to P-waves during REMS (Karashima et al., 2010). Also, theta synchrony during REMS in the hippocampus-mPFC-amygdala network was related to the strength of the conditioned fear memory (Popa et al., 2010). Similarly, findings in humans describe a stronger connectivity between hippocampus and PFC during fear memory recall after sleep (Sterpenich et al., 2007; Payne and Kensinger, 2011). Higher frontal cortical theta oscillations during REMS in humans have been shown to predict a successful dream recall upon awakening (Marzano

ET AL., 2011). Also, theta synchrony between the medial temporal lobe and neocortical structures was found to coincide with richly detailed autobiographical recollection (FUENTEMILLA ET AL., 2014). This latter finding is in accordance with the suggestion that the medial temporal lobe might drive the reciprocal exchange of information with neocortical areas through theta oscillations (SIROTA ET AL., 2008).

Another potential function assigned to theta oscillations is "tagging" of relevant memories for consolidation during sleep. A replay study in rats has reported that, after acquisition of a spatial-reward task, during subsequent SWS those prefrontal cell assemblies were preferentially re-activated that had been firing at the time of high theta coherence between the PFC and the hippocampus in the course of learning (BENCHENANE ET AL., 2010). Thus, synchronous hippocampo-prefrontal theta activity during encoding of a memory trace might constitute a "tag" for later consolidation during sleep. This "theta-tagging" might equally account for the preferential consolidation of emotional and reward-related memories, as emotion and reward circuits are activated and synchronized by theta (PARÉ ET AL., 2002; SEIDENBECHER ET AL., 2003; BATTAGLIA ET AL., 2011; BENCHENANE ET AL., 2011; FUJISAWA AND BUZSÁKI, 2011; LESTING ET AL., 2011). In support of this theory, theta oscillations have also been implicated in the identification of novel (potentially dangerous) *vs.* familiar (safe) environments (JEEWAJEE ET AL., 2008; LEVER ET AL., 2010; JACINTO ET AL., 2013; WELLS ET AL., 2013; LIKHTIK ET AL., 2014) and innate anxiety (GORDON ET AL., 2005; ADHIKARI ET AL., 2010, 2011; JACINTO ET AL., 2013). Emotional processing in general has been associated with theta activity in limbic, as well as cortical structures (MITCHELL ET AL., 2008). Interestingly, in PTSD patients high frontal theta activity is associated with the intensity of negative emotional experience induced by emotion-provoking pictures (COHEN ET AL., 2013). As theta activity is elevated in the amygdala in response to fearful faces (MARATOS ET AL., 2009) and PTSD patients show a hyper-activation of the amygdala in response to fearful stimuli (YOO ET AL., 2007; ADMON ET AL., 2009), these data support the hypothesis that frontal activity in the theta range is related to amygdalar hyper-reactivity in PTSD.

Based on early studies in rats and rabbits (KRAMIS ET AL., 1975), two kinds of hippocampal theta oscillations with distinct pharmacological and behavioral profiles have been described (ROBINSON ET AL., 1977; BLAND, 1986): **(I) THETA 1** oscillations between 7-12 Hz, which are non-cholinergically mediated, as they were shown to be insensitive to the muscarinic antagonist atropine, and which occur mostly during locomotion and exploratory behavior; and **(II) THETA 2** oscillations within the 4-7 Hz frequency range, which are cholinergically mediated (abolished by atropine), and related to immobility and highly arousing and vigilant conditions. This functional divergence of theta oscillatory activity seems not to be restricted to rodents. In a human magnetoencephalographic study, improved spatial cognition in a virtual Morris maze was associated with increased theta 1 activity in the left dorsal hippocampus, whereas increased anxiety ratings (due to the threat of a potential painful punishment) was associated with increased left dorsal hippocampal activity in the theta 2 range (CORNWELL ET AL., 2012). Furthermore, a

recent study performed in rats revealed that targeted disruption of the generation of specifically theta 2 oscillations resulted in less anxiety of the animals (Hsiao et al., 2013).

Theta activity during REMS appears to represent a mixture of the two theta types since atropine abolishes lower theta frequencies during REMS while leaving higher theta frequencies intact (Robinson et al., 1977; Shin et al., 2005a). Similarly, mice lacking the M_1-type muscarinic receptor signal transducer phospholipase β1 show no theta 1 activity while awake and only lower theta frequencies during REMS (Shin et al., 2005a). A genetic study in mice with a deficiency in short-chain acyl-coenzyme A dehydrogenase, involved in fatty acid metabolism, indicates that theta generation during WAKE and during REMS might be of different origin (Tafti et al., 2003). In humans, theta activity during REMS seems to be more sporadic and of lower frequency compared to theta in rodents (Bódizs et al., 2001; Cantero et al., 2003; Clemens et al., 2009).

The Role of the Amygdala in Memory Consolidation during Sleep

Memories of future relevance are particularly strengthened across sleep (Wilhelm et al., 2011) and emotionally significant memories are remembered best (Cahill and McGaugh, 1998; Wagner et al., 2001; McGaugh, 2004; Hu et al., 2006; Holland and Lewis, 2007; Walker, 2009; Lewis et al., 2011). When being exposed to an emotionally arousing situation, numerous hormonal and neurotransmitter systems are activated, a subset of which is also known to be involved in consolidating and enhancing processes for emotional memories (McGaugh, 2000).

A series of studies have identified the amygdala as the site of integration of these modulatory influences emerging from e.g. noradrenergic, adrenergic or glucocorticoid signals (McGaugh, 2000; McIntyre et al., 2003; Paré, 2003; de Quervain et al., 2009). Epinephrine, for example, does not freely pass the blood-brain-barrier but activates peripheral β-adrenergic receptors on vagal afferents projecting to the solitary tract nucleus in the brainstem, from which noradrenergic projections modulate the activity also in the amygdala (McGaugh et al., 1996). The memory enhancing effect of glucocorticoids and norepinephrine have been demonstrated to be mediated via the amygdala (Roozendaal and McGaugh, 1996; Quirarte et al., 1997, 1998; Ferry et al., 1999; LaLumiere et al., 2003). Glucocorticoid receptors are also located in the hippocampus, however memory enhancing effects of glucocorticoids in the hippocampus are modulated by the amygdala (Quirarte et al., 1997; Roozendaal and McGaugh, 1997; Roozendaal et al., 1999). Due to its connection to the hippocampus, the septal nuclei, the PFC and the thalamus (Amaral and Price, 1984; Kita and Kitai, 1990; McDonald, 1998; Pitkänen et al., 2000; Petrovich et al., 2001), the amygdala is presumably involved in assigning affective meaning and significance to situations, stimuli, environmental cues and memories

(Vandekerckhove and Cluydts, 2010; Chau and Galvez, 2012). Amygdalar function and activity has been implicated in stress-response, motivation, fear, anxiety and emotional learning, as well as modulating alertness during sleep and wakefulness in animals and in humans (LeDoux, 2000; Morrison et al., 2000; Phelps, 2006; Jacobs et al., 2012). Interestingly, among individuals with damage of the vmPFC or the amygdala, the incidence of PTSD is much lower than in subjects with lesions in other parts of the brain (Koenigs et al., 2008). Patients with amygdalar lesions furthermore display mnemonic deficits (Adolphs et al., 2005). Also, during encoding of an emotional situation in humans, the activation of the amygdala is particularly high and correlates with subsequent memory (Cahill et al., 1996; Nili et al., 2010). Whether, however, the amygdala represents an actual storage site of fear memory or rather only modulates the storage of memory in other brain areas (e.g. the hippocampus and the neocortex) remains debatable.

On the one hand, rather than only playing a role at the time of encoding, the lateral part of the amygdala (LA) is a key site of fear learning-related plasticity processes (Blair et al., 2001; Schafe et al., 2005; Ostroff et al., 2010, 2011; Hong et al., 2011). Specifically the basolateral part of the amygdala (BLA) has been suggested as a site of permanent storage of fear memories in the brain (Cahill et al., 1999; Fanselow and Gale, 2003; Gale et al., 2004; Schafe et al., 2005). Also, two different cell populations in the LA seem to be involved in the initiation of learning and long-term memory storage (Repa et al., 2001). The relevance of the amygdala as a storage site for long-term fear associations is underlined by reports of impaired fear memory retention by disruption of the protein synthesis in this structure after the acquisition of a cued fear conditioning (Nader et al., 2000; Schafe and LeDoux, 2000; Duvarci et al., 2008; Kwapis et al., 2011).

On the other hand, electrical stimulation (Goddard, 1964), as well as lesion and inactivation studies in rodents (Packard et al., 1994; Paré, 2003) support the hypothesis that the amygdala may exert a decisive influence on memory consolidating processes in other brain sites (McGaugh, 2004), thereby acting as an encoder of situations and reinforcing the consolidation of memories of high emotional value and importance (Paz and Paré, 2013). One possible mechanism, by which the amygdala could influence the storage of certain memories, is the regulation of gating mechanisms of the rhinal cortices which control the transfer of information between the neocortex and the hippocampus (Brown and Aggleton, 2001; de Curtis and Paré, 2004; Paz et al., 2006; Bauer et al., 2007). In the same way, the amygdala might modulate the processing of reward-related memories at the basis of cortico-striatal communication (Popescu et al., 2007, 2009). Also, amygdalar projections to the inhibitory thalamic reticular nucleus (Zikopoulos and Barbas, 2012), which controls thalamo-cortical interactions and possibly determines the focus of our brain's attention (Pinault, 2004), might allow for direct amygdalar modulation of attention and gating and filtering of information to be conveyed to the neocortex (Chau and Galvez, 2012). The amygdala might therefore be important not only for the acquisition and learning of fear-related memories but possibly plays a

major role in affecting the saliency of behaviorally relevant information and facilitating the consolidation of all forms of memories (Chau and Galvez, 2012). However, subdivisions of the amygdala (BLA, LA, central medial amygdala), with differential functional connectivity, probably fulfill distinct roles in fear and fear memory processing (Phelps et al., 2004; Jovanovic and Ressler, 2010; Paré and Duvarci, 2012; Wotjak and Pape, 2013).

The amygdala, furthermore, seems to play an important role in the consolidation of memories during sleep (Pape and Paré, 2010), as it is highly active during sleep in rodents (Pelletier et al., 2005) and humans (Morrison et al., 2000; Dang-Vu et al., 2010). Changes in neuronal firing patterns in the amygdala in cats and rats have been found to be related to the sleep-wake cycle (Reich et al., 1983; Mgaloblishvili and Mandzhavidze, 1986; Zhang et al., 1986; Frysinger et al., 1988). The amygdala has also been implicated in the regulation of sleep, and particularly REMS (Sanford et al., 1995; Calvo et al., 1996; Dong et al., 2012; Wellman et al., 2013). Amygdalar lesions in primates have been shown to strongly affect sleep-wake behavior, resulting in elevated amounts of total sleep and REMS percentage (Benca et al., 2000). Sleep deprivation not only has disruptive effects on the consolidation of fear memories, but also on hippocampal and amygdalar activity (Cai et al., 2009; Hagewoud et al., 2011). Indeed, upon induction of LTP in the amygdala, an up-regulation of zif-268 in the amygdala, among other brain areas, has been observed during REMS in rats (Ribeiro et al., 2002). Zif-268 is an immediate early gene which is considered to be involved in stabilizing the effects of LTP in neurons, and in this role, similarly to other immediate early genes like c-fos, has been implicated in neuronal plasticity, learning and memory (Tischmeyer and Grimm, 1999). Finally, a recent study performed in humans identified the BLA as being involved in the REMS-related consolidation of fear memories (Menz et al., 2013).

The Role of the Hippocampus in Memory Consolidation during Sleep

The hippocampus (Andersen et al., 2006) is a brain structure with profound involvement in learning and memory (Eichenbaum, 2004). This widely accepted view has its origin in studies of humans with hippocampal damage, like H.M., showing loss of recent memories (Scoville and Milner, 1957). Since then, numerous reports have demonstrated the mnemonic function of the hippocampus. For example, lesions of the entire hippocampus in rodents impair spatial, (Morris et al., 1982, 1990; Deacon et al., 2002a) but also non-spatial memory tasks (Meck et al., 1984; Fortin et al., 2002; Kesner et al., 2002; Mariano et al., 2009). Furthermore, the hippocampus, particularly its dorsal part, is involved in spatial navigation and the creation of "cognitive maps" (O'Keefe and Nadel, 1978; Wilson and McNaughton, 1993), with place cells coding for a particular location in an environment by

showing theta-phase-precision-firing (Burgess et al., 2011). Most importantly, however, the hippocampus seems to play an important role in certain aspects of emotional processing, as hippocampal lesioning also results in reduced anxiety in rodents (Gray and McNaughton, 1983, 2000; Deacon et al., 2002b). Hippocampal theta power has been shown to predict learning success in an eyeblink conditioning task in rabbits: the power of theta oscillations predicted how fast and strong the association between an auditory stimulus and an airpuff stimulus at the eye was acquired (Nokia et al., 2009, 2010; Nokia and Wikgren, 2010). Theta responses to the conditioned stimulus have been suggested to represent the retrieval of conditioned memory and to initiate a situational, adequate action to that memory trace (Nokia and Wikgren, 2013).

Based on patterns of gene expression, it was found that the hippocampus can be subdivided into three parts along its longitudinal axis (Thompson et al., 2008; Dong et al., 2009). It has become clear that different sub-regions of the hippocampus (Amaral, 1987; Moser and Moser, 1998; Sasaki et al., 2004) are implicated in different behaviors and, thus, possibly also consolidation of different memories (reviewed by (Barkus et al., 2010; Fanselow and Dong, 2010)). Lesion studies revealed that the dorsal hippocampus (dHPC) seems to be implicated mainly in spatial learning and spatial navigation (Moser et al., 1993, 1995; Hock and Bunsey, 1998; Bannerman et al., 1999, 2002; Pothuizen et al., 2004), whereas the ventral hippocampus (vHPC) rather might play a role in emotional learning and behavior[1] (Henke, 1990; Maren, 1999; Richmond et al., 1999; Kjelstrup et al., 2002; Bannerman et al., 2003, 2004; McHugh et al., 2004; Chudasama et al., 2008; Ballesteros et al., 2014). Human studies confirm the dominance of posterior hippocampal input on functions beyond spatial cognition (Maguire et al., 1998, 2000; Greicius et al., 2003; Kumaran et al., 2009; Poppenk and Moscovitch, 2011).

The anatomical connectivity of the hippocampus corroborates the functional divergence between its ventral and dorsal compartments (Swanson and Cowan, 1977; Moser and Moser, 1998; Fanselow and Dong, 2010). The vHPC shows strong connections with the PFC, the amygdala, the bed nucleus of the stria terminalis (a structure implicated in diverse anxiety features (Davis et al., 2009; Walker et al., 2009; Kim et al., 2013)), the NAC (an area important for reward and motivational aspects (Kelley et al., 2005)) and other subcortical structures related to the hypothalamic-pituitary-adrenal (HPA) axis, accountable for stress responses of the body (de Kloet et al., 2005; Ulrich-Lai and Herman, 2009; Lucassen et al., 2014). The amygdala, as the key region in mediating fear behavior and fear memory processing, most likely receives direct hippocampal input from the vHPC only, to its basolateral part (BLA) (Maren and Fanselow, 1995; Pitkänen et al., 2000; Petrovich

[1] The dorsal (or septal) part of the hippocampus in rodents is an equivalent to the nomenclature of the posterior hippocampus in humans. Accordingly, the murine ventral (or temporal) hippocampus corresponds to the human anterior hippocampus.

ET AL., 2001). The dHPC, on the other hand, forms a cortical network with the retrosplenial and the anterior cingulate cortical areas (FANSELOW AND DONG, 2010), which belong to the default-mode network critically involved in cognitive processes like learning and memory (BUCKNER ET AL., 2008). More recent lesion studies and experiments using LFP/multi-unit recordings or optogenetic methods have also verified differential functional roles of affect (vHPC) and cognition (dHPC), and stress the role of the vHPC in modulating fear and anxiety in the interplay with the BLA and the mPFC (ADHIKARI ET AL., 2010, 2011; ROYER ET AL., 2010; SOTRES-BAYON ET AL., 2012; FELIX-ORTIZ ET AL., 2013; O'NEILL ET AL., 2013). However, some studies also report the involvement of both, the vHPC and dHPC, in spatial memory performance (FERBINTEANU AND MCDONALD, 2001; RUDY AND MATUS-AMAT, 2005; SCHMIDT ET AL., 2013A; WANG ET AL., 2013); the discordance might possibly be due to discrepant anatomical definitions (FANSELOW AND DONG, 2010). The intermediate part of the hippocampus presumably exerts a distinct role in spatial information processing rather than being only a transitional zone between the dorsal and the ventral poles of the hippocampus (BAST, 2007; BAST ET AL., 2009; RUEDIGER ET AL., 2012; KENNEY AND MANAHAN-VAUGHAN, 2013), also due to its heterogeneous connectivity, as compared to the vHPC and dHPC (FANSELOW AND DONG, 2010).

Also theta rhythms seem to be generated by multiple oscillators in the hippocampus (MONTGOMERY ET AL., 2009). Theta phase shifts have been observed across the septotemporal axis; thus, theta rhythm presents as traveling waves propagating from the septal to the temporal pole of the hippocampus (LUBENOV AND SIAPAS, 2009; PATEL ET AL., 2012). A study in patients with varying degrees of left medial temporal pathology has shown that reciprocal modulatory influences between the amygdala and the anterior hippocampus (vHPC) seem to be necessary for effective encoding of emotional memories (RICHARDSON ET AL., 2004). The authors report that while the severity of vHPC pathology predicted memory performance for both, neutral and emotional items, in a verbal encoding task, the severity of amygdala pathology was related solely to the memory for emotional items. Moreover, ventral hippocampal activity coincident with successfully remembered emotional items was associated with the degree of amygdalar pathology, while activity in the amygdala was related to the degree of ventral hippocampal pathology. These results further support the notion that the coupling and exchange between hippocampus and amygdala underlies the consolidation of emotional memories.

The functional differentiation between the dorsal and ventral parts of the hippocampus is further underlined by findings obtained in a functional imaging study in PTSD patients: it revealed "disorder-specific deficits" in the posterior hippocampus as compared to patients with generalized anxiety disorder and healthy controls (CHEN AND ETKIN, 2013). In this context, reduced hippocampal volume in PTSD seems to predominantly affect the posterior hippocampus (BONNE ET AL., 2008). A recent animal study has demonstrated that the infusion of glucocorticoids into the dHPC results in impaired memory retrieval, generalized

fear and hyper-reactivity of the amygdala, i.e. a phenotype resembling that seen in PTSD patients (KAOUANE ET AL., 2012).

In both, animals and humans, the hippocampus generates local theta activity during wakefulness and REMS (BUZSÁKI ET AL., 2003; CANTERO ET AL., 2003; MORONI ET AL., 2007; MONTGOMERY ET AL., 2008, 2009; LUBENOV AND SIAPAS, 2009; FERRARA ET AL., 2012). Hippocampal theta rhythm during REMS and its synchrony, also with the amygdala (POPA ET AL., 2010), are subject to reorganization during REMS, and are strongly linked to neuronal plasticity in the CA1 region of the hippocampus (GROSMARK ET AL., 2012). Also, it has been shown that the dHPC, as well as the amygdala, receive direct anatomical projections from the P-wave generating cells in the pons, which, upon excitation, increase glutamate release in the hippocampus and enhance the frequency of hippocampal theta rhythm and amygdalar-hippocampal synchrony (DATTA ET AL., 1998; KARASHIMA ET AL., 2002, 2004, 2010; DATTA, 2006). Acquisition of an avoidance task further increased P-wave activity and expression of learning and memory-related proteins and immediate early genes in the dHPC and amygdala, whereas lesioning of the P-wave generator suppressed this expression (DATTA ET AL., 2008).

Taken together, numerous human and animals studies draw the conclusion that the consolidation of memories occurs during sleep, with NREMS and REMS serving distinct memory strengthening functions. The amygdala, as well as the hippocampus (specifically its ventral part), have particularly been implicated in memory consolidating processes of experiences with high emotional load. Oscillatory communication between these two brain regions seems to occur preferentially within the theta frequency range, also during sleep (REMS). Low (theta 2) and high (theta 1) theta frequencies have been suggested to account for distinct behavioral aspects, i.e. fear/anxiety and cognition, respectively.

THE HARM OF EMOTIONS. WHAT CAN WE LEARN FROM ANIMAL STUDIES?

> *"The usefulness of all the passions consists in their strengthening and prolonging in the soul thoughts which are good for it to conserve (…) and all the harm they can do consists in their strengthening and conserving these thoughts more than is necessary"*
>
> *Descartes, The Passions of the Soul, 1647*

Revision of the above discussed reports about PTSD patients, and the attempt to embed knowledge on emotional regulation, memory consolidation and emotion-related processes during sleep into a plausible construct addressing the pathological mechanisms of PTSD, raises a plethora of open questions, unresolved issues and theories.

What is PTSD? A mis-consolidation of the trauma (during sleep) resulting in generalized fear? A hyper-consolidation of the traumatic event, so that an extinction of the robust memory is prohibited? A disturbed down-regulation of the emotional affect tagged to the traumatic memory, potentially related to sleep disturbances seen in PTSD patients? Or the excessive retrieval (hyper-replay) of the traumatic memory, during night and day, presented as flashbacks and nightmares?

The present work addresses several of these questions, albeit with modest expectations of achieving unequivocal answers. By the use of an established animal model of PTSD, we aim to approach certain aspects of the mentioned theories and discuss potential mechanisms underlying the pathology of PTSD.

Animal Models of PTSD

PTSD is a highly complex disorder that develops in a proportion of people after suffering the experience of a traumatic event. Given the variety of not only traumatic situations that can trigger PTSD, but also the diversity of symptoms that can occur, without any doubt it is impossible to adequately model the entire complex etiology and symptomatology of the human disease in a single animal model (GOSWAMI ET AL., 2013). Still, modelling of selected phenotypes that reflect the core features of the disorder provides the possibility to examine the neurobiological correlates, mechanisms and possible treatment of the illness (SIEGMUND AND WOTJAK, 2006). Moreover, animal models, in contrast to experiments performed in patients, provide the possibility to design prospective studies, thus

separating pre-existing from acquired factors, allow for the controllability of timing, intensity and duration of the trauma, and permit the performance of invasive experiments in order to investigate underlying processes which are often hidden from non-invasive techniques (Goswami et al., 2013).

Animal models of PTSD (for review see (Gafford and Ressler, 2011; Johnson et al., 2011; Cohen et al., 2012a; Pitman et al., 2012; Daskalakis et al., 2013; Goswami et al., 2013)) can be classified according to the type of the applied stressor, as well as by its duration (acute *vs.* chronic), controllability (controllable *vs.* uncontrollable), and frequency of exposure (single *vs.* repeated) (Goswami et al., 2013). Physical stressors, described in the literature, comprise under water holding or forced swimming (Richter-Levin, 1998; Wang et al., 2000; Moore et al., 2012), inescapable (unsignaled) foot shocks (Servatius et al., 1995; Pynoos et al., 1996; Armario et al., 2004, 2008; Manion et al., 2007; Siegmund and Wotjak, 2007a; Rau and Fanselow, 2009), immobilization and restraint stress (Vyas et al., 2002; Armario et al., 2004, 2008; Belda et al., 2008, 2012), or combinations of multiple stressors. The single prolonged stress paradigm, for example, applies sequentially restraint stress, forced swimming, and ether exposure (Liberzon et al., 1997; Yamamoto et al., 2009; Takei et al., 2011; Knox et al., 2012). Psychological stressors, on the other hand, include housing instability, social defeat, and social isolation paired with other stressors (Huhman et al., 1992; Huhman, 2006; Zoladz et al., 2008, 2012; Pulliam et al., 2010; Narayanan et al., 2011; Saavedra-Rodríguez and Feig, 2013), although these models are also partly used as models of depression (Krishnan et al., 2008). Yet another subtype of stressors are psychogenic stressors that usually involve no pain, but the exposure to a species-relevant predator (predator stress) (Adamec and Shallow, 1993; Adamec et al., 1998, 2006; Diamond et al., 1999; Hebb et al., 2003; Nanda et al., 2008; Park et al., 2008; Zoladz et al., 2008, 2012) or its odor (predator threat) (Blanchard and Blanchard, 1988; Blanchard et al., 2001, 2003; Cohen et al., 2006a, 2006b, 2012b; Roseboom et al., 2007). Further animal models of PTSD apply stressors during early life (Imanaka et al., 2006; Cohen et al., 2007; Diehl et al., 2012) or make use of genetic traits, e.g. for high anxiety or deficits in extinction learning (Landgraf and Wigger, 2002; Neumann et al., 2011; Holmes and Singewald, 2013).

A Contextual Fear Conditioning based Mouse Model for PTSD

Here, we inspected our scientific questions with the help of a mouse model of PTSD developed in our laboratory, which applies a contextual fear conditioning paradigm in mice of the C57BL/6N strain (Siegmund and Wotjak, 2006, 2007a). Compared to other trauma-inflicting stressors described in the literature, the impact has to be rated as moderate, although the applied foot shock intensity of 1.5mA is 5-fold higher than the defined pain threshold in C57BL/6N mice and can certainly be rated as a severely aversive experience for the animals (Siegmund et al.,

2005). Within this paradigm, a single electric foot shock of 1.5 mA can trigger the development of PTSD-like symptoms in mice. These PTSD-like symptoms include contextual as well as generalized fear, hyperarousal, avoidance behavior, and reduced social interaction.

The validity of our animal model (BELZUNG AND LEMOINE, 2011) with regard to face, etiological, construct and predictive aspects, has been described and discussed in previous studies (SIEGMUND ET AL., 2009B, 2005, 2009A; SIEGMUND AND WOTJAK, 2006, 2007A, 2007B; GOLUB ET AL., 2009, 2011; PAMPLONA ET AL., 2011; HERRMANN ET AL., 2012; SAUERHÖFER ET AL., 2012). **(I) FACE VALIDITY** (Is the model accompanied by the development of a phenotype that resembles the symptoms of the disease?) is verified, as mice show symptom-like hyperarousal and trauma-associated memory persisting for at least one month. The specificity of this memory, however, vanishes with time; that is, animals show a more generalized fear and generalized avoidance behavior one month, but not 2 days, after the shock (SIEGMUND AND WOTJAK, 2007A, 2007B). **(II)** The application of the foot shock as a defined aversive stimulus results in the development of a PTSD-resembling symptomatology. Thus **ETIOLOGICAL VALIDITY** (evaluation of the inducing condition) is warranted. **(III)** Although at the moment no specific therapy for PTSD exists, selective serotonin re-uptake inhibitors (SSRIs) and exposure therapy constitute the present first choice treatment of the illness (SPOORMAKER AND MONTGOMERY, 2008; MCNALLY, 2012). Animals treated for 14 days with the SSRI fluoxetine one month after the shock, display a significant improvement of the PTSD-like behavioral phenotype (PAMPLONA ET AL., 2011; HERRMANN ET AL., 2012). Also, extinction training early (one day) as well as late (28 days) after the shock reduces associated fear memories (GOLUB ET AL., 2009). Therefore our animal model fulfills the criterion of **PREDICTIVE VALIDITY** (Can the model replicate treatment outcomes seen in the human disease?). **(IV)** To a large extent, the biological correlates of PTSD are unknown. In humans, only a specific percentage of subjects confronted with a trauma develops PTSD. However, the causation of increased sensitivity or resilience remains obscure. Even in our model, using inbred mice, a biological inter-individual variety in the strength of the developed associative and non-associative fear components exists. Environmental factors (e.g. maternal care) seem to play a substantial role for the individual predisposition to develop a PTSD-like behavioral phenotype (SIEGMUND ET AL., 2009A) together with genetic components (DAHLHOFF ET AL., 2010). In addition, we determined low N-acetylaspartate (a marker of neuronal integrity) levels in the hippocampus before the foot shock to be associated with stronger and more sustained PTSD-like symptoms after the trauma (SIEGMUND ET AL., 2009B). The shock exposure was also associated with a decrease in hippocampal volume (GOLUB ET AL., 2011) which coincided with reduced expression of synaptic and axonal markers (GOLUB ET AL., 2011; HERRMANN ET AL., 2012). Similar neuroanatomical changes have been described in PTSD patients (see **FUNCTIONAL NEUROANATOMY IN PTSD, P.14 FF.**). Thus, **CONSTRUCT VALIDITY** (Does the model imply the same biological mechanisms

like the illness?), as the fourth criterion to describe an appropriate animal model, is fulfilled as well.

Sleep Alterations in Animal Models

So far, sleep-related phenotypes in animal models of PTSD have been studied only barely. Sleep behavior has been assessed mainly in rodent models using immobilization stress or electric shocks / fear conditioning as a trauma. Most of the studies focus on the acute effects on sleep after the exposure to the traumatizing stressor. Findings vary considerably, strongly depending on the stressor, the protocol (e.g. contextual or cued conditioning, strength of the shock, duration, frequency and circadian time point of the stress), the sleep recording approach (length, time point of the recordings), and the species, strain and gender of the animals ((Polta et al., 2013); for review see (Pawlyk et al., 2008)).

Immobilization studies in rodents revealed a strong dependency of subsequent sleep alterations on the stress intensity. Short periods of immobilization (1-2 hours) resulted in increased amount of sleep, and particularly REMS, after stress (Rampin et al., 1991; Gonzalez et al., 1995; Bonnet et al., 1997; Bouyer et al., 1998; Marinesco et al., 1999; Vazquez-Palacios and Velazquez-Moctezuma, 2000; Meerlo et al., 2001; Koehl et al., 2002; Tiba et al., 2003; Dewasmes et al., 2004), while longer periods (Marinesco et al., 1999), lasting even over several days (Papale et al., 2005; Hegde et al., 2008, 2011), produced rather inconsistent results. Interestingly, a more detailed analysis of REMS characteristics, differentiating between sequential REMS periods (separated by less than 3 min) and single REMS periods (separated by more than 3 min), showed that the observed increase in REMS after a 90 min immobilization stress was particularly due to an elevated number of sequential REMS episodes, indicating more fragmented REMS after stress (Dewasmes et al., 2004). Analysis of the sleep-wake behavior 11 or 21 days after a prolonged stress exposure revealed increased hippocampal theta activity during REMS specifically in animals that showed simultaneously enhanced amounts of REMS. Additionally, diminished amygdalar-hippocampal coupling in the theta frequency range was found in these animals during REMS (Hegde et al., 2008, 2011).

In the case of an electric shock as the applied stressor, the following broad effects on sleep architecture have been observed: a fear conditioning in the beginning of the light (inactive) diurnal phase resulted in an acute (4-22 hours after treatment) decrease of REMS amounts in rats (Palma et al., 2000; Sanford et al., 2001; Jha et al., 2005; Pawlyk et al., 2005; Liu et al., 2009, 2011; Yang et al., 2009; Deschaux et al., 2010) and mice (Liu et al., 2003; Sanford et al., 2003a, 2003b, 2003c; Wellman et al., 2008, 2013; Yang et al., 2013). Only in one study the conditioning had been applied at the end of the dark (active) diurnal phase, thereby producing increased REMS amounts and number of REMS episodes in rats (Vazquez-Palacios

AND VELAZQUEZ-MOCTEZUMA, 2000). However, when differentiating between sequential and single REMS episodes, increased amounts and number of sequential REMS episodes have been observed directly after the conditioning, as well as two weeks later upon re-exposure to the conditioned stimulus, especially in stress-sensitive Wistar-Kyoto rats (DASILVA ET AL., 2011A, 2011B). It was reported that controllability, as well as predictability of stress, essentially influence sleep-wake alterations after fear conditioning in rodents. A situation where mice were able to control the stress by escaping from the foot shock revealed contrasting results (increase in REMS), as compared to the uncontrollable situation (decrease in NREMS and REMS) (SANFORD ET AL., 2010). When the shock was signaled by a tone, thus allowing prediction and anticipation by the animals, both stress situations (controllable or not) lead to a decrease in NREMS and REMS, suggesting that cue and contextual information have competing influences on post-stress sleep (YANG ET AL., 2011; MACHIDA ET AL., 2013). Also long-term effects on sleep-wake behavior of up to 21 days after fear conditioning have been observed (PHILBERT ET AL., 2011).

Most of the described studies investigating the effect of fear conditioning on the sleep-wake behavior of rodents documented a decrease in REMS during the hours following the stressor. Only a few studies recorded sleep-wake patterns over 24 hours. The experiments also vary with regard to the circadian phase during which the fear conditioning was performed (inactive phase *vs.* active phase), the conditioning protocol (many studies use several shocks over several days; cued *vs.* contextual fear conditioning), and the time point of recording (many studies record the sleep-wake behavior immediately after the re-exposure to the conditioned stimulus). Although it is important to measure the direct effects of stress on sleep, and also interesting to see that there are strong parallels with respect to REMS being affected by different fear conditioning protocols, we propose that **(I)** using a single foot shock event (resembling a trauma) **(II)** during the natural active phase of the animals (without waking the animals and interfering with their sleep) and **(III)** measuring its long-term effects on sleep-wake architecture as well as limbic activity patterns **(IV)** within a validated model of PTSD (including additional behavioral measures for a PTSD-like phenotype), is a crucial experiment to be performed. In that way, the connections between sleep alterations and fear-related symptoms in PTSD could further be illuminated, and results could stimulate further research in this direction.

In this work we applied a reliable animal model of PTSD to explore the following issues and hypotheses:

(I) As disturbed REMS has been proposed as a hallmark of PTSD, we hypothesize that REMS alterations can be reproduced in an animal model of PTSD as a consequence of a trauma-like experience. We further expect that basal (*pre* shock) and/or early sleep disturbances after the traumatic event (*post* shock) might be related to a PTSD-like phenotype in this model.

(II) Nightmares, emotional dreaming and strengthening of memories potentially occur during REMS, and replay of emotional memory has been shown to facilitate memory consolidation. We hypothesize that, in an animal model of PTSD used here, similar activity changes in the amygdala and the hippocampus arise during

- a situation where retrieval of the traumatic memory is deliberately evoked, and
- spontaneously during REMS *post* trauma.

(III) Emotional sensitivity, nightmares and sleep disturbances have been identified as potential risk factors for PTSD in humans. Thus, we suggest that basal sleep-wake architecture might serve as a likely biomarker of PTSD. Further, we hypothesize that certain hippocampal and/or amygdalar activity patterns might predetermine the "pathological" outcome already prior to the trauma and thus may constitute reliable cues for the distinction of vulnerability *vs.* resilience traits, also beyond the animal model.

Chapter 2 | The Relevance of Rapid Eye Movement Sleep in a Mouse Model of Post-Traumatic Stress Disorder.

CONTRIBUTIONS

The author of the present thesis contributed to the first experiment by conceiving of the experimental questions and hypotheses, designing the experimental schedule, conducting the experiment (including surgeries, recording of electrophysiological data, behavioral tests) and analyzing its data (sleep scoring, behavioral readout, statistical analysis). She also wrote the manuscript and designed figures and tables of the resulting publication in "Frontiers in Behavioral Neuroscience" (POLTA ET AL., 2013).

Coauthors of the latter publication contributed in the following way: TF and CTW advised the conceiving of the experimental questions, hypotheses and procedures and critically reviewed the manuscript; JV provided expertise in sleep scoring and critically reviewed the manuscript; MK provided equipment and expertise in sleep recording and sleep scoring and critically reviewed the manuscript; AY provided expertise and supported the statistical analysis of the data and critically reviewed the manuscript.

MATERIAL AND METHODS

ANIMALS

Laboratory animal care and experimental procedures were in compliance with the European Union recommendations for the care and use of laboratory animals. All experimental procedures were approved by the Committee on Animal Health and Care of the Government of Upper Bavaria (AZ55.2-1-54-2532-43-09).

Adult male C57BL/6N mice (Martinsried, Germany; n=16; aged 10-12 weeks at arrival) were housed individually with *ad libitum* access to food and water under inverse 12–12 h light-dark cycle (lights ON at 9 p.m.; adaptation to the inverse rhythm for at least 2 weeks). Recordings of vigilance states were performed in the home cages (custom made; 26 cm × 26 cm × 35 cm; clear Lucide® walls; wood shaves as bedding material).

Experimental groups were assigned randomly with 8 mice in the non-shocked and shocked group respectively.

SURGERY AND STEREOTACTIC IMPLANTATION OF ELECTRODES

Sleep recordings performed in this experiment comprised signals gathered by electroencephalogram (EEG) and electromyogram (EMG) electrodes (**FIGURE 1B**).

Implantation of four epidural EEG electrodes (EEG1, EEG2, reference and ground) and bilateral EMG electrodes (EMG1, EMG2) into the nuchal musculature of the mice was performed under isoflurane anesthesia (Isofluran, DeltaSelect GmbH, Germany; anesthesia device: Agn-Thoas AB, Sweden) in combination with meloxicam as a perioperative analgesic (0.5 mg/kg body weight *s.c.*; Metacam, Braun Melsungen, Germany). Electrodes were made of gold wires with ball-shaped endings and were soldered to standard PCB socket connectors. Fixation to the skull was achieved by bonding of electrodes, two fixation screws and the PCB socket with superglue and dental cement (Paladur, Heraeus-Kulzer, Germany). Post-operatively, meloxicam was added to the drinking water for 5 days (0.5 mg/kg body weight).

FIGURE 1A depicts the experimental schedule of experiment 1. After surgery, animals were given a recovery period of 2 weeks before being moved to the sound-attenuated recording chambers [constant temperature (23 +/- 1 °C), inverse light-dark cycle (12–12 h, lights ON at 9 p.m.)]. Here, the animals were connected to the recording cable and the swivel system, which allows for free movement. After a habituation period to the cable/swivel of 12 days, baseline sleep-wake recordings were performed (**FIGURE 1A**: box "3 to 1 day before"). On the shock day, animals were exposed to two unsignaled electric foot shocks followed by four consecutive days of recordings (**FIGURE 1A**: boxes "shock", "1 day later", "2 days later", "3 days later"). After this recording period, mice were moved to the animal facility and remained under the same housing conditions before behavioral testing 1 month after the shock. Another month later, animals were habituated to the recording cable/swivel for 4 days before recordings were performed for additional 3 days (**FIGURE 1A**: box "2 months later").

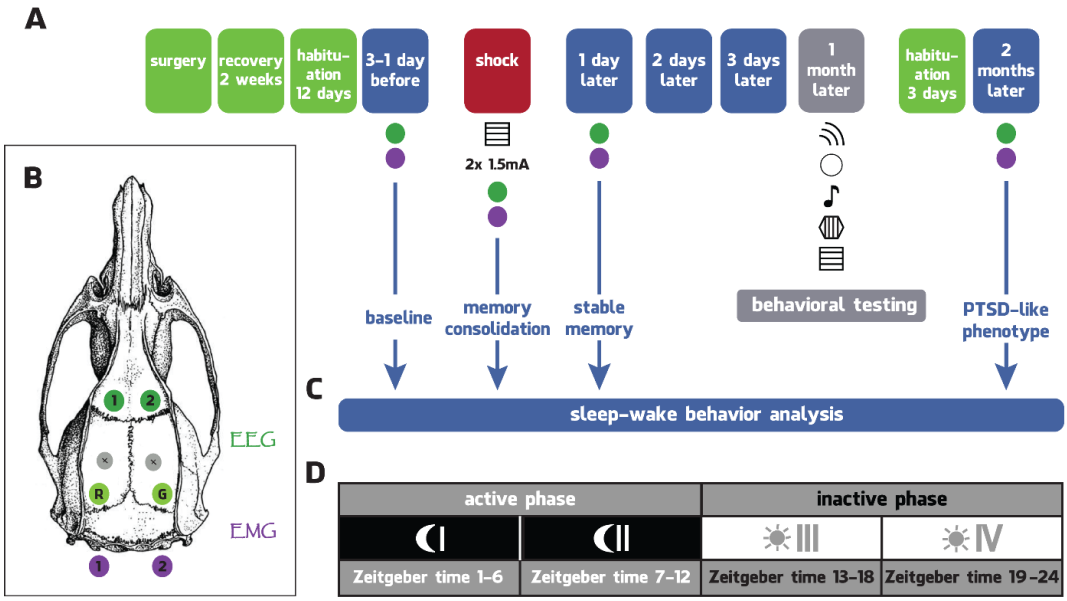

Figure 1 | Experimental Design 1 |
Testing for a PTSD-like phenotype of arousal, sleep-wake and fear-related behavior in mice (n = 16). (A) Experimental Schedule: the time course is depicted by experimental day boxes; green: surgery, recovery and habituation; blue: experimental days in the recording chamber; red: contextual fear conditioning in the shock context (hatched square symbol; two shocks of 1.5 mA); gray: behavioral testing of (i) the acoustic startle response (volume symbol) and freezing behavior upon exposure to (ii) a novel environment (circle symbol), (iii) a neutral tone (note symbol), (iv) a context with reminder features of the shock context (hatched hexagon symbol) and (v) the shock context (hatched square symbol). EEG/EMG recordings are indicated by a green/purple filled circle below the experimental day box. (B) Positioning of four epidural EEG electrodes (EEG '1', EEG '2', reference 'R' and ground 'G'), two bilateral EMG electrodes in the nuchal musculature (EMG '1', EMG '2') and two fixation screws ('x'). Adapted from: (Paxinos and Watson, 1998)[1]. (C) Indication of the recording days which were included into the sleep-wake behavior analysis. (D) Illustration of the sub-division of the total 24 hour recording time into four separate 6 hour time intervals: phase I (first half) and phase II (second half) of the dark i.e. active period; phase III (first half), and phase IV (second half) of the light i.e. inactive period. Adapted from (Polta et al., 2013).

[1] Reprinted from "The Rat Brain in Stereotaxic Coordinates", Edition 4, George Paxinos, Charles Watson, © 1998, with permission from Elsevier.

Shock Procedure and Behavioral Testing for PTSD-like Symptoms

Shock procedure and behavioral tests were applied during the active (dark) diurnal phase (between 9.30 am and 4.00 pm). Light intensity was kept to a minimum during testing to reduce the stress for the animals.

Shock and no-shock procedures took place in the sound-attenuated recording chambers. The two experimental groups were spatially separated for the procedure and the entire duration of the recordings to exclude possible influence of vocalization and olfactory signals. For the shock application, mice were placed in the shock chamber [MED Associates Inc., St. Albans, VT, USA; cubic shape, Plexiglas walls with checkered pattern on the back and side walls, floor metal grid, 0.6 lux, cleaned with water containing isoamylacetate (1:2000; banana aroma) between animals]. After exploration of the environment for 5 min, two scrambled, unsignaled electric foot shocks (1.5 mA, 2 s, 1 min interval between shocks; MED Associates Inc., St. Albans, VT, USA) were delivered via the metal grid. Animals remained in the chamber for another 1 min before being transferred back to their home cages. The non-shocked group was placed into the shock chamber for the equivalent amount of time (7 min) without the delivery of any shocks.

Testing for PTSD-like symptomatology was conducted one month after the shock (**Figure 1A**). The setup was placed within the animal facility [constant temperature (23 +/- 1 °C), inverse light-dark cycle (12–12 h, lights ON at 9 p.m.)] in a separate sound-tight procedure room. The setup has been described in detail in previous studies (Kamprath and Wotjak, 2004; Siegmund and Wotjak, 2007b; Golub et al., 2009, 2011).

First, the manifestation of a **hyperarousal**-like phenotype was investigated on the basis of the acoustic startle response (ASR, day 1 of testing), i.e. the startle response to a sudden acoustic stimulus with varying intensity. Second, **generalized anxiety**-like behavior was explored by introducing the animals to a novel neutral environment (day 2 of testing) in which a neutral tone was presented, and to a novel environment which contained reminder features of the shock context (day 3 of testing). Third, **contextual fear** was examined by re-exposing the animals to the original shock context (day 3 of testing). The order of testing was not randomized deliberately, but followed the sequence - neutral context, reminder context, shock context - as used in previous studies by our group (e.g., (Golub et al., 2011)).

Hyperarousal

Mice were put into one of six identical plexiglas cylinders (inner diameter 4 cm, length 8 cm) mounted onto a plastic platform in a sound-attenuated chamber (SR-LAB, San Diego Instruments, San Diego, CA, USA). Movement of the mouse was measured by the detection of the cylinder movement by a piezoelectric sensor mounted under the platform. The voltage output of the sensor was amplified (MAUCH, 2010) and digitized at a sampling rate of 1 kHz by a computer interface (I/O-board provided by San Diego Instruments, San Diego, CA, USA). The strength of the startle response was defined as the peak voltage output within the first 50 ms after stimulus onset (identified by means of SR-LAB software, San Diego Instruments, San Diego, CA, USA). Each chamber was calibrated for its response sensitivity at the beginning of the ASR testing session to assure identical output levels. Startle stimuli and background white noise were delivered through a high-frequency speaker placed 20 cm above each cylinder. The 3 different startle stimuli consisted of white noise bursts of 20 ms duration and 75, 105 or 115 dB(A) intensity combined with constant background noise of 50 dB(A). After an acclimation period of 5 min, 10 control trials (only background noise) and 20 startle stimuli of each intensity were presented in pseudorandom order with an inter-stimulus interval of 15 s in the average (13-17 s, pseudo-randomized). The cylinders were cleaned with soapy water and dried after each animal.

Contextual and Generalized Fear

To measure conditioned contextual fear and fear generalization, mice were put into 3 different contexts differing in shape, material, surface texture of the walls, floor texture, light intensity and odor. First, mice were introduced to a neutral context (cylinder shape, Plexiglas wall, wood shavings, 0.3 lux, cleaned with 1% acetic acid between animals) for 3 min, in which a neutral tone (80 dB, 9 kHz) was presented for another 3 min, followed by another 1 min in the context before returning to the home cage. On the next day, mice were exposed for 3 min to a novel context which contained a reminding feature of the shock context (hexagonal shape, non-transparent Plexiglas walls, metal grid floor as a dominant reminder of the shock context, 0.3 lux, cleaned with 70% ethanol between animals). Six hours later on the same day, mice were re-exposed to the original shock chamber for 3 min [cubic shape, Plexiglas walls with checkered pattern on the back and side walls, floor metal grid, 0.6 lux, cleaned with water containing isoamylacetate (1:2000; banana aroma) between animals]. All tests were videotaped and freezing behavior

(immobility except for respiration movements; (KAMPRATH AND WOTJAK, 2004)) over the entire 3 min intervals was quantified off-line by an observer (SAP) who was unaware of the experimental condition using the EVENTLOG® scoring program (ROBERT HENDERSON, 1986).

EMG AND EEG RECORDINGS

EEG and EMG signals were processed through a pre-amplifier (1000-fold amplification, custom made) and a main amplifier (10-fold amplification, custom made). EEG and EMG signals were measured differentially against an EEG reference electrode (indicated by "R" in **FIGURE 1B**) and the second EMG electrode respectively, against the common ground (indicated by "G" in **FIGURE 1B**). EEG signals were processed through an analog band-pass filter with bandwidth cut-offs of 0.5 Hz and 32 Hz (filter frequency roll-off 48 dB/octave) and digitized at a sampling rate of 64 Hz (AD board, NI PCI-6070, National Instruments, Austin, TX, USA). EMG signals were processed by a root mean square function before digital conversion at a sampling rate of 64 Hz. The window length for further analysis was set to 4 s (equivalent to one epoch).

SIGNAL ANALYSIS AND SLEEP SCORING

To determine the present vigilance state of each 4s epoch, spectral analysis of the signal by Fast Fourier Transform (FFT) was applied to consecutive EEG epochs at 0.25 Hz steps. Wakefulness (WAKE), non-rapid eye movement sleep (NREMS) and rapid eye movement sleep (REMS) were classified semi-automatically using a FFT-based algorithm on a LabVIEW® based acquisition program (SEA, Cologne, Germany). Decisive frequency bands included the delta (δ: 0.5–5 Hz), theta (θ: 6–9 Hz), alpha (α: 10–15 Hz), eta (η: 16–22.5 Hz) and beta (β: 23–31.75 Hz) band. The scoring algorithm applied (adapted from (LOUIS ET AL., 2004)) specifies the delta and theta value for each epoch using the above defined frequency bands: $\delta = \delta \times \alpha/\eta \times \beta$ and $\theta = \theta \times \theta/\delta \times \alpha$ (FENZL ET AL., 2007). Vigilance stages were classified as follows: (a) Epochs were indexed as WAKE if the EMG-amplitude was above a manually set threshold (separating movement from immobility). WAKE episodes that lasted less than three epochs (12 s), were defined as microarousals (MA) (LÉNA ET AL., 2004). (b) If the calculated delta-value was below a manually set threshold (separating high delta power from low delta power) and (c) the calculated theta-value was above a manually set threshold (separating high theta power from low theta power), the epoch

was defined as REMS. The remaining epochs were indexed as NREMS. All epochs scored semi-automatically by this method were proof-read manually. One animal of the non-shocked group was excluded from the sleep-wake analysis due to poor quality of the EEG signals.

Twenty-four hour recordings of sleep-wake behavior (a) under **BASELINE** conditions (1 day before shock), (b) during the **MEMORY CONSOLIDATION** phase, i.e. the 24 hours directly after the shock (shock day), (c) under **STABLE FEAR MEMORY** conditions, i.e. after the completion of memory consolidation 1 day after the shock and (d) after the development of a **PTSD-LIKE PHENOTYPE** (2 months after shock) were scored by an investigator (SAP) who was unaware of the experimental condition (**FIGURE 1C**).

Mice's sleep composition and architecture were scrutinized by assessing the time and number of episodes spent in MA, WAKE, NREMS and REMS. Further, the mean duration of each episode and the number of transitions between the vigilance states were evaluated. The EEG spectral composition, based on the FFT calculations for defined frequency bands (delta, theta, alpha, eta, beta) within WAKE, NREMS, and REMS, was computed by applying measurements of the area under the curve (AUC) using the trapezoidal rule (technique for estimating the definite integral by approximating the region under the graph of the function as a trapezoid and calculating its area). All parameters were normalized to the group mean value under baseline conditions and are shown as change to **BASELINE** (with 100% denoting baseline levels).

The analysis of the sleep-wake behavior was based on 6 h time windows, because of the phasic alterations of WAKE, NREMS, and REMS amounts over the circadian light-dark-rhythm, seen in rodents and humans. The resulting four circadian phases were defined as (**FIGURE 1D**): **PHASE I** (first half of the dark period: Zeitgeber time 1–6 h), **PHASE II** (second half of the dark period: Zeitgeber time 7–12 h), **PHASE III** (first half of the light period: Zeitgeber time 13–18 h), and **PHASE IV** (second half of the light period: Zeitgeber time 19–24 h). Since animals underwent fear conditioning during phase I on the shock day, this period was excluded from the analysis.

STATISTICS

The ASR was tested for statistical effects of the group (shock *vs.* no shock) and the stimulus intensity by analysis of variance (ANOVA) for repeated measures. Group effects on the freezing behavior in the different environments were statistically analyzed by t-tests for independent samples. Sleep-wake architecture was analyzed separately for each circadian phase. Multivariate analysis of variance (MANOVA) with repeated measures design was performed to detect group, day and group x day interaction effects. Due to the variety of

considered parameters possibly resulting in collinearity, subgroups of dependent variables were built and treated by MANOVA. Significant main and/or interaction effects were followed by univariate F-test to locate variables with significant effects. *Post hoc* contrast test in MANOVA detected significant group and day differences regarding these variables. All *a posteriori* test were performed with the Bonferroni correction to keep the type I error less or equal to 0.05. For detection of possible associations between sleep parameters and behavioral testing responses, Pearson and Spearman correlations were applied. No correction for multiple comparison was used, due to low statistical power (n=8 per group). The statistical significance level was set to $p < 0.05$ for all tests. Data are presented as mean +/- SEM.

RESULTS

This experiment aimed to investigate the following hypotheses: **(1)** A singular traumatic event (electric foot shock) induces the development of a PTSD-like phenotype in mice. This phenotype includes trauma-associated and non-associated behavioral features as well as alterations in the sleep-wake behavior, in particular in REMS. **(2)** REMS characteristics before and/or in the early aftermath of the trauma-like event correlate with the severity of the PTSD-like phenotype developed after one month.

SHOCK EXPOSURE INDUCES DEVELOPMENT OF A PTSD-LIKE PHENOTYPE

Behavioral testing performed one month after the shock revealed the development of a PTSD-like phenotype in shocked, but not in non-shocked mice, in both, trauma associated (contextual fear) and non-associated (hyperarousal, generalized fear) aspects (**FIGURE 2**).

Although the acoustic startle response (ASR; **FIGURE 2A**) was only marginally affected by the shock itself *[F(1,1) = 3.02, p = 0.10]* and by the shock dependent on the acoustic stimulus intensity *[stimulus x shock, F(1,4) = 2.09, p = 0.09]* , inspection of the responses at the highest stimulus intensity (115 dB) revealed a significant difference between shocked and non-shocked animals *[t(14) = 1.88, p < 0.05, one-tailed unpaired t-test]*, as expected based on previous studies (SIEGMUND AND WOTJAK, 2007A, 2007B; GOLUB ET AL., 2009).

Contextual fear, assessed by means of quantification of freezing behavior in the shock context, was elevated in the shocked group *[t(14) = 3.542, p < 0.005;* **FIGURE 2B***]*. Also, this group showed evidence for more generalized fear behavior, as freezing responses were increased upon exposure to a novel context *[t(14) = 2.175, p < 0.05]* and to a neutral tone *[t(14) = 2.239, p < 0.05]*, compared to non-shocked controls. However, no significant differences in fear behavior could be observed upon exposure to the context containing a reminding feature (grid floor) of the shock context *[t(14) = 1.66, p = 0.12]*.

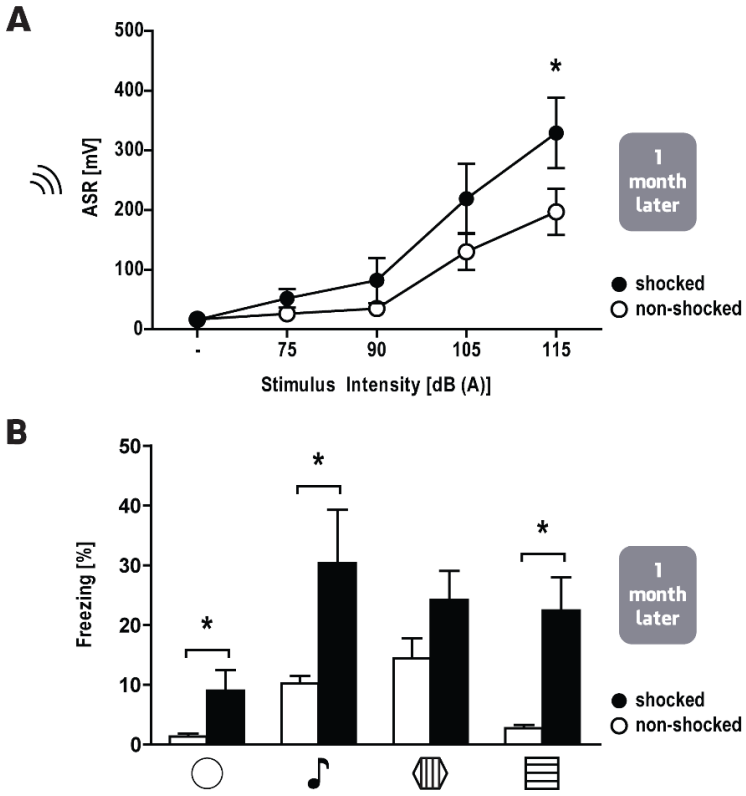

Figure 2 | Development of Hyperaroual, Contextual and Generalized Fear | Behavioral tests were performed 1 month post-shock. (A) Acoustic Startle Response (ASR; volume symbol) presented as group mean +/- SEM per intensity. *p < 0.05 between shocked (filled circles) *vs.* non-shocked (open circles) animals (unpaired t-test, one-tailed). (B) Percent time (mean +/- SEM) mice spent freezing upon exposure to a novel environment (circle symbol), a neutral tone (note symbol), a context with reminder features of the shock context (hatched hexagon symbol) and the shock context (hatched square symbol) *p < 0.05 between shocked (solid bars) *vs.* non-shocked (open bars) mice (unpaired t-test). Adapted from (POLTA ET AL., 2013).

BASELINE SLEEP-WAKE BEHAVIOR

In order to examine whether the developed behavioral PTSD-like phenotype was accompanied by sleep alterations, we first inspected the basal sleep-wake behavior of the animals prior to the shock. Under baseline conditions, the distribution of wakefulness (WAKE), non-rapid eye movement sleep (NREMS) and rapid eye movement sleep (REMS) followed a physiological pattern over the dark-light cycle in both experimental groups (**FIGURE 3**) with mice being awake longer during the active (dark) phase and longer asleep during the inactive (light) phase. The 24 hour recordings were split into 6 hour bins according to the Zeitgeber time (see **METHODS P.51** and **FIGURE 1D**): **PHASE I** (first half of the dark period: Zeitgeber time 1-6h), **PHASE II** (second half of the dark period: Zeitgeber time 7-12h), **PHASE III** (first half of the light period: Zeitgeber time 13–18h), and **PHASE IV** (second half of the light period: Zeitgeber time 19-24h). Shocked and non-shocked mice displayed a similar composition of vigilance states in each of the phases *(MANOVA, $p > 0.05$;* **TABLE 1***)*.

Taken together, baseline sleep-wake composition was similar between shocked and non-shocked mice and presented a natural dark-light course.

Table 1 | Basal Sleep Wake Distribution in Shocked vs. Non Shocked Mice |
Percentage of time spent in WAKE, NREMS and REMS under basal conditions during the four circadian phases (mean +/- SEM).

phase	vigilance state	non-shocked (Mean ± SEM [%])	shocked (Mean ± SEM [%])
I	WAKE	83.0 ± 3.5	89.6 ± 2.8
	NREMS	16.4 ± 3.4	10.3 ± 2.8
	REMS	0.6 ± 0.2	0.2 ± 0.1
II	WAKE	67.8 ± 1.2	68.4 ± 4.1
	NREMS	30.0 ± 1.0	30.0 ± 3.8
	REMS	2.3 ± 0.3	1.6 ± 0.4
III	WAKE	28.0 ± 1.7	24.5 ± 1.3
	NREMS	63.6 ± 1.3	66.4 ± 1.1
	REMS	8.5 ± 0.6	9.1 ± 0.6
IV	WAKE	22.2 ± 1.3	24.1 ± 1.2
	NREMS	65.9 ± 1.6	65.5 ± 1.0
	REMS	8.9 ± 0.8	7.6 ± 0.5

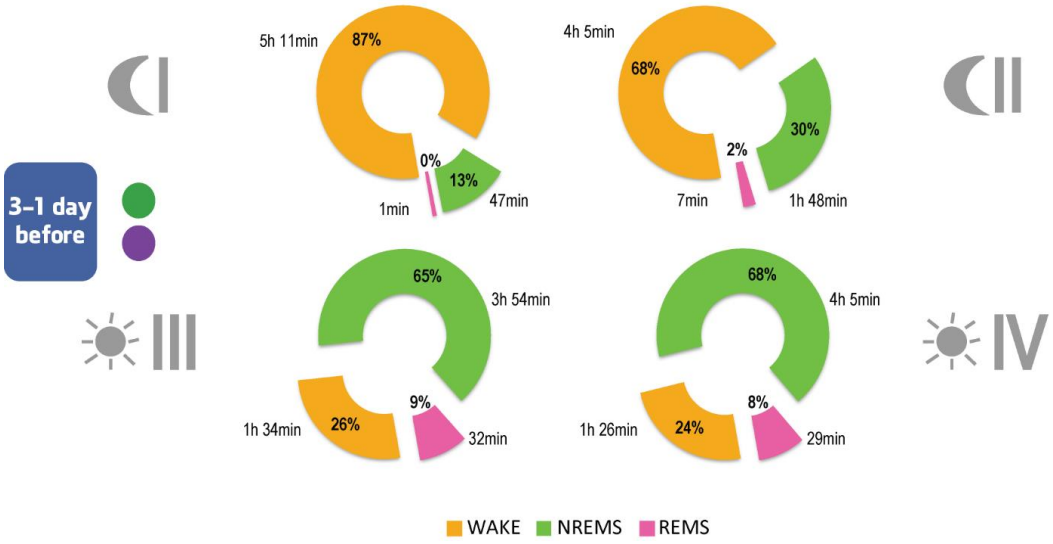

Figure 3 | Pre-Shock Sleep Wake Behavior |
Circle diagrams show mean percentage of time spent in WAKE (orange), NREMS (green) and REMS (pink). Actual time values are depicted aside. The four diagrams represent the four 6-h phases of the circadian rhythm, as illustrated in **FIGURE 1D**. Data are represented as means including both experimental groups (n=15). Adapted from (POLTA ET AL., 2013).

Upon excluding basal differences in sleep-wake architecture between the groups, we examined the hypothesized sleep alterations in the aftermath of the traumatic event. Individual changes were analyzed by normalization of data to the group means obtained under baseline conditions. **FIGURE 4** shows relative changes to baseline values in the shocked *vs.* the non-shocked animals for **PHASE III** and **IV** (inactive diurnal phases). No significant group differences could be observed for the time spent in WAKE, microarousals, NREMS and REMS during the first part of the inactive phase (**PHASE III; FIGURE 4**), nor during active **PHASES I** and **II** on all experimental days post-shock *(MANOVA, $p > 0.5$,* data not shown*)*. Although statistical analysis for **PHASE III** revealed a significant group x day interaction effect on the shock day *[group x day: $F(9,90) = 2.78$, $p < 0.01$; day: $F(9,90) = 6.57$, $p < 0.001$]*, which emerged to be REMS-specific *[group x day: $F(3,39) = 3.90$, $p < 0.02$]*, comparison between groups did not reveal a statistically significant difference *($p > 0.05$)*. However, in comparison to their baseline, controls showed an increased time spent in REMS during this phase after the exposure to the novel context *[$F(1,6) = 17.95$, $p < 0.008$]*.
In contrast, for **PHASE IV** significant group *[$F(2,11) = 7.81$, $p < 0.01$]*, day *[$F(8,90) = 6.51$, $p < 0.001$]*, and group x day interaction effects *[$F(8,90) = 3.29$, $p < 0.01$]*, which were again associated with REMS only *[group: $F(1,13) = 9.21$, $p < 0.01$; day: $F(3,39) = 13.41$, $p < 0.01$; group x day: $F(3,39) = 5.53$, $p < 0.001$]*, emerged as significant differences also between groups. While on the shock day, shock-exposed mice spent significantly more time in REMS as compared to their own baseline *[shock day vs. baseline: $F(1,7) = 16.06$, $p < 0.005$]*, one day later this increase also resulted in a significant difference compared to controls *[1 day later vs. baseline: $F(1,7) = 58.92$, $p < 0.001$; shocked vs. non-shocked: $F(1,13) = 9.30$, $p < 0.01$]*. Interestingly, even 2 months after the shock exposure, REMS levels remained increased during this phase *[2 months later vs. baseline: $F(1,7) = 33.63$, $p < 0.001$; shocked vs. non-shocked: $F(1,13) = 18.73$, $p < 0.001$]*.

In accordance with our hypothesis, animals that had been exposed to the shock displayed an altered sleep behavior. More specifically, they spent more time in REMS as compared to their baseline amounts and to controls. In a next step, we examined the features of this REMS increase in detail.
To this end, we assessed how often mice entered REMS (i.e. the number of REMS episodes), how long these REMS episodes lasted on average (i.e. the mean duration of REMS episodes) and the REMS quality, according to the spectral characteristics of the EEG (as measured by the EEG power in pre-defined frequency bands). The same analysis was also performed for the vigilance states WAKE, NREMS and the microarousals (MA). Furthermore, the number of transitions between all states was counted.

No significant group effect or factorial interaction was seen for the described parameters during any circadian phase *(MANOVA, $p > 0.05$)*. **TABLE 2** depicts the percental changes, as compared to baseline values of the respective experimental group. As shown in the fourth column of the table (shocked group in **PHASE IV**), early-onset and long-lasting increases in REMS cannot be explained by a single process: while some of the shocked animals entered more often into REMS, others had on average longer REMS episodes. Also, the transitions between vigilance states were comparable between groups. Likewise, EEG power during REMS in the pre-defined frequency bands (delta, theta, alpha, eta, beta) was not affected by the shock exposure, nor significantly differed between groups *($p > 0.05$)*.

It can be concluded that, although mice developed an early onset, yet long-lasting increase in REMS amounts after the exposure to the shock, the nature of this increase varies between individuals and cannot be ascribed to a single underlying process. In addition, independently of the experimental day, shocked and non-shocked animals displayed similar sleep architecture in terms of sleep fragmentation in general and of REMS fragmentation in particular, as measured by the number and duration of epochs and transitions between vigilance states (**TABLE 2**). Therefore, elevated REMS levels *per se*, but not REMS fragmentation, can be hypothesized as a symptomatic feature of the PTSD-like phenotype in our animal model.
To follow up our second hypothesis, in a next step we questioned whether sleep (and in particular REMS) may have not only symptomatic but also prognostic value.

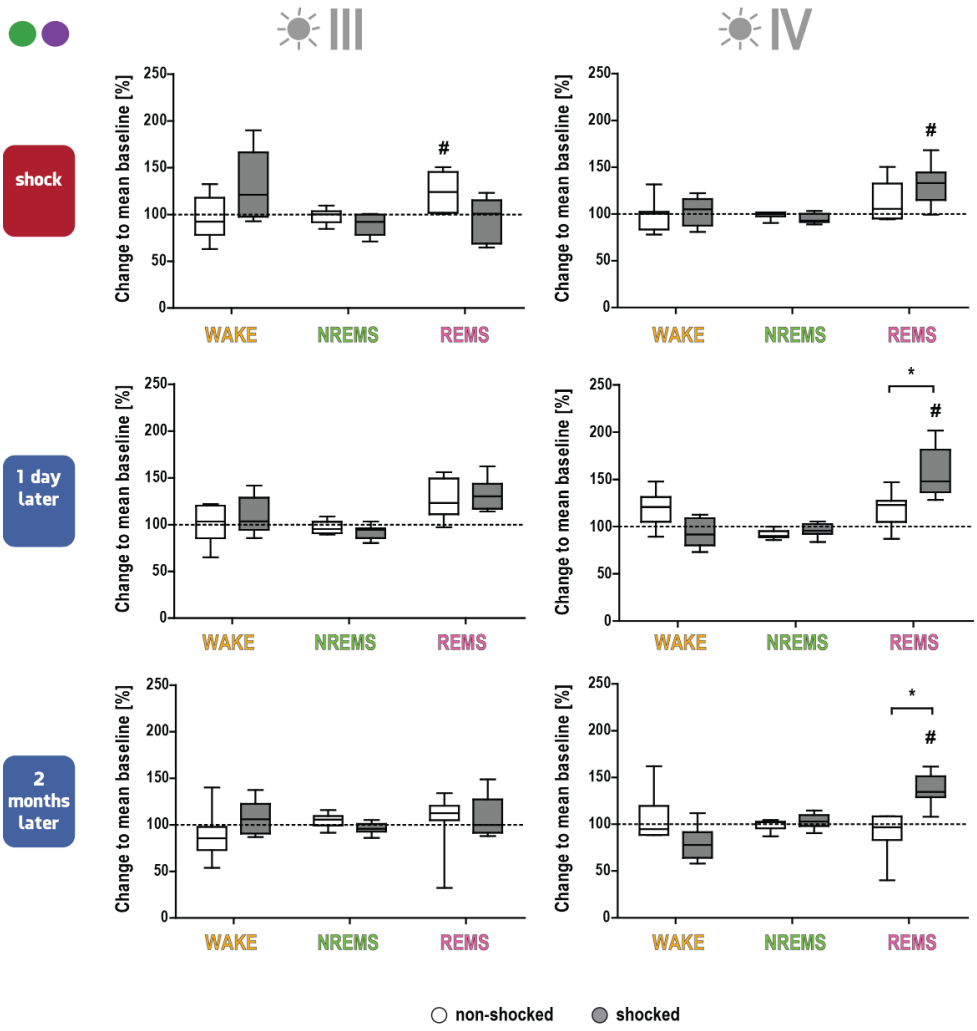

Figure 4 | Long-lasting REMS increase after the shock |
Change in time (%) spent in WAKE, NREMS and REMS during the inactive circadian phases relative to the group mean under baseline conditions (dotted horizontal line). Data are presented as box and whisker plots with boxes showing lower, median and upper quartile, and whiskers showing the minimum and maximum for the sample. #$p < 0.05$ indicates a statistically significant difference to the baseline condition. *$p < 0.05$ between shocked (gray) vs. non-shocked (white) mice (MANOVA). Adapted from (POLTA ET AL., 2013).

Table 2 | REMS characteristics after the shock |

Change (%) of REMS characteristics during circadian phases I-IV compared to the group mean under baseline conditions (mean +/- SEM). Number (REMS_N) and mean duration (REMS_MD) of REMS episodes; transitions between REMS (RM) and WAKE (WK), microarousals (MA) or NREMS (NR); spectral δ, θ, α, η, β EEG power.

shock

	shocked		non-shocked		shocked		non-shocked		shocked		non-shocked		shocked		non-shocked	
	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM
REMS_N	100.0	22.2	155.6	43.6	102.5	7.5	140.4	15.9	111.0	12.0	89.7	7.1	100.5	6.1	115.4	10.1
REMS_MD	158.9	18.9	194.2	30.6	113.2	7.3	116.4	8.0	113.4	9.3	105.2	5.3	108.1	5.1	113.1	6.5
NR-RM	103.9	23.1	155.6	43.6	105.2	7.7	141.1	15.8	110.4	11.8	91.0	7.2	100.0	6.0	115.5	10.5
RM-NR	63.6	0.0	100.0	0.0	87.5	0.0	88.9	0.0	63.0	12.5	59.1	11.8	34.0	5.7	57.1	7.2
RM-MA	90.0	20.0	90.9	11.9	70.6	12.6	108.7	20.2	94.6	10.2	68.2	9.4	104.1	12.6	106.9	10.1
MA-RM	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	114.3	14.3	88.9	0.0	114.3	14.3	100.0	11.1
RM-WK	125.0	22.7	173.3	44.8	125.5	12.1	153.7	15.8	148.7	22.2	121.4	16.2	141.6	15.4	134.1	16.0
WK-RM	87.5	0.0	100.0	0.0	77.8	0.0	100.0	11.1	100.0	0.0	80.0	0.0	100.0	12.5	100.0	0.0
DELTA	104.6	5.3	98.3	3.2	99.7	3.6	82.8	8.3	98.7	5.0	104.2	3.5	101.7	4.7	101.9	3.4
THETA	97.0	6.0	98.1	6.8	90.7	6.3	95.4	6.6	102.1	6.7	92.9	6.5	98.0	6.4	98.9	6.9
ALPHA	100.8	1.9	97.8	2.9	100.7	4.2	92.8	3.4	101.9	3.2	100.5	5.1	101.1	2.2	98.9	3.7
ETA	99.5	1.9	97.6	2.8	101.5	1.7	91.8	1.7	100.6	2.1	98.0	3.8	100.1	1.7	98.6	3.2
BETA	98.8	1.1	97.8	2.2	99.4	2.1	94.8	1.4	100.2	1.7	99.8	2.8	99.4	1.2	98.1	2.5

1 day later

	shocked		non-shocked		shocked		non-shocked		shocked		non-shocked		shocked		non-shocked	
	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM
REMS_N	163.0	44.1	150.0	36.6	92.4	12.5	133.3	14.5	121.4	6.0	124.3	9.3	106.4	8.0	134.3	10.6
REMS_MD	161.0	19.2	197.0	32.9	117.1	17.4	98.0	9.7	99.7	3.9	106.4	5.1	108.8	6.0	112.7	5.0
NR-RM	169.2	45.8	150.0	36.6	94.8	12.8	135.7	14.8	119.8	6.1	125.6	9.5	106.5	8.1	133.3	10.6
RM-NR	63.6	0.0	100.0	0.0	87.5	0.0	88.9	0.0	48.2	10.5	81.8	25.5	32.1	5.7	81.0	16.8
RM-MA	130.0	41.6	81.8	9.1	52.9	7.6	73.9	10.3	125.8	19.7	103.6	16.7	146.6	24.6	149.3	20.7
MA-RM	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	128.6	18.4	100.0	11.1	114.3	14.3	122.2	16.3
RM-WK	190.0	47.0	173.3	41.3	121.6	16.0	163.4	20.2	140.5	19.2	153.1	16.7	116.9	18.1	128.6	23.4
WK-RM	87.5	0.0	100.0	0.0	77.8	0.0	88.9	0.0	114.3	14.3	80.0	0.0	87.5	0.0	100.0	0.0
DELTA	111.5	4.7	109.3	3.4	104.6	7.9	87.7	8.8	113.1	7.5	114.9	5.4	112.2	5.1	108.6	4.3
THETA	95.8	5.3	100.2	6.3	101.4	6.1	96.5	5.9	100.7	6.9	98.8	9.1	97.7	5.8	99.4	6.5
ALPHA	105.8	2.8	103.6	4.5	102.1	2.4	90.3	4.7	109.1	4.1	107.5	5.6	104.8	1.9	102.2	3.5
ETA	105.2	2.2	101.0	3.3	102.3	4.2	96.2	2.6	102.2	1.7	102.4	3.5	101.0	1.7	99.1	3.3
BETA	101.9	1.9	98.9	2.5	98.2	1.2	98.8	2.1	101.1	1.7	100.3	2.6	98.8	1.7	98.7	2.7

2 months later

	shocked		non-shocked		shocked		non-shocked		shocked		non-shocked		shocked		non-shocked	
	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM
REMS_N	92.6	22.5	144.4	39.2	92.4	16.0	126.3	25.6	76.9	9.6	89.3	6.2	78.1	9.1	108.2	9.9
REMS_MD	124.6	13.8	140.6	11.6	136.3	11.0	114.1	7.5	133.2	6.9	121.4	6.0	114.7	5.4	122.0	6.1
NR-RM	96.2	23.4	144.4	39.2	94.8	16.5	128.6	26.0	76.9	9.6	89.6	5.9	78.5	9.1	108.8	9.9
RM-NR	72.7	9.1	112.5	12.5	112.5	16.1	88.9	0.0	77.8	20.4	59.1	6.7	30.2	5.6	92.5	21.8
RM-MA	70.0	0.0	72.7	0.0	85.3	26.4	121.7	28.7	66.7	11.6	73.6	10.2	91.8	17.6	120.6	17.7
MA-RM	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	88.9	0.0	100.0	0.0	88.9	0.0
RM-WK	120.0	30.4	166.7	44.4	92.2	16.9	126.8	25.6	96.0	14.4	114.3	21.4	102.6	13.4	101.7	13.4
WK-RM	87.5	0.0	100.0	0.0	77.8	0.0	88.9	0.0	100.0	0.0	100.0	13.1	87.5	0.0	100.0	0.0
DELTA	119.9	7.2	110.8	4.5	130.6	15.3	92.7	6.5	137.0	26.7	131.4	19.6	115.7	7.1	112.1	5.2
THETA	87.2	6.0	98.8	9.0	78.1	5.2	104.9	12.8	89.1	9.2	101.9	10.7	88.1	5.6	97.6	9.3
ALPHA	98.7	4.2	100.3	3.0	100.5	6.2	93.6	4.2	108.8	12.5	108.8	6.4	100.2	4.1	100.1	3.0
ETA	100.1	3.0	97.3	2.0	103.4	4.0	99.0	4.0	102.9	6.9	101.1	5.6	99.5	3.4	95.7	2.1
BETA	99.9	2.1	96.4	1.9	100.9	3.6	100.6	3.6	100.3	2.6	99.2	2.5	100.1	1.9	97.0	1.9

Although baseline vigilance distributions were similar between groups, we hypothesized that the quality or amount of sleep before and/or immediately after a traumatic event could predict how severely the PTSD-like phenotype will be expressed by the individuals exposed to the trauma. Therefore, we performed correlation analyses between data of PTSD-like behavior (ASR, freezing to the shock context) and various REMS parameters (REMS percentage, number of REMS episodes, mean duration of REMS episodes, transitions from and to REMS) measured before or 1 day after the shock.

The number of REMS episodes during **PHASE IV** prior to the shock was significantly correlated with the ASR at the highest stimulus intensity in the shocked *(***FIGURE 5A**, *r = 0.78, p < 0.05)* but not in the non-shocked group *(***FIGURE 5B**, *r = 0.2, p > 0.05)*. Similarly, transitions to *(Pearson r = 0.80, p < 0.05)* and from REMS *(REMS to WAKE: r = 0.72, p < 0.05; REMS to NREMS: r = 0.80, p < 0.05)* during **PHASE IV** showed an association with the startle response in shocked mice only. In contrast, the total amount of REMS was not correlated with the ASR *(Pearson r = 0.59, Spearman r = 0.62, p > 0.05)*, indicating that low REMS continuity (i.e. more interruptions of REMS), but not REMS duration *per se*, was associated with the severity of the emerging hyperarousal in the shocked group.

The contextual fear response was not correlated with any of the REMS parameters in both groups *(***FIGURE 5C, D***; shocked: r < 0.21, p > 0.62; non-shocked: r < 0.38, p > 0.50)*.

In summary, the results described above suggest that in mice REMS characteristics under baseline conditions might be associated with the emergence of non-associative behavioral PTSD-like symptoms after the exposure to a traumatic event in mice. Additionally, long-lasting REMS variation, as observed after the exposure to an electric foot shock, coincided with the development of hyperarousal, contextual and generalized fear in our animal model of PTSD.

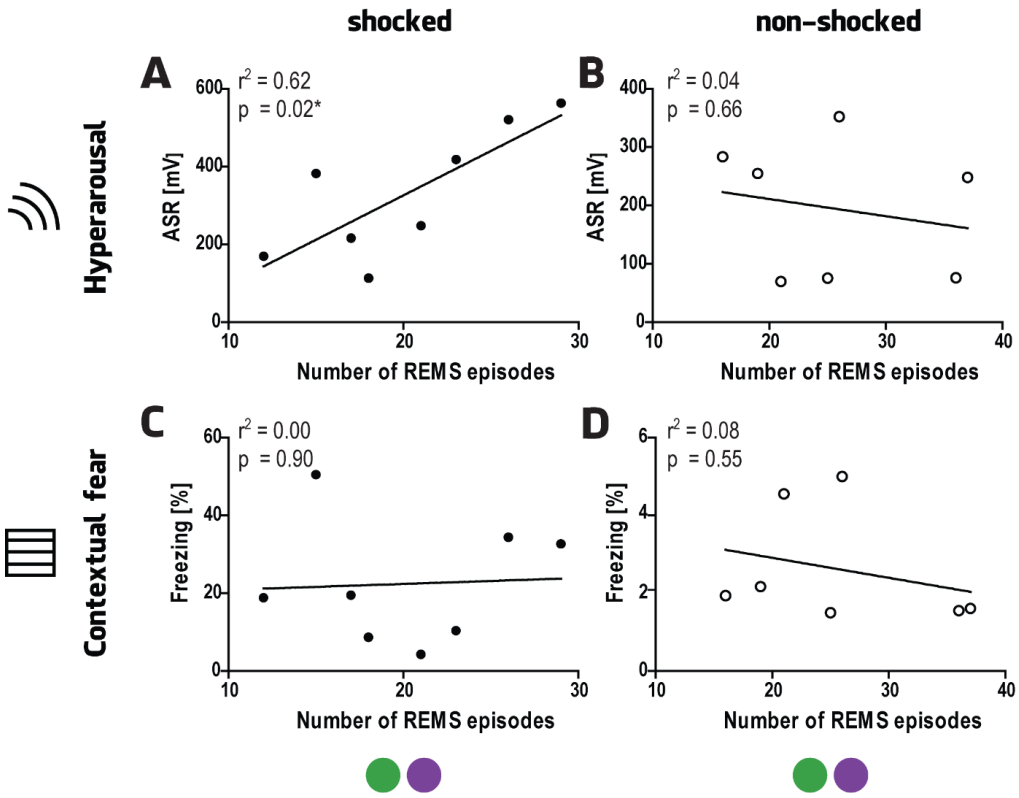

Figure 5 | Association between basal REMS and hyperarousal developed one month post shock |

Correlation between the number of REMS episodes under baseline conditions in phase IV and the ASR at intensity of 115 dB (**A, B**), or the freezing behavior in the shock context (**C, D**) 1 month after the shock. Solid circles: shocked group, open circles: non-shocked group. r^2: correlation coefficient as obtained from linear regression analysis (Pearson correlation), *p < 0.05. Adapted from (POLTA ET AL., 2013).

Chapter 3 | Limbic Activity Patterns during Reliving of a Traumatic Situation and its Re-Occurrence during Rapid Eye Movement Sleep in Mice.

CONTRIBUTIONS

The author of the present thesis contributed to the second experiment by conceiving of the experimental questions and hypotheses, designing the experimental schedule, conducting the experiment (including surgeries, recordings of electrophysiological data, behavioral tests) and analyzing its data (signal processing, sleep scoring, behavioral readout, signal analysis, statistical analysis). She also wrote the program routines in MATLAB® for the processing and analysis of the electrophysiological data.

ANIMALS

Laboratory animal care and experimental procedures were in compliance with the European Union recommendations for the care and use of laboratory animals and all experimental procedures were approved by the Committee on Animal Health and Care of the Government of Upper Bavaria (AZ55.2-1-54-2532-43-09).

Adult male C57BL/6N mice (Martinsried, Germany; n = 26; aged 10-12 weeks at arrival) were housed individually with *ad libitum* access to food and water under inverse 12–12 h light-dark cycle (lights ON at 9 p.m.).

Home cages (custom made; 26 cm × 26 cm × 35 cm; clear Lucide® walls; wood shaves as bedding material) served at the same time as recording cages. As only one animal underwent the experimental schedule a time, experimental groups were assigned in time series starting with 18 shocked and proceeding with 8 non-shocked mice. Successful targeting of the region of the basolateral amygdala (BLA) and the CA1 region of the dorsal hippocampus (CA1) was certified in 61.5% of the animals (see **ELECTRODE POSITIONING, P.68** and **FIGURE 6E**). Only signals from these mice (n=16) were processed further and included into the analysis.

SURGERY AND STEREOTACTIC IMPLANTATION OF ELECTRODES

Sleep recordings were based on signals derived from electroencephalogram (EEG) and electromyogram (EMG). Additionally, signals from the BLA and CA1 were obtained in this experiment (**FIGURE 6B**). Implantation of three epidural EEG electrodes (EEG, reference and ground), two deep electrodes (BLA, CA1) and one EMG electrode (EMG) into the nuchal musculature of the mice was performed under isoflurane anesthesia (Isofluran, DeltaSelect GmbH, Germany; anesthesia device: Agn-Thoas AB, Sweden) in combination with meloxicam as a perioperative analgesic (0.5 mg/kg body weight *s.c.*; Metacam, Braun Melsungen, Germany). EEG and EMG electrodes consisted of gold wires with ball-shaped endings. Self-made deep electrodes (Teflon-coated wire, stainless steel, Science Products, Hofheim, Germany, uncoated Ø 75µm, coated Ø 140µm, impedance ~50kΩ) were implanted stereotactically targeting the BLA (coordinates: anterior/posterior -1.58 mm from Bregma, medial/lateral -3.4 mm from Bregma, dorsal/ventral -4.8 mm from skull surface) and the CA1

(coordinates: anterior/posterior -1.82 mm from Bregma, medial/lateral -1.00 mm from Bregma, dorsal/ventral -1.50 mm from skull surface). All electrodes were soldered on a standard PCB socket connector. Fixation to the skull was achieved by bonding of electrodes, two fixation screws and the PCB socket with superglue and dental cement (Paladur, Heraeus-Kulzer, Germany). Post-operatively, meloxicam was added to the drinking water for 5 days (0.5 mg/kg body weight).

EXPERIMENTAL DESIGN

FIGURE 6A depicts the experimental schedule of experiment 2. Recordings were continued during behavioral manipulations (indicated in red) except for the time during the shock delivery, due to the interfering signal of the electric shock device. Animals were not disconnected from the recording cable for any of the behavioral manipulations. All recordings and behavioral tests were conducted in a sound-attenuated Faraday cage recording chamber [constant temperature (23 +/- 1 °C), inverse light-dark cycle (12–12 h, lights ON at 9 p.m.)]. Only one mouse at a time was recorded and behaviorally tested, therefore surgeries were performed in a staggered arrangement. After surgery, each animal was given a recovery period of 12-30 days before being moved to the recording chamber. Here, it was connected to the recording cable and the swivel system. After a habituation period to the cable/swivel of 2 days, baseline recordings were performed in the home cage (**FIGURE 6A**: box "1 day before"). The following day, the animal was introduced to a novel environment followed by 3 recording days in the home cage. On the shock day, the animal was exposed to two unsignaled electric foot shocks in the shock chamber followed by three consecutive days of recordings in the home cage (**FIGURE 6A**: boxes "shock", "1 day later", "2 days later"). The following day, the mouse was re-exposed to the shock chamber for 30 min and put back in its home cage for another 24 hour recording. The last experimental day comprised another re-exposure to the shock chamber, this time lasting for only 5 min. Subsequently the animal was de-connected from the recording cable.

Electrode Positioning

To assure correct electrode positioning in the BLA and CA1, electric lesions were generated in the brain tissue by applying electric current to the electrodes (BLA: 3.5 µA for 3 min; CA1: 2.5 µA for 3 min) under deep isoflurane anesthesia. The animals were rapidly decapitated and the brain was removed and snap-frozen frozen in pre-chilled isopentane on dry ice.

Cryo-sections (30 µm thick) of the entire hippocampus and amygdala were stained with Cresyl violet for visual localization of the lesions under a low-magnification microscope. Successful targeting of BLA and CA1 was certified in 61.5% of the animals by comparing the position of the lesion with classifications in the mouse brain atlas ((Franklin and Paxinos, 2008); **Figure 6E**). Only signals from mice with correct electrode positioning (n=16) were processed further and included into the analysis.

Shock Procedure and Behavioral Testing

The shock procedure and behavioral tests were applied during the active (dark) diurnal phase of the animals (between 9.30 am and 11.30 am). Light intensity was kept to a minimum during testing to reduce the stress for the animals.

To test for novelty-induced fear and as a within-subject control exposure, mice were introduced to a novel context (cylinder shape, Plexiglas wall, wood shavings, house light, cleaned with 1% acetic acid between animals) for 7 min. The animal was transferred back to the home cage afterwards.

For the shock application, the mouse was placed into the shock chamber [MED Associates Inc., St. Albans, VT, USA; cubic shape, Plexiglas walls with checkered pattern on the back and side walls, floor metal grid, house light, cleaned with water containing isoamylacetate (1:2000; banana fragrance) between animals]. After allowing for exploration of the chamber for 5 min, two scrambled, unsignaled electric foot shocks (1.5 mA, 2 s, 1 min interval between shocks; MED Associates Inc., St. Albans, VT, USA) where delivered via the metal grid. The animal remained in the chamber for another 1 min before being transferred back to the home cage. Mice of the non-shocked group were placed into the shock chamber for the equivalent amount of time (7 min) without the delivery of any shocks.

To test for contextual fear memory, re-exposure to the shock context under the same conditions (light, odor, and way of handling) was performed 3 days after the shock. A time interval of 30 min was chosen, as it has been observed by our research group that this time interval is enough to initiate extinction of the fear memory by the prolonged exposure (Golub et al., 2009). To test for fear extinction memory, another day later the mouse was re-exposed to the shock chamber for 5 min. After each testing, the animal was transferred into its home cage.

All tests were videotaped and freezing behavior (immobility except for respiration movements; (Kamprath and Wotjak, 2004)) was quantified off-line by a person (SAP) unaware of the experimental condition using the EVENTLOG® scoring program (Robert Henderson, 1986) for pre-defined time windows (see **Signal Processing and Sleep Scoring** below).

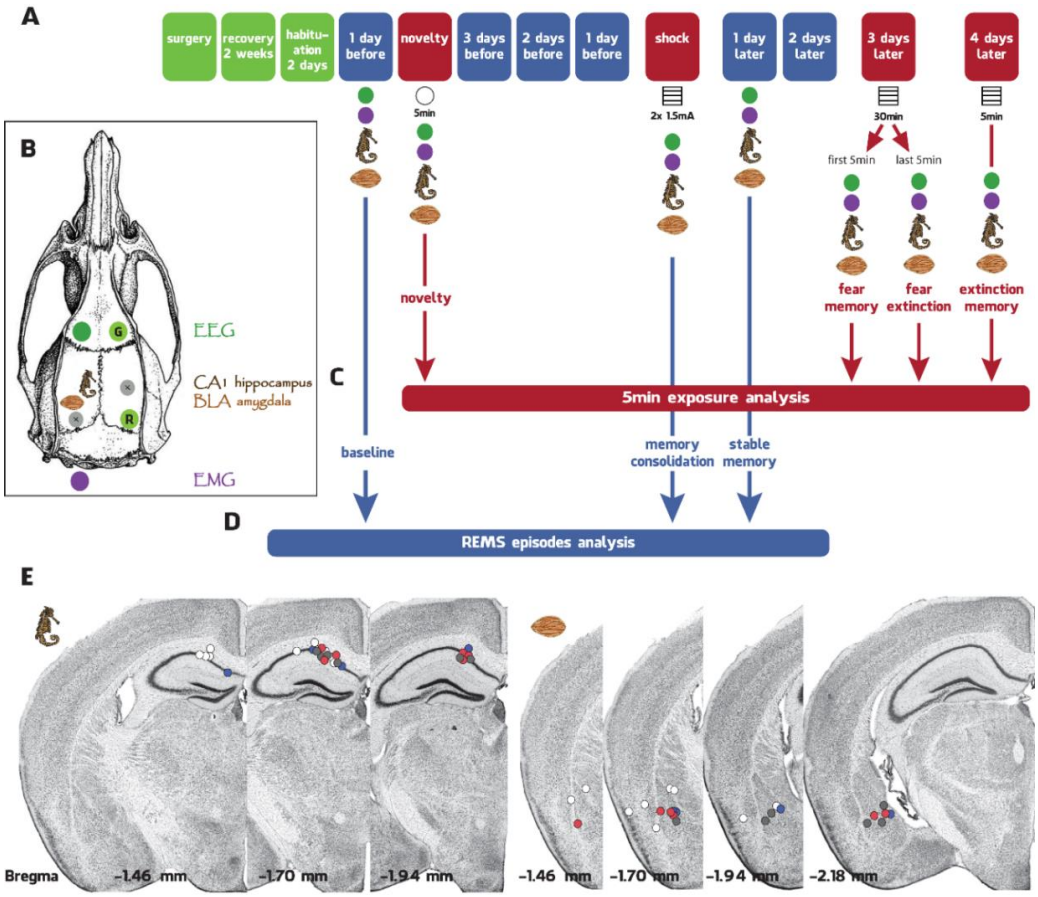

Figure 6 | Experimental Design 2 |
Analysis of limbic activity patterns during REMS and upon exposure to different contexts in mice (n = 26). (A) Experimental Schedule: the time course is depicted by experimental day boxes; green: surgery, recovery and habituation; blue and red: experimental days in the recording chamber (24 hour recordings); red: experimental days of exposure challenges, i.e. mice were exposed to (i) a novel environment (circle symbol), (ii) a contextual fear conditioning in the shock context (hatched square symbol; two shocks of 1.5 mA), (iii) a extinction training in the shock context (hatched square symbol; 30 min) and (iv) fear extinction memory test in the shock context (hatched square symbol). Continuous 24 hour EEG/EMG and CA1/BLA recordings are indicated below the experimental day boxes by a green/purple filled circle and a seahorse/almond symbol, respectively. (B) Positioning of three epidural EEG electrodes (EEG, reference 'R' and ground 'G'), one EMG electrode into the nuchal musculature, two deep electrodes into BLA (almond symbol) and CA1 (seahorse symbol) and two fixation screws ('x'). Adapted from: (PAXINOS AND WATSON, 1998)[1].

[1] Reprinted from "The Rat Brain in Stereotaxic Coordinates", Edition 4, George Paxinos, Charles Watson, © 1998, with permission from Elsevier.

(C) Indication of the exposure challenges (5 min intervals) which were included into the analysis of fear behavior, EMG activity and limbic activity patterns. (D) Indication of the recording days which were included into the analysis of sleep-wake behavior as well as limbic activity patterns during REMS. (E) *Post mortem* identification of the positioning of deep electrodes targeting CA1 and BLA; white spots: animals with unsuccessful targeting (not included into any analysis); blue spots: successful targeting in low responders; red spots: successful targeting in high responders; gray spots: successful targeting in non-shocked animals. For the definition of the three animal subgroups please refer to the results text below (**THE EMG AS FREEZING DETECTOR, P.83 FF.**). Adapted from (FRANKLIN AND PAXINOS, 2008)[1].

EMG, EEG, BLA AND CA1 RECORDINGS

EEG, EMG, BLA and CA1 signals were processed through an impedance converter (i.e. headstage on the head of the mouse with no amplification; npi electronic GmbH, Tamm, Germany) and an amplifier (1000-fold amplification; npi electronic GmbH, Tamm, Germany). All signals were analog band-pass filtered with cut-offs of 0.1 Hz and 100 Hz and digitized at a sampling rate of 1 kHz (Data Acquisition Bord, DT3010, Data Translation GmbH, Bietigheim-Bissingen, Germany) using a commercial acquisition program (SciWorks®, Datawave Technologies, Loveland, CO, USA). EMG, BLA and CA1 signals were measured against a common ground (indicated by 'G' in **FIGURE 6B**). EEG signals were measured differentially against an EEG reference electrode (indicated by 'R' in **FIGURE 6B**), against the common ground. Recorded signals were converted from the software format *.ddf* to *.txt* for further processing in MATLAB® (MathWorks, Natick, MA, USA; release 2011).

SIGNAL PROCESSING AND SLEEP SCORING

All signal processing and analysis was performed on the basis of self-written subroutines in MATLAB® (MathWorks, Natick, MA, USA; release 2011) and it's built in functions originally provided in the "Statistics Toolbox" and the "Signal Processing Toolbox".

[1] Reprinted from "The Mouse Brain in Stereotaxic Coordinates", Edition 3, Keith B.J. Frankin, George Paxinos, © 2008, with permission from Elsevier.

At first, due to RAM capacity limitations, all 24 hour recordings were split into one hour files in order to extract data for each channel separately (EEG, EMG, BLA, CA1). All recordings during behavioral manipulations were processed further in their original recording length (7 min and 30 min, respectively).
The following pre-defined behavioral conditions were analyzed within the scope and hypotheses of this work (see **FIGURE 6**): **(1)** all time points of behavioral manipulations (**FIGURE 6C**) except for the shock application; these are (a) **NOVELTY**, (b) **CONTEXTUAL FEAR MEMORY**, i.e. the first minutes of the re-exposure 3 days after the shock, (c) **FEAR EXTINCTION**, i.e. the last minutes of the re-exposure 3 days after the shock and (d) **FEAR EXTINCTION MEMORY**, i.e. the re-exposure to the shock context 4 days after the shock. A time window of 5 min was analyzed for each condition. **(2)** All REMS episodes of the 24 hour recordings (**FIGURE 6D**) (a) under **BASELINE** conditions, i.e. one day before the novelty exposure, (b) during the **MEMORY CONSOLIDATION** phase, i.e. the 24 hours directly after the shock and (c) under **STABLE FEAR MEMORY** conditions, i.e. after the completion of memory consolidation 1 day after the shock. REMS epochs were extracted from 24 hour recordings as described below.

Filtering and Down-Sampling

All signals were processed with an analog filtering routine (self-written MATLAB® routine using the built-in double reverse filtering routine '*filtfilt*') using a low pass filter with a cut-off frequency at 47 Hz and a high pass filter with a cut-off frequency at 0.5 Hz (Butterworth filter). Additionally, all signals were down-sampled by a factor of 10, resulting in a sampling frequency of 100 Hz. The windowlength for further analysis was set to 4 s (equivalent to one epoch).

Sleep Scoring

WAKE, NREMS and REMS were classified semi-automatically by means of the EEG and EMG signal using a FFT-based algorithm (LabVIEW® based sleep scoring software developed together with MK; (KREUZER ET AL., 2013, 2014)). In a first step, the EEG signal was filtered for distinct frequency bands including the delta (δ: 0.5–5 Hz), theta (θ: 6–9 Hz), alpha (α: 10–15 Hz), eta (η: 16–22.5 Hz) and beta (β: 23–31.75 Hz) band. Subsequently, both filtered EEG frequency bands and the EMG signal were processed with a root mean square function

$$RMS = \sqrt{\frac{1}{N}\sum_{i=0}^{N-1}|x_i|^2}$$

where N is the number of data points in the 4 s epoch and x_i are the discrete amplitude values in the 4 s sequence with i ranging from 1 to N. The scoring algorithm applied (adapted from (LOUIS ET AL., 2004)) makes use of the specification of decisive thresholds of delta (Δ) and theta (Θ) activity within the EEG signal, according to which the vigilance state is designated (FENZL ET AL., 2007). Based on RMS vectors of the above defined frequency bands, Δ and Θ traces were derived from

$$\Delta = \frac{\delta_{RMS}\,\alpha_{RMS}}{\eta_{RMS}\,\beta_{RMS}}\;;\;\Theta = \frac{\theta^2_{RMS}}{\delta_{RMS}\,\alpha_{RMS}}$$

Vigilance stages were classified as follows: (a) Epochs were indexed as WAKE if the EMG amplitude was above a manually set threshold (separating movement from no movement). (b) If the calculated delta-value was below a manually set threshold (separating high delta power from low delta power) and the calculated theta-value was above a manually set threshold (separating high theta power from low theta power), the epoch was defined as REMS. (c) If the calculated delta-value was below the threshold and the calculated theta-value also remained below the threshold, the epoch was defined as quiet wakefulness (QWAKE), except when (d) these epochs were followed by a REMS epoch, in which case these epochs were indexed as pre-REMS. The remaining epochs were indexed as NREMS. All epochs semi-automatically scored by this method were proof-read manually.

Extraction of REMS Episodes

The above described sleep scoring allowed for the generation of a scoring vector, by which corresponding REMS-epochs within the recorded signals from BLA and CA1 could be extracted. For each REMS episode, the number of REMS epochs forming this episode, and the corresponding circadian phase were stored. Moreover, the time spent in REMS, as well as the number and mean duration of REMS episodes was evaluated for each phase (as described in **CHAPTER 2, P.51**, and see **FIGURE 1D**). These parameters were normalized to the individual value obtained under **BASELINE** conditions and are shown as change to baseline (with 100% denoting baseline levels).

General Aspects

EEG signals were used for the definition of vigilance states only (see section **SLEEP SCORING**, **P.72 F.** above). EMG data was analyzed for its spectral composition (see section **POWER SPECTRAL DENSITY**, **P.75 F.** below). BLA and CA1 data were explored for all parameters listed below. In general, the basis for all further analysis was data collected within 4 s epochs (equivalent to 400 datapoints at a sampling frequency of 100 Hz). For each parameter, which was assessed as specified below, the following calculations were applied per animal: (1) 5 min exposure data were averaged over the respective 5 min (equivalent to 75 epochs). (2) For each REMS episode the median was applied to the respective REMS epochs it consisted of (i.e. over variable number of epochs). (3) REMS data were additionally analyzed when normalized to the individual baseline value (as percentage).

Definition of the Frequency Bands Theta 1 and Theta 2

The hypotheses of this study were based on observations by the group of H.-C. Pape who observed an increased synchronous activity between the amygdala and the hippocampus upon re-exposure of mice to the conditioned stimulus or conditioned context within the theta frequency range (SEIDENBECHER ET AL., 2003). The literature describes differentiation between two distinct theta bands occurring in the hippocampus, theta 1 (θ_1, 8-12 Hz) and theta 2 (θ_2, 4-8 Hz), based on both, their acetylcholine independency *vs.* dependency and their possible function regarding exploratory *vs.* fear-related behavior (**SEE CHAPTER 1, THETA OSCILLATIONS, P.28 FF.**). Theta 1 and theta 2 and their supposable functions have been described in rodents as well as in humans (BLAND, 1986; CORNWELL ET AL., 2012). Thus, we focused our analysis on these two frequency bands since first, amygdalar and hippocampal communication seems to be based on oscillations in this frequency range and second, the distinct functionality could help to disentangle fear-related from non fear-related brain activity processes.

Power Spectral Density

In order to examine the spectral composition of EMG, BLA and CA1, the discrete time signal (sampled with 100 Hz) was converted to the frequency domain using the Welch's method named after P.D. Welch (WELCH, 1967). In general, the Fourier Transformation (FT) describes a deterministic, continuous signal $s(t)$ as a continuum of sine waves having different amplitudes and phases:

$$S(\omega) = \int_{-\infty}^{\infty} s(t)e^{-i\omega t}dt = F\{s(t)\}$$

with the angular frequency $\omega = 2\pi f$ (where f is the temporal frequency), and the complex frequency domain presentation $S(\omega)$:

$$S(\omega) = |S(\omega)|e^{i\theta(\omega)}$$

$|S(\omega)|$, the absolute value of the complex number, represents the amplitude spectrum and $\theta(\omega)$ the phase spectrum (COHEN, 2006).
The square of the amplitude spectrum $|S(\omega)|^2$, termed power spectrum, describes the distribution of the signal's power on the frequency axis. It decomposes the content of the signal into different frequencies present and helps identify periodicities (COHEN, 2006).
For stochastic signals, such as brain activity measures, applying the FT would result in a sample *(stochastic)* function on the frequency axis as well (COHEN, 2006). However, applying the FT to the autocorrelation function of the stochastic signal (which itself is *deterministic*) is defined as the power spectral density (PSD), which similarly to the power spectrum "describes the density of power on the frequency axis" (COHEN, 2006), with no resulting phase spectrum:

$$S_{ss}(\omega) = F\{r_{ss}(\tau)\} = \int_{-\infty}^{\infty} r_{ss}(\tau)e^{-i\omega\tau}d\tau = PSD[s(t)]$$

with r_{ss} being the autocorrelation function.
For a *discrete* (sampled) signal $s(m)$, the Discrete Fourier Transformation (DFT), calculated most effectively (much faster) by means of the Fast Fourier Transformation (FFT), provides an estimate for the FT (COHEN, 2006):

$$S(k) = \sum_{m=0}^{N-1} s(m)e^{-ikm} = DFT\{s(m)\}$$

with N samples and a frequency resolution of $\Delta f = \frac{2\pi f_s}{N} = \frac{2\pi}{T}$ at a sampling frequency $f_s = \frac{\omega}{2\pi} = \frac{2\pi}{T_s}$, where T_s is the sampling interval and T the duration of the data window.

Welch's method is an approach to spectral density estimation for non-deterministic (stochastic) signals. Using the built-in *pwelch* function in MATLAB®, the data (4 s epoch) was divided into segments of an equal length of 200 datapoints (corresponding to 2s) overlapping by 100 datapoints. These segments were windowed by the use of a Hamming window to reduce spectral leakage. PSD was then calculated by applying the FFT to each of the windowed segments using a frequency resolution of 0.125 Hz and computing the square of the resulting amplitude spectrum. Last, the individual spectra were averaged.
In order to compare the PSD between different behavioral challenges or between individual REMS episodes, PSD was normalized to the average power of the entire duration of exposure or to the average power of the whole REMS episode respectively. The resulting PSD was plotted on a logarithmic scale against the frequency vector.
The average power of the signals over the frequency bands θ_1 and θ_2 was examined by integrating the PSD over the respective band using the trapezoidal method (function *trapz* in MATLAB®) per epoch. For the EMG, the average power was integrated over the frequencies from 3.5 to 10 Hz as deduced from observations described in the results part **THE EMG AS FREEZING DETECTOR, P.83 F.** below.

Spectral Coherence

In order to evaluate the relation between the BLA and the CA1 signals, the spectral coherence (also referred to as magnitude-squared coherence estimate) was calculated using the *mscohere* function in MATLAB®. Spectral coherence indicates how well a signal x corresponds to a signal y at each frequency (MATLAB® release 2011 documentation). It is a function of the PSD $S_{xx}(\omega)$ of x and $S_{yy}(\omega)$ of y and the cross power spectral density $S_{xy}(\omega)$ of x and y, estimated by the Welch's method:

$$C_{xy}(\omega) = \frac{|S_{xy}(\omega)|^2}{S_{xx}(\omega)S_{yy}(\omega)}$$

This quotient is a real number between 0 and 1 that measures the correlation between x and y at the frequency ω. The spectral coherence was calculated dividing each epoch of BLA and CA1 recordings into equal overlapping sections of 200 data points (corresponding to 2s) overlapping

by 100 data points, windowing the sections by a Hamming window and using a FFT with a frequency resolution of 0.125 Hz for the PSD estimates. The average coherence of BLA and CA1 within the frequency bands θ_1 and θ_2 were examined by integrating the spectral coherence over these bands using the trapezoidal method (function *trapz* in MATLAB®) per epoch.

Instantaneous Phase, Frequency, Amplitude, Time Lag and Phase Coherence

The Hilbert transformation (HT), named after the German mathematician David Hilbert, like the FFT is a linear operator, however unlike the FFT it expresses frequency as a rate of change in phase; frequency can thus vary with time (FREEMAN, 2007). Therefore it is useful for analyzing non-stationary signals by deriving the analytic representation of a signal. Whereas the FFT gives a high spectral resolution, HT provides a high temporal resolution. Using this transformation, amplitude and phase can be analyzed independently for a pre-defined frequency band over time.

The analytic signal derived by the HT

$$X(t) = x_r(t) + ix_i(t)$$

has a real part, x_r which is the original data, and an imaginary part, x_i which contains the Hilbert transform. The imaginary part is the original data phase-shifted by $\pi/2$ (90°). Sines are therefore transformed to cosines and vice versa (MATLAB® release 2011 documentation).

FIGURE 7 documents the process how instantaneous phase, frequency and time shift were derived from the HT. We aimed for these parameters during exposure challenges and REMS episodes, to investigate first, the prevailing phase and frequency within CA1 and BLA, and second, the frequency-based interaction between CA1 and BLA (time lag, phase coherence).

PANEL A shows the original signal from CA1 and BLA for a 16 s recording. The analytic signal was calculated from the filtered CA1 and BLA signal (in the example between 4-8 Hz; **PANEL B**, black curve) by applying the Hilbert transform. Imagining the transformation on a complex plane, the vector length at each time step (the absolute value of the HF) represents the instantaneous amplitude, i.e. the envelope of the original signal (**PANEL B**, red curve). The instantaneous phase, on the other hand, is the arctangent of the angle of the vector with respect to the real axis (function *atan2* in MATLAB®): a saw tooth curve ranging from $-\pi$ to π and flipping from π to $-\pi$ once each cycle (FREEMAN, 2007) (**PANEL C**). Since we wanted to

determine the predominant phase and frequency within each epoch, we chose to unwrap the analytic phase in 4 s steps (400 data points) by adding the number of cycles $* 2\pi$ to the arctangent function at each reset from π to $-\pi$ (FREEMAN, 2007). The resulting linear slope represents the unwrapped analytic phase for each epoch (**PANEL D**). The slope of the analytic phase (i.e. the time rate of change of the instantaneous phase) represents the instantaneous frequency at each time step. It was calculated as the derivative of the unwrapped instantaneous phase signal (function *diff* in MATLAB®) and converted into units Hz (**PANEL E**). Importantly, since the analytic phase shows spurious discontinuities, which are defined as phase slips and result from interferences between overlapping signals of various frequencies and amplitude modulations (FREEMAN, 2007), instantaneous frequencies outranging the filtered frequency band by +/- 1 Hz, were discarded as *NaN* values. For each epoch, the median instantaneous frequency was assessed.

The time lag between the signals from CA1 and BLA was estimated by the use of the calculated instantaneous frequencies. We assumed that at each discrete time step, the ratio between the instantaneous frequencies of CA1 and BLA gives information about the time lag between the two signals at this very certain point in time. We defined

$$timelag\ (\Delta t) = \frac{f_{inst}(BLA)}{f_{inst}(CA1)}\ \Delta t$$

with Δt as the time step of 10 ms at a sampling frequency of 100 Hz (**PANEL F**). For each epoch the median time lag was estimated by applying the median to the calculated time lags (10 ms steps) and multiplying it by 400 to incorporate the time development within one epoch (4 s equivalent to 400 10 ms steps).

Last, the phase coherence between BLA and CA1 was assessed by applying the coherence function on the instantaneous phases of CA1 and BLA (*mscohere* function in MATLAB®; settings as for **SPECTRAL COHERENCE, P.76** above).

The average phase coherence of BLA and CA1 within the frequency bands θ_1 and θ_2 was examined by integrating the mean of the spectral coherence over these bands using the trapezoidal method (function *trapz* in MATLAB®) per epoch.

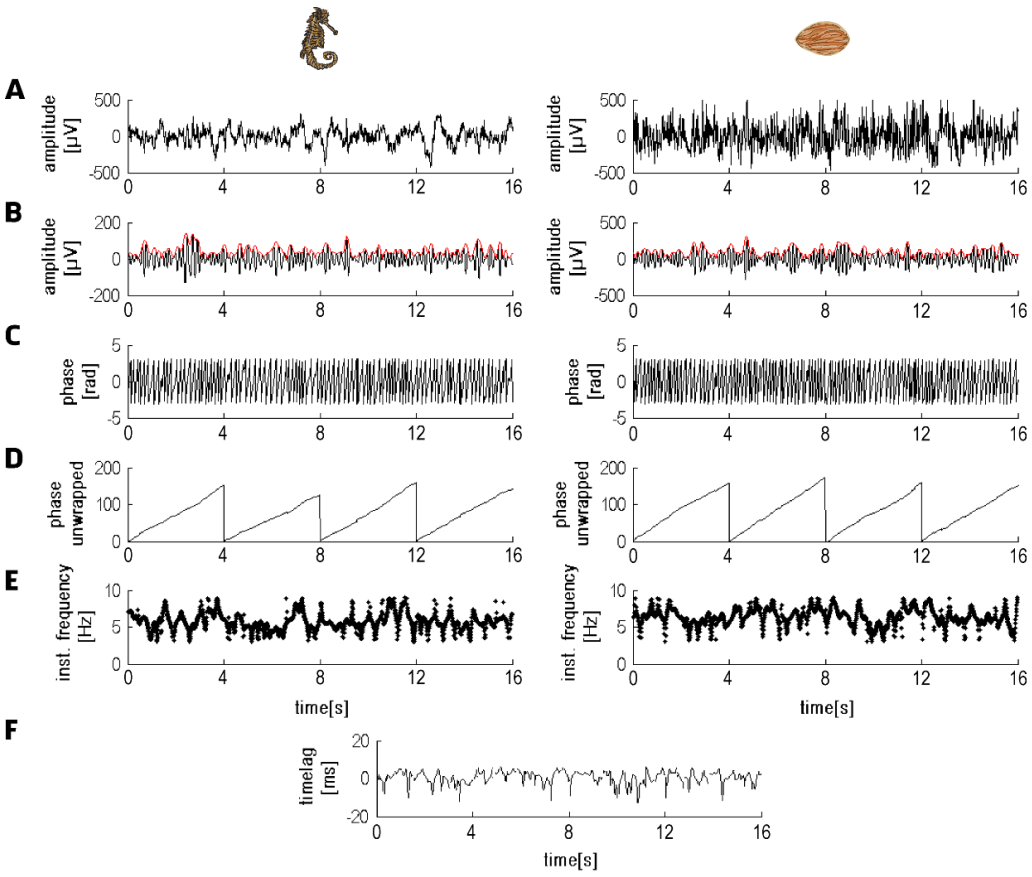

Figure 7 | Hilbert transformation, phase and time lag |

Illustration of the stepwise calculation of the analytic phase and time lag (for details see text). (**A**) Two exemplary original 16 s signals from the CA1 (left trace) and BLA (right trace) regions. (**B**) Black trace: filtered version of the original signal (between 4-8 Hz); red trace: instantaneous amplitude (envelope) of the filtered signal. (**C**) Instantaneous phase of the filtered signal. (**D**) Unwrapped instantaneous phase per 4 s epoch. (**E**) Instantaneous frequency. (**F**) Time lag (temporal offset) between the signals from BLA and CA1.

Z-Score Analysis

The z-score was used as a measure of change in fear-related parameters with regard to basal conditions. It describes how many standard deviations a certain observation (from one animal) varies from the group mean under a control condition. Z-scores were calculated on the basis of the integrated theta 2 power data from the BLA.

(I) All data from the behavioral exposure challenges was compared to the **NOVELTY** condition:

$$Z_{exposure} = \frac{observation\ (exposure) - mean_{group}(novelty)}{std_{group}(novelty)}$$

(II) All REMS episodes were compared to the **BASELINE** condition, whereupon the z-score for each REMS episode was calculated independently:

$$Z_{REMS} = \frac{observation\ (REMS\ episode) - mean_{group}(baseline)}{std_{group}(baseline)}$$

In a following step, based on observations detailed in the results section **Z-SCORE ANALYSIS** (**P.95 F.**), REMS episodes were categorized based on the obtained z-score Z_{REMS}. REMS episodes with a z-score value > 0.5, < 0.5 and in-between were scrutinized for their percental occurrence, mean duration and characteristics by means of BLA and CA1 signal coherence (see section **SPECTRAL COHERENCE, P.76 F.**), phase coherence and time lag (see section **INSTANTANEOUS PHASE, FREQUENCY, AMPLITUDE, TIME LAG AND PHASE COHERENCE, P.77 FF.**).

Data are presented as mean +/- SEM. The statistical significance level was set to $p < 0.05$ for all tests.

In general, effects of the group (shock *vs.* no shock or low responders *vs.* high responders *vs.* no shock respectively), the day (or testing condition) and group x day (or group x testing condition) interactions were assessed by analysis of variance (ANOVA) for repeated measures followed by a *post hoc* contrast test to detect significant group differences (Tukey) and within group differences between days or testing conditions (Tukey). P-values were adjusted to account for multiple comparisons. Additionally, we tested for differences in baseline REMS data by one-way ANOVA.

Associations between EMG power and freezing responses, as well as between EMG power/freezing responses and REMS parameters were tested by Pearson correlations.

For the behavioral challenges, only time points of **NOVELTY** (exposure to a novel context), contextual **FEAR MEMORY** (first 5 min of the extinction training in the shock context) and **FEAR EXTINCTION MEMORY** (re-exposure to the shock context after extinction training) but not **FEAR EXTINCTION** itself (last 5 min of the extinction training) was included into the statistical analysis, since it addresses a different scientific question (fear extinction in shocked *vs.* decreased alertness in non-shocked animals). Here, we rather focused on the investigation of acute fear parameters comparing groups of different fear phenotypes.

Due to poor EMG signals, two animals of the non-shocked group had to be excluded from the EMG analysis only. Sleep scoring in these animals was based on EEG signals only.

RESULTS

We conducted this experiment to test the following hypotheses: **(1)** A singular aversive event (electric foot shock), which has been shown to induce the development of a PTSD-like phenotype in mice (see **CHAPTER 2, P.43 FF.** and (POLTA ET AL., 2013)), results in activity changes within and between the limbic brain regions BLA and CA1. These fear-related activity changes can be observed when animals are re-introduced to the original shock context. **(2)** Similar activity patterns occur spontaneously (i.e. without being "triggered" by the exposure to the shock context) during REMS in the aftermath of the shock. **(3)** Spontaneously occurring fear-related activity patterns during REMS are associated with the strength of the fear behavior upon re-exposure to the shock context.

FEAR RESPONSES DURING DIFFERENT EXPOSURE CHALLENGES REVEAL SUBGROUPS OF HIGH AND LOW RESPONDERS

Freezing Responses

Since we intended to compare amygdalar and hippocampal activity during states of fear with states of novelty-induced arousal and states of no fear or rather decreased arousal, in a first step we assessed the freezing behavior in a novel and the shock context, respectively (**FIGURE 8A**). The freezing response was significantly affected by the shock *[F(1,14) = 24.53, p < 0.001]*, depending on the testing condition *[F(2,28) = 16.04, p < 0.001]*. Before the shock, both groups displayed similar levels of freezing in a novel environment *[**NOVELTY**; shocked vs. non-shocked: F(1,15) = 0.32, p > 0.05]*. However, after exposure to the shock, mice showed an increased fear response when being re-introduced to the shock context 3 days later (**FEAR MEMORY**), as compared to non-shocked controls *[shocked vs. non-shocked: F(1,15 = 6.68, p < 0.001]* and to freezing levels in the novel context *[novelty vs. fear memory: F(1,9) = 14.51, p < 0.001]*. Extinction training of shocked mice in the shock context (30 min), resulted in decreased freezing levels during retrieval testing the next day *[**EXTINCTION MEMORY**; fear memory vs. extinction memory: F(1,9) = 5.68, p < 0.01]*. However, as compared to non-shocked animals and to the **NOVELTY** condition, the fear response remained elevated *[shocked vs. non-shocked: F(1,15 = 4.24, p < 0.001; novelty vs. extinction memory: F(1,9) = 8.83, p < 0.001]*. In contrast, no significant changes in the freezing response were

observed in the control group when comparing the three exposure challenges.

Taken together, in line with our assumption, shocked animals displayed increased fear-related behavior upon **FEAR MEMORY** testing in the shock context. Also, fear extinction attenuated the fear response as assessed during retrieval of the **EXTINCTION MEMORY**.
During the last 5 min of the extinction training (**FEAR EXTINCTION**), non-shocked animals showed an unexpected increase in their freezing response, in contrast to low freezing levels during all other conditions. Evaluation of video recordings makes it very difficult to distinguish between immobility due to fearful freezing and immobility due to plain inactivity in mice. Since control mice, without a shock experience, showed low levels of freezing in general, we suspected that the animals simply stopped exploring the context after having been in the same environment for 25 min, and this was manually erroneously scored as freezing response (KÄFER, 2013). We therefore, in a next step, analyzed the EMG signal and its capacity to serve as a more precise fearful freezing detector, assuming that voluntary immobility and fear-related freezing would be distinguished by different muscle tone.

The EMG as Freezing Detector

By assessing the PSD estimate of the EMG signal for the **FEAR MEMORY** test condition (**FIGURE 8B**), we identified a frequency window between 3.5 and 10 Hz, which showed obvious differences in power between shocked and non-shocked mice and was significantly correlated with the freezing response of the animals *($r^2 = 0.63$, $p < 0.001$)*. As shown in **FIGURE 8D**, two subgroups of the shocked animals could be identified by means of $EMG_{3.5\text{-}10\ Hz}$ power and freezing responses, which are from now on referred to as high responders and low responders. Importantly, when $EMG_{3.5\text{-}10\ Hz}$ power was calculated for all the conditions for the three groups (**FIGURE 8C**), in contrast to the freezing behavior (**FIGURE 8E**), non-shocked animals did not show an increase in the last 5 min of the exposure (**FEAR EXTINCTION**). Nevertheless, an effect of the group on both freezing *[$F(2,13) = 41.78$, $p < 0.001$]* and $EMG_{3.5\text{-}10\ Hz}$ power *[$F(2,11) = 25.28$, $p < 0.001$]* was apparent, dependent on the testing condition *[freezing, group x condition: $F(4,26) = 11.58$, $p < 0.001$]*. This effect was only marginally significant for $EMG_{3.5\text{-}10\ Hz}$ power *[group x condition: $F(4,22) = 2.59$, $p = 0.06$]*, probably due to low statistical power, since 2 animals had to be excluded from EMG analysis (see paragraph **STATISTICS, P.81**). High responders showed a significantly increased freezing response compared to low responders and

non-shocked animals during testing of **FEAR MEMORY** *[low responders vs. high responders: $F(1,9) = 5.55$, $p < 0.01$; non-shocked vs. high responders: $F(1,11) = 13.54$, $p < 0.001$]* and **FEAR EXTINCTION MEMORY** *[low responders vs. high responders: $F(1,9) = 5.82$, $p < 0.001$; non-shocked vs. high responders: $F(1,11) = 9.63$, $p < 0.001$;* **FIGURE 8E***]*. Accordingly, $EMG_{3.5\text{-}10\ Hz}$ power was significantly elevated in the high responders for the conditions **FEAR MEMORY** *[low responders vs. high responders: $F(1,9) = 8.20$, $p < 0.001$; non-shocked vs. high responders: $F(1,11) = 7.67$, $p < 0.001$]* and **FEAR EXTINCTION MEMORY** *[low responders vs. high responders: $F(1,9) = 4.84$, $p < 0.01$; non-shocked vs. high responders: $F(1,11) = 4.53$, $p < 0.01$;* **FIGURE 8C***]*. Within group comparison revealed the increase for **FEAR MEMORY** to be significant, as compared to the **NOVELTY** condition *[freezing: $F(1,5) = 14.41$, $p < 0.001$; $EMG_{3.5\text{-}10\ Hz}$ power: $F(1,5) = 5.08$, $p < 0.01$]* and the **FEAR EXTINCTION MEMORY** *[freezing: $F(1,5) = 4.70$, $p < 0.01$; $EMG_{3.5\text{-}10\ Hz}$ power: $F(1,5) = 4.16$, $p < 0.05$]*, indicating that the fear extinction procedure resulted in a decreased fear response in the high responders.

Together, these results allow the conclusion that the EMG signal can be used as a detector of fearful freezing in mice upon recall of a conditioned fear memory in the conditioning context (KÄFER, 2013). Furthermore, all following analyses were performed within the three above described groups of low responders, high responders and non-shocked mice, which were defined on the basis of the EMG measures. The amount of expressed fear behavior was highly scattered among the shocked animals, thus resulting in the formation of two subgroups. Therefore, in order to be considered as indicative of fear, changes in limbic brain activity should display similar subgroup variations.

ABSENCE OF POST-SHOCK REMS VARIATIONS AND PRE- OR POST-SHOCK FREEZING RELATED REMS CHARACTERISTICS

We have observed that animals which were exposed to an aversive event (electrical foot shock) developed an early onset, yet long-lasting increase in REMS amount ((POLTA ET AL., 2013); see **CHAPTER 2 SYMPTOMATIC VALUE OF REMS, P.58**). Although in this experiment we did not test for the late time point (2 months after the shock), we analyzed REMS variations in the early aftermath of the shock (on the **SHOCK DAY** and **1 DAY LATER**) during the inactive phases of the mice (**PHASE III** and **IV**) as compared to basal measures (**FIGURE 9**). The group (low responder *vs.* high responder *vs.* non-shocked) had no effect on the

amount of time mice spent in REMS *[phase III: $F(2,13) = 1.73$, $p = 0.22$; phase IV: $F(2,13) = 1.35$, $p = 0.29$]*, neither did the number of entered REMS episodes *[phase III: $F(2,13) = 2.23$, $p = 0.15$; phase IV: $F(2,13) = 1.55$, $p = 0.25$]*, nor the mean duration of REMS episodes *[phase III: $F(2,13) = 0.29$, $p = 0.75$; phase IV: $F(2,13) = 0.84$, $p = 0.45$]*, also not dependent on the day *[group x day interaction; $p > 0.05$]*.

From these results, the conclusion can be drawn that high responders, low responders and non-shocked animals displayed a similar level of presence and composition of REMS after the exposure to the shock or the control exposure to the mere chamber, respectively. However, baseline characteristics of REMS had been shown to be related to the development of an exaggerated startle response 1 month after the shock in the previous study ((POLTA ET AL., 2013); see **CHAPTER 2 PROGNOSTIC VALUE OF REMS, P.62**). Although startle measures have not been obtained in the current experiment, we tested for a possible association between fear behavior displayed in the **FEAR MEMORY** testing condition (re-exposure to the shock context) and REMS properties in the shocked animals. For this purpose we performed correlation analyses between REMS data collected before (**BASELINE**) or after the shock (**MEMORY CONSOLIDATION** phase) and the freezing behavior or EMG activity (power within the 3.5- 10 Hz frequency band) evaluated during the **FEAR MEMORY** test (**FIGURE 10**). In basal and post-shock REMS recordings, neither the number of REMS episodes (**FIGURE 10A, B**), nor percental amounts of REMS (**FIGURE 10C, D**) or the mean duration of REMS episodes (**FIGURE 10E, F**) revealed to be significantly correlated with freezing *($r^2 < 0.08$, $p > 0.45$)* or $EMG_{3.5\text{-}10\ Hz}$ power levels *($r^2 < 0.30$, $p > 0.10$)*.

This leads to the interpretation that both, basal and REMS characteristics during the memory consolidation phase, were not indicative of the strength of the fear response expressed towards the environment in which the aversive experience has taken place. This implies that the amount and continuity of REMS before or immediately after the shock failed to predict how strong the memory of the shock experience was consolidated.

Nevertheless, animals exposed to the shock expressed distinct fear levels when being re-introduced to the shock chamber, leading to their subdivision into high and low responders; that is, high and low responders apparently did process the shock experience in somewhat different modes. Although mice showed equal quantitative REMS characteristics after the shock, we were interested in whether qualitative aspects of REMS differed between mice with and without the shock experience, and accordingly, between those which developed a strong fear memory and such showing only a weak fear response towards the shock chamber. Therefore, spectral composition of BLA and CA1 signals during REMS episodes and, as a control for fear-relatedness, during the different context exposure challenges, was obtained.

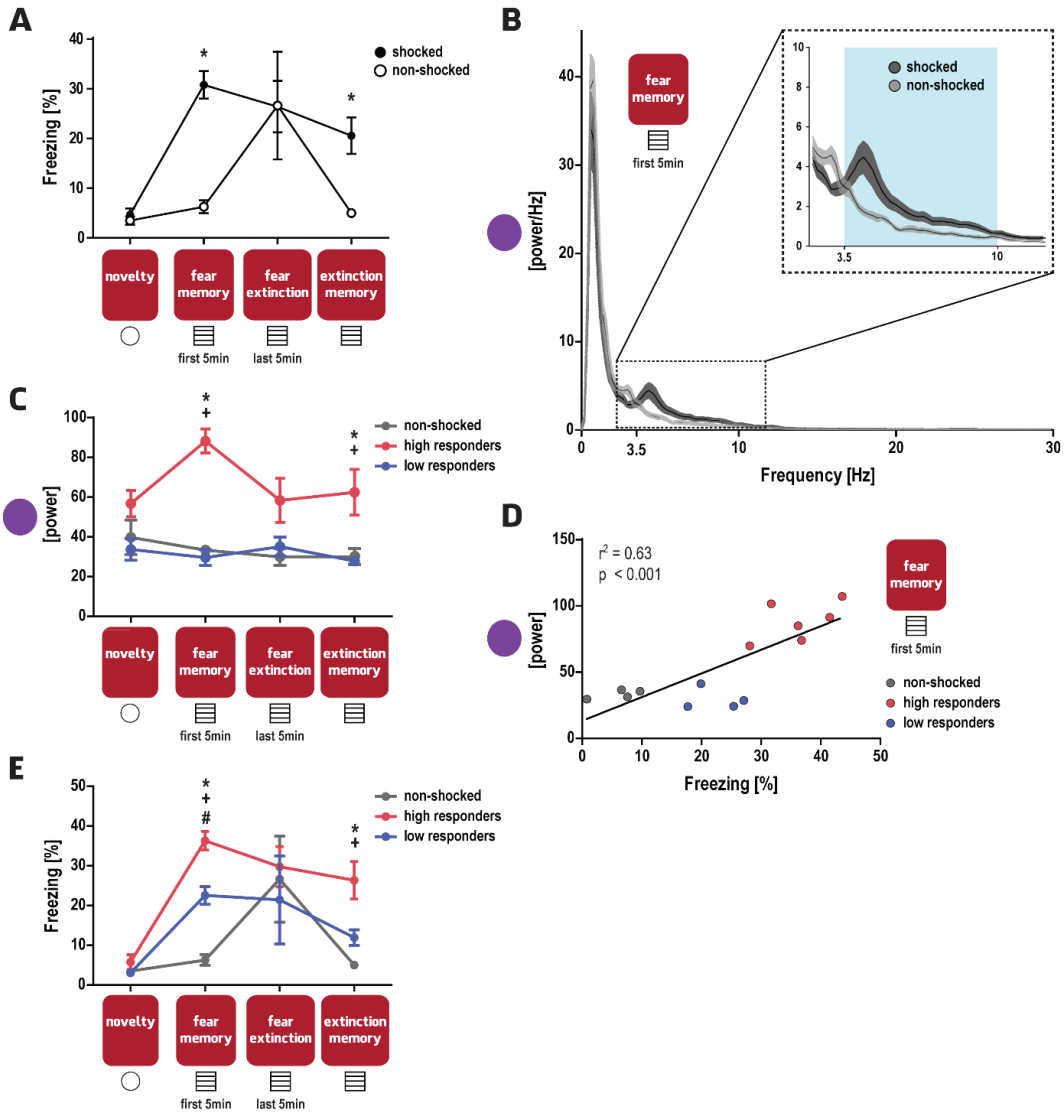

Figure 8 | The EMG as a Freezing Detector Reveals Subgroups of High Responders and Low Responders |

Freezing behavior (percentage, **A, E**) and EMG activity (integrated power 3.5-10 Hz, **C**) measured during the different exposure challenges presented as group mean +/- SEM. *p < 0.05 indicates a statistically significant difference between shocked (black) and non-shocked animals (white), or between high (red) and low responders (blue), respectively (2-way ANOVA). +p < 0.05 indicates a statistically significant difference between high responders (red) and non-shocked (gray) mice (2-way ANOVA). #p < 0.05 indicates a statistically significant difference between low (blue) responders and non-shocked (gray) mice (2-way ANOVA). (**B**) PSD of the EMG signal between 0-30 Hz comparing shocked (dark gray) vs. non-shocked (light gray) mice; group mean +/- SEM; insert: magnification of the frequency window between 3.5-10 Hz. (**D**) Correlation between freezing behavior and EMG activity (integrated power 3.5-10 Hz). r^2: correlation coefficient as obtained from linear regression analysis (Pearson correlation). See also (KÄFER, 2013).

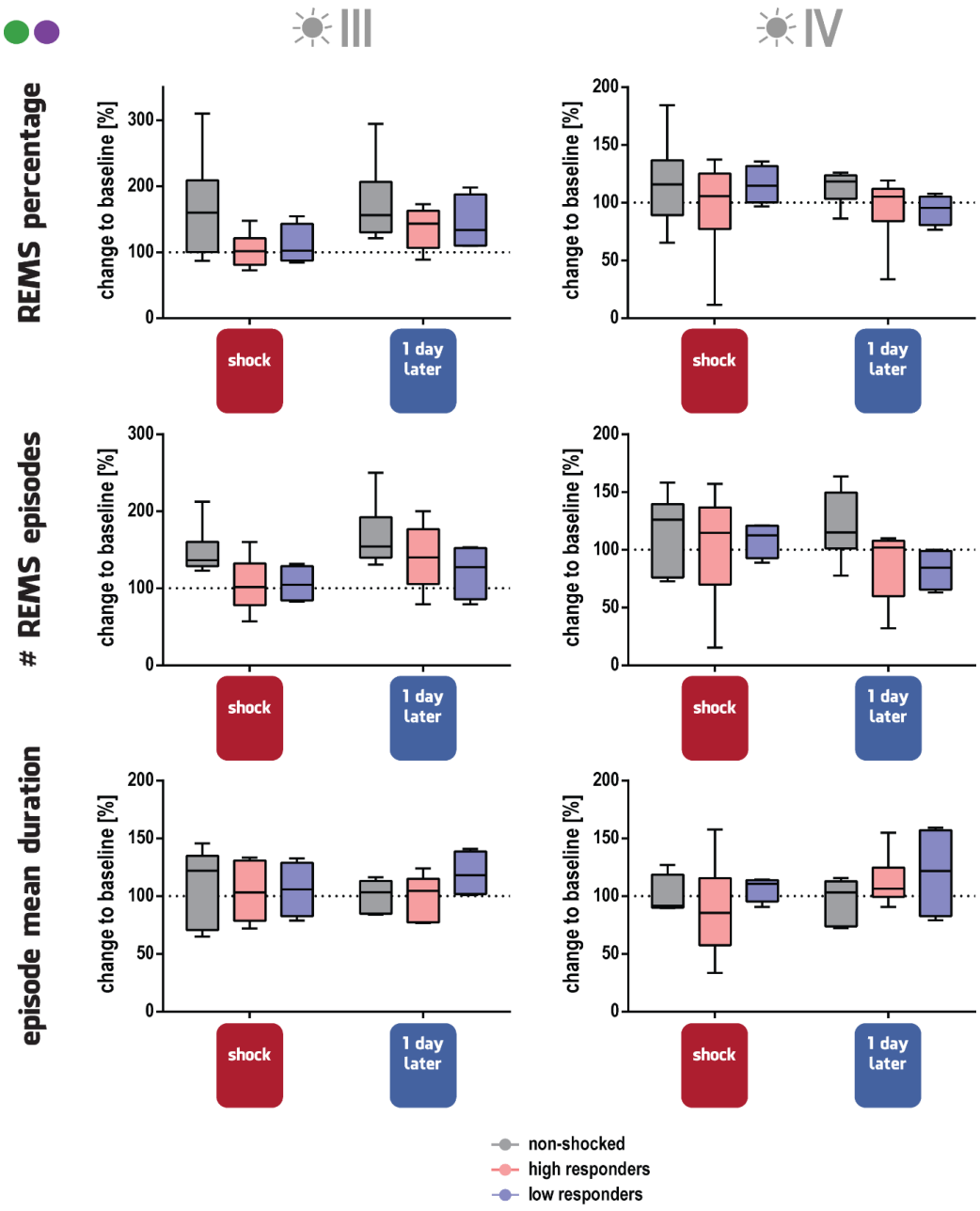

Figure 9 | No Post Shock REMS Variations in High and Low Responders |
Changes (%) in time (upper row), number of episodes (middle row) and mean duration of episodes (lower row) spent in REMS during the inactive circadian phases, relative to the group mean under baseline conditions (dotted horizontal line). Data are presented as box and whisker plots with boxes showing lower quartile, median and upper quartile, and whiskers showing the minimum and maximum of the sample. Gray: non-shocked mice, red: high responders, blue: low responders.

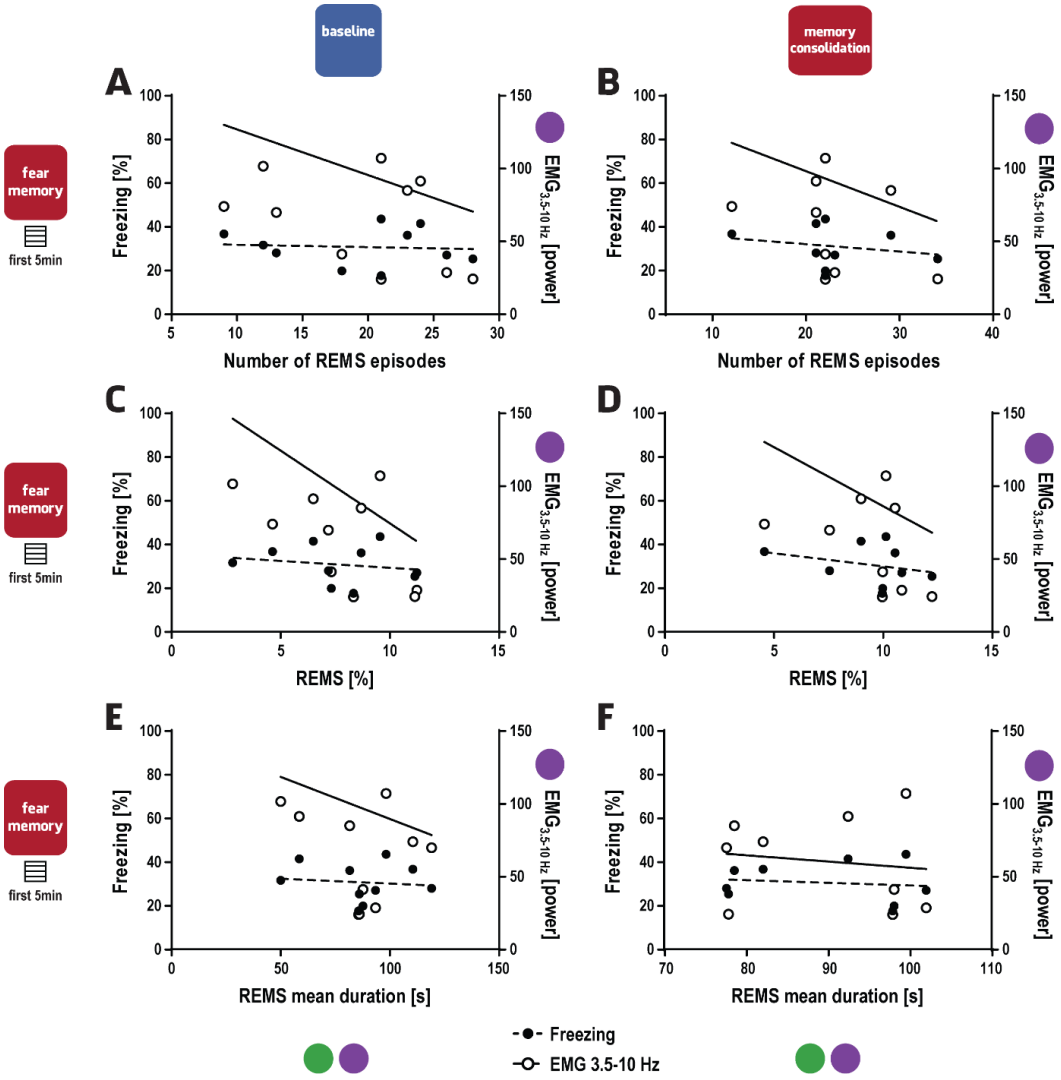

Figure 10 | Lack of Association between Freezing Behavior and Basal or Early Post Shock REMS Architecture |

Correlation between REMS characteristics under **BASELINE** conditions or early after the shock during the **MEMORY CONSOLIDATION** phase and the freezing behavior (black circles) or the EMG activity (3.5-10 Hz; white circles) during testing of the fear memory in the shock context. (A, B) number of REMS episodes; (C, D) percentage of REMS; (E, F) mean REMS episode duration.

SIMILAR AMYGDALAR AND HIPPOCAMPAL ACTIVITY CHANGES DURING EXPOSURE CHALLENGES AND REMS AFTER THE SHOCK

We calculated the PSD of BLA and CA1 signals to estimate how strong theta frequencies were represented in the field potential activities of the two structures.

Amygdalar and Hippocampal Power during the Exposure Challenges

Inspection of the resulting spectral plots revealed obvious differences in amygdalar (**FIGURE 11A, B**) and hippocampal (**FIGURE 11D, E**) power between groups when mice were exposed to a novel context or to the shock chamber. Especially, high responders showed an increased activation within the theta frequency range and beyond. Integration of theta 2 and theta 1 power for all conditions, statistically confirmed this observation (**FIGURE 11C, F**). Theta 2 and theta 1 power were significantly affected by the group in BLA *[θ_2: F(2,13) = 24.62, p < 0.001; θ_1: F(2,13) = 21.35, p < 0.001]* and CA1 *[θ_2: F(2,13) = 5.70, p < 0.05; θ_1: F(2,13) = 8.17, p < 0.01]*, however independent of the condition *(condition x group: p > 0.17)*. During **FEAR MEMORY** testing, high responders expressed significantly elevated theta 2 power in the BLA. This effect was observed in comparison to low responding animals *[F(1,9) = 7.08, p < 0.001]* and to non-shocked controls *[F(1,11) = 5.19, p < 0.01]*. Also, amygdalar theta 2 power remained significantly elevated in the high responder group during **FEAR EXTINCTION MEMORY** testing when compared to low responding mice *[F(1,9) = 4.01, p < 0.05]* and by trend compared to non-shocked mice *[F(1,11) = 3.43, p = 0.05]*. Similar findings were documented for amygdalar theta 1 power *[high responders vs. low responders: F(1,9) > 5.85, p < 0.001; high responders vs. non-shocked: F(1,11) > 5.52, p < 0.01]* and hippocampal theta 2 *[high responders vs. low responders: F(1,9) > 3.67, p < 0.05]* and theta 1 power *[high responders vs. low responders: F(1,9) > 4.38, p < 0.01; high responders vs. non-shocked: F(1,11) > 3.99, p < 0.05]*. However, here group differences were already present for the **NOVELTY** condition *[high responders vs. low responders; CA1 θ_2: F(1,9) = 2.98, p = 0.10; CA1 θ_1: F(1,9) = 5.33, p < 0.01; BLA θ_1: F(1,9) = 7.61, p < 0.001; high responders vs. non-shocked: CA1 θ_1: F(1,11) = 4.13, p < 0.05; BLA θ_1: F(1,11) = 6.78, p < 0.001]*.

Taken together, except for theta 2 power in the amygdala, higher theta power (1 and 2) was measured in the high responding animals already pre shock, upon mere exposure to a novel environment.

In summary, all behavioral challenges resulted in distinct amygdalar and hippocampal theta activation between groups. Theta 2 power in the amygdala, however, increased upon **FEAR MEMORY** testing only in those animals which also displayed a pronounced fear behavior, whereas other group differences presented already before the shock in the **NOVELTY** testing condition.

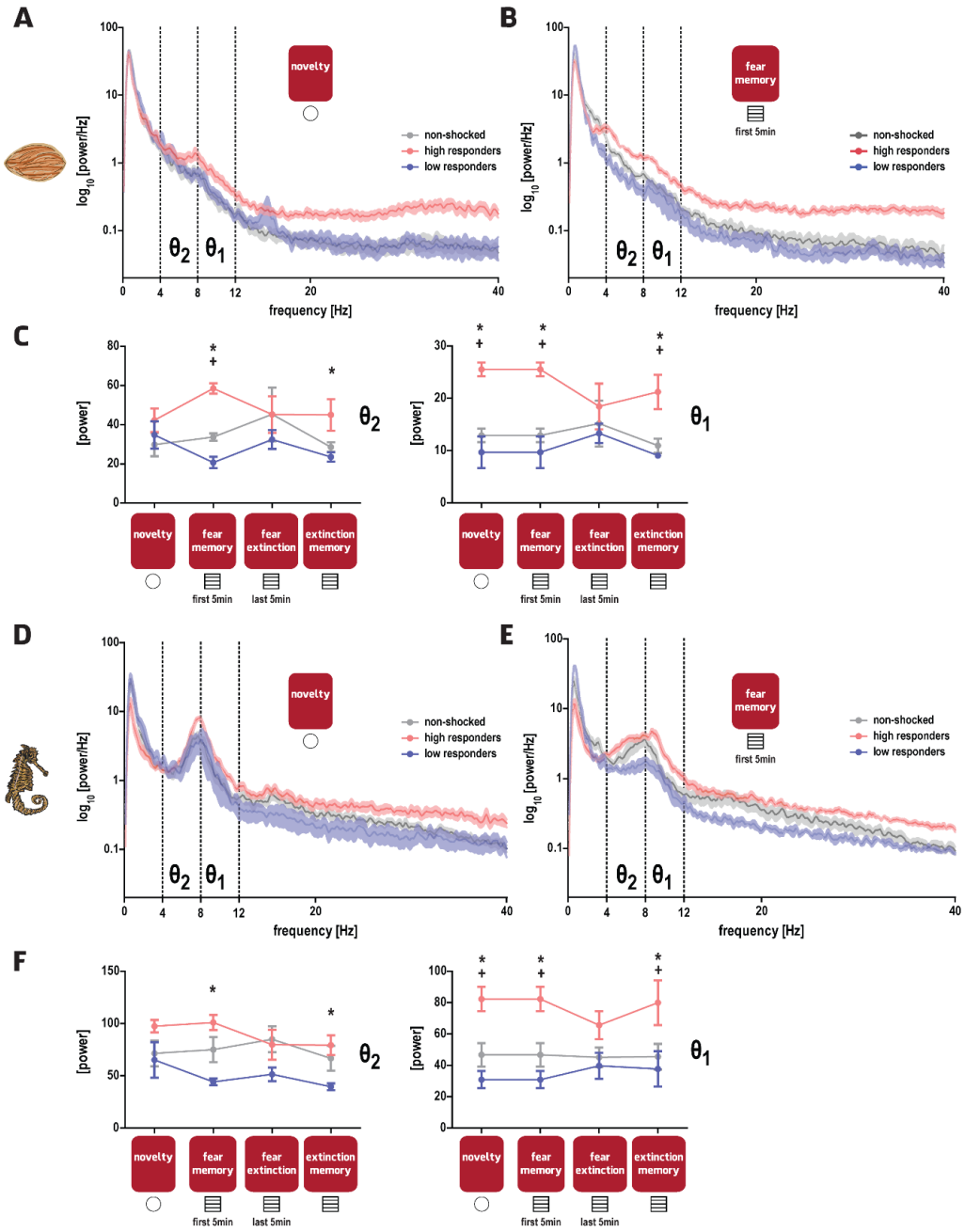

Figure 11 | Hippocampal and Amygdalar Activity during Exposure Challenges |

PSD in BLA (**A-C**) and CA1 (**D-F**) during the different exposure challenges. (**A, D**) Power-frequency plot of activity during exposure to a novel context (line: mean, range: SEM). (**B, E**) Power-frequency plot of activity during the first 5 minutes of the re-exposure to the shock context (line: mean, range: SEM). (**C, F**) Integrated power within the theta 2 and theta 1 frequency bands. All data are presented as group mean +/- SEM. Red: high responders; blue: low responders; gray: non-shocked animals. *p < 0.05 indicates a statistically significant difference between high (red) and low (blue) responders (2-way ANOVA). +p < 0.05 denotes a statistically significant difference between high responders (red) and non-shocked (gray) mice (2-way ANOVA).

Amygdalar and Hippocampal Power during REMS

Next, we evaluated whether similar BLA and CA1 activity could be observed during REMS. We calculated the estimate of PSD over all REMS episodes measured before the shock, i.e. during **BASELINE** recordings, in the 24 hours after the shock, i.e. during the **MEMORY CONSOLIDATION** period, and 1 day after the shock, when a new experience is assumed to be already consolidated into a **STABLE MEMORY**. In the interpretation of the results, one should keep in mind that this is a very approximate approach, since all REMS episodes were taken into account independently of their duration, circadian phase or other characteristics.

The spectral plots shown in **FIGURE 12** demonstrate that, although under **BASELINE** conditions groups seemed to have similar spectral distribution of power of BLA (**A**) and CA1 (**B**) within the theta frequency range, subtle to pronounced power changes compared to basal levels were present in all groups during the **MEMORY CONSOLIDATION** phase (BLA: **C**, CA1: **D**) and when a **STABLE MEMORY** had been formed (BLA: **E**, CA1: **F**). Particularly, statistical analysis of the integrated theta power revealed no **BASELINE** differences for theta 2 in the amygdala (**G**) *[F(2,13) = 2.21, p > 0.05]* and the hippocampus (**H**) *[F(2,13) = 1.95, p > 0.05]*, and for theta 1 in the amygdala (**I**) *[F(2,13) = 0.07, p > 0.05]*. However, high responders showed significantly greater basal theta 1 power in the hippocampus (**J**) *[F(2,13) = 9.14, p < 0.01]* as compared to non-shocked animals *[F(1,11) = 5.73, p < 0.01]* and to low responders *[F(1,11) = 4.28, p < 0.05]*. Power changes on the two days after the shock were significantly affected by the group factor for theta 2 frequencies in the CA1 region *[F(2,13) = 4.35, p < 0.05]* and by trend for theta 2 *[F(2,13) = 2.76, p = 0.10]* and theta 1 *[F(2,13) = 3.40, p = 0.06]* frequencies in the amygdala. Only for theta 2 activity in the BLA, a significant group effect was observed depending on the development over the days *[F(4,26) = 2.75, p < 0.05]*. Within both brain regions, increased theta 2 power was observed in the high responding animals during the **MEMORY CONSOLIDATION** phase as compared to low responders *[CA1: F(1,9) = 3.59, p < 0.05; BLA: F(1,9) = 3.47, p = 0.05]* (**G, H**). Non-shocked animals also displayed an increased theta 2 power but the difference to low responders was only detectable by trend *[CA1: F(1,9) = 2.97, p = 0.11; BLA: F(1,9) = 3.27, p = 0.07]*. In contrast, low responders showed a trend towards decreased theta 1 power in the amygdala compared to controls *[F(1,9) = 3.25, p = 0.07]*. Also within group comparisons revealed that whereas theta 2 power in the BLA increased after the shock in high responders *[F(1,5) = 3.73, p < 0.05]* and non-shocked animals *[F(1,5) = 4.00, p < 0.05]*, low responders showed no change to **BASELINE** measures *(p > 0.34)*. After the formation of a **STABLE MEMORY**, the difference in theta 2 power between high responders and

low responders was preserved in the hippocampus only *[F(1,11) = 3.59, p < 0.05]*.

In conclusion, amygdalar and hippocampal activity within the theta frequencies during REMS changed differentially in the three groups after the shock / no shock (novelty) experience. In comparison to theta power during wakefulness, i.e. during re-exposure to the shock context, high responding mice displayed a similar increase of amygdalar theta 2 power during REMS after the shock. However, contrary to the fear memory testing situation, this difference appeared to be significant in comparison to low responding animals only, whereas non-shocked animals showed a similar power level. In other terms, limbic activity during REMS after the shock developed differently specifically in those mice which formed a poor contextual fear memory (i.e. the low responders). In contrast, non-shocked animals and mice with a strong contextual fear memory (i.e. high responders) displayed a similar power development during REMS after the novelty *vs.* shock experience.

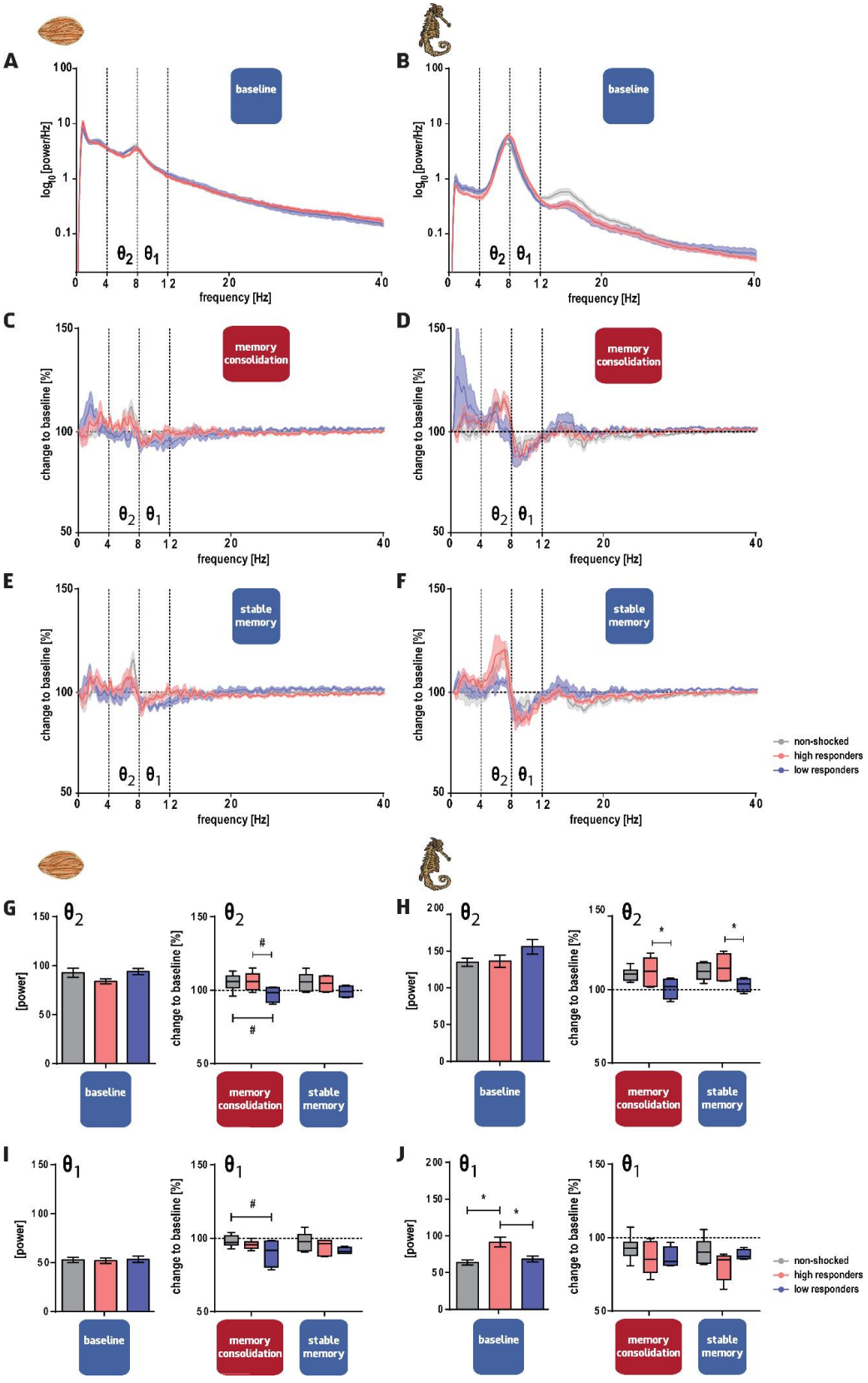
A
B
baseline
log10 [power/Hz]
frequency [Hz]
θ2 θ1
C
D
memory consolidation
change to baseline [%]
E
F
stable memory
non-shocked
high responders
low responders
G
H
θ2
[power]
change to baseline [%]
baseline
memory consolidation
stable memory
I
J
θ1

Figure 12 | Hippocampal and Amygdalar Activity during REMS |
PSD in BLA (A, C, E, G, I) and CA1 (B, D, F, H, J) during the different exposure challenges. (A, B) Power-frequency plot of activity during **BASELINE** REMS (line: mean, range: SEM). (C, D) Power-frequency plot of activity during REMS in the 24 hours **MEMORY CONSOLIDATION** phase after the shock (line: mean, range: SEM). (E, F) Power-frequency plot of activity during REMS 1 day after the shock when a **STABLE MEMORY** had been formed (line: mean, range: SEM). (G-J) Integrated power within the theta 2 (G, H) and theta 1 (I, J) frequency bands. **BASELINE** data are presented as group mean +/- SEM. Data of the **MEMORY CONSOLIDATION** and the **STABLE MEMORY** phase are presented as box and whisker plots with boxes showing lower quartile, median and upper quartile, and whiskers showing the minimum and maximum of the sample. Red: high responders; blue: low responders; gray: non-shocked animals. *p < 0.05 indicating a statistically significant difference between groups (2-way ANOVA); # 0.1 > p > 0.05 indicating a statistical trend between groups (2-way ANOVA).

Z-SCORE ANALYSIS

Since the findings described above revealed amygdalar theta 2 power to be influenced by the shock experience during both, awake re-exposure to the shock context (**FIGURE 11**) and REMS after the shock (**FIGURE 12**), we calculated the z-score for this parameter with respect to the control conditions **NOVELTY** exposure and **BASELINE** REMS. The advantages of this analysis comprise, (i) the normalization to the control condition, i.e. basal group differences can be accounted for; (ii) the possibility to classify REMS episodes by the resulting z-score value in order to permit consideration of the high variability of REMS episodes. So far, all REMS episodes had been merged independently of their duration, circadian phase or other characteristics.

The z-score describes, by how many standard deviations the measure (i.e. amygdalar theta 2 power of one animal) differs from the group mean under the control condition. In the case of the exposure challenges it states the change compared to the **NOVELTY** exposure, in case of the REMS data it depicts the change compared to **BASELINE** REMS. Interestingly, the resulting z-scores for exposure challenges and REMS displayed equal directions and similar developments comparing the three groups of animals (**FIGURE 13A**).

A significant effect of the group was observed for the exposure challenges *[$F(2,13) = 9.20$, $p < 0.01$]*. High responders showed a significantly increased positive z-score in the **FEAR MEMORY** condition as compared to low responders which displayed a z-score below 0 *[low responders vs. high responders: $F(1,9) = 5.78$, $p < 0.001$]*. That is, theta 2 power in the BLA was elevated compared to the **NOVELTY** condition in high responders, and accordingly reduced compared

to the **NOVELTY** exposure in the low responding group (as can also be seen in **FIGURE 11C**). In non-shocked animals, an increased z-score could be documented as well *[non-shocked vs. low responders: $F(1,9) = 3.48$, $p < 0.05$]*, however it was less pronounced than in high responders, but not significantly different *[non-shocked vs. high responders: $F(1,11) = 2.57$, $p = 0.18$]*. No significant differences between groups were detected for all other exposure challenges.

Similarly, during REMS after the shock, high responders and non-shocked mice showed a positive, whereas low responders displayed a negative variation from the group mean under **BASELINE** conditions. Although the group factor did not have a statistically significant effect *per se* *[$F(2,13) = 0.54$, $p = 0.60$]*, the z-score was significantly affected by the group x day interaction *[$F(4,26) = 3.13$, $p < 0.05$]*. Group differences after the shock did not appear as statistically significant *[high responders vs. low responders: $F(1,9) = 2.5$, $p = 0.19$]*; however high responders showed a significantly increased z-score compared to the group **BASELINE** measure during the **MEMORY CONSOLIDATION** phase *[$F(1,5) = 4.57$, $p < 0.01$]* and by trend after a **STABLE MEMORY** had been formed *[$F(1,5) = 3.27$, $p = 0.07$]*.

Taken together, the directionality of change compared to the control condition (z-score below/above 0) was different in low and high responders. Whereas theta 2 power upon re-exposure to the shock context was increased by at least 0.5 standard deviations in all high responding mice, in low responders it was decreased by at least 0.5 standard deviations. Also, although no correlation was observed between z-scores (*$r^2 < 0.06$, $p > 0.48$)*, the same observations of directionality of change could be made for theta 2 power in REMS after the shock. As the z-score was also significantly correlated with the fear behavior mice displayed in the shock context (**FIGURE 13B**) *(freezing: $r^2 = 0.71$, $p < 0.01$; $EMG_{3.5\text{-}10\ Hz}$: $r^2 = 0.94$, $p < 0.001$)* and, therefore, associated with a fearful behavioral state, we decided to use it as an attribute for the classification of REMS episodes.

CHARACTERISTICS OF SELECTED "FEAR" REMS EPISODES

We assigned all REMS episodes to one of the following three categories: (i) episodes with a z-score higher than 0.5, (ii) episodes with a z-score lower than -0.5 and (iii) episodes with a z-score different from the previous, i.e. between -0.5 and 0.5. The mean percental distribution of REMS episodes within these categories is depicted in **FIGURE 13C**. Independently of the group, the different REMS episode types were unequally distributed across the time course, although being statistically significant only for the **MEMORY CONSOLIDATION** phase

[group x episode type: F(4,26) = 0.61, p = 0.66; episode type: F(2,26) = 3.43, p < 0.05] and after a **STABLE MEMORY** had been formed *[group x episode type: F(4,26) = 0.93, p = 0.46; episode type: F(2,26) = 4.54, p < 0.05]* and by strong trend for the **BASELINE** day *[group x episode type: F(4,26) = 0.23, p = 0.92; episode type: F(2,26) = 3.36, p = 0.05]*. However, compared to basal conditions, high responders and non-shocked mice, but not low responders, had more episodes with a z-score > 0.5 on the shock day *[**MEMORY CONSOLIDATION**; non-shocked: F(1,5) = 2.97, p < 0.05; high responders: F(1,5) = 4.01, p < 0.05; low responders: F(1,3) = 1.34, p = 0.62]* as well as one day later *[**STABLE MEMORY**; non shocked: F(1,5) = 2.84, p < 0.01; high responders: F(1,5) = 3.66, p < 0.05; low responders: F(1,3) = 0.14, p = 1.00]*. In the high responding group, this increase clearly appeared at the expense of episodes with a z-score < -0.5 *[memory consolidation: F(1,5) = 4.01, p < 0.05; stable memory: F(1,5) = 3.66, p < 0.05]*. Non-shocked animals displayed a substitutional non-significant reduction of both, z-score episodes < -0.5 *[F(1,5) < 2.97, p > 0.11]* and episodes in the category "others" *[F(1,5) < 1.67, p > 0.47]*.

In summary, mice which experienced the same aversive event split up into subgroups with distinctive strength of fear behavior towards re-exposure to the shock context. After the shock, the same subgroups also varied with regard to the proportion of time spent in distinct REMS episodes, as classified by their divergence in amygdalar theta 2 power.
Surprisingly, like the high responders, non-shocked controls spent more of their REMS time in episodes with a higher amygdalar theta 2 power. However, non-shocked mice had also not been left undisturbed in their home cages but experienced the exposure to a novel environment. Thus, we asked whether the increase in REMS episodes, as characterized by a high BLA theta 2 power could be associated with the process of memory consolidation in general or whether these particular REMS episodes differ in other aspects between the groups. To this end, we analyzed the three REMS episode types for additional features and compared them between experimental groups. Besides the spectral power in BLA and CA1, we scrutinized the length of episodes and coherence, phase coherence and time lag between signals of the limbic structures. First, we analyzed these parameters comparing the three episode types ($REMS_{>0.5}$, $REMS_{<-0.5}$, $REMS_{others}$) under **BASELINE** conditions in order to characterize the episode types. Then, we selected the episode type with a z-score > 0.5 ($REMS_{>0.5}$), which had a stronger presence in high responders and non-shocked animals after the experience, and inspected the temporal development of parameters for this episode type only, comparing groups. For a comparison, we examined amygdalar and hippocampal parameters also during the behavioral exposure challenges, where mice were awake and displayed fearful behavior.

Duration of REMS Episodes Varies between Episode Types

The duration of different types of REMS episodes under **BASELINE** conditions was not affected by the group *[F(2,13) = 0.61, p = 0.56;* **FIGURE 14F***]*. Similarly, the group had no effect on $REMS_{>0.5}$ over time *[F(2,13) = 0.10, p = 0.91;* **FIGURE 15E***]*. However, independently of the group *[group x episode type: F(4,26) = 0.82, p = 0.52; episode type: F(2,26) = 11.62, p < 0.001]*, $REMS_{>0.5}$ were shorter than $REMS_{<-0.5}$ *[F(1,31) = 4.55, p < 0.01]* and $REMS_{<-0.5}$ again shorter than $REMS_{others}$ *[F(1,31) = 6.29, p < 0.001;* **FIGURE 14F***]*. The analysis of the temporal development, on the other hand, revealed that, independently of the group *[group x day: F(4,26) = 0.37, p = 0.83; day: F(2,26) = 5.51, p < 0.05]*, $REMS_{>0.5}$ increased in length during **MEMORY CONSOLIDATION** *[F(1,31) = 3.35, p = 0.06]* and after a **STABLE MEMORY** had been formed *[F(1,31) = 4.27, p < 0.05;* **FIGURE 15E***]*.

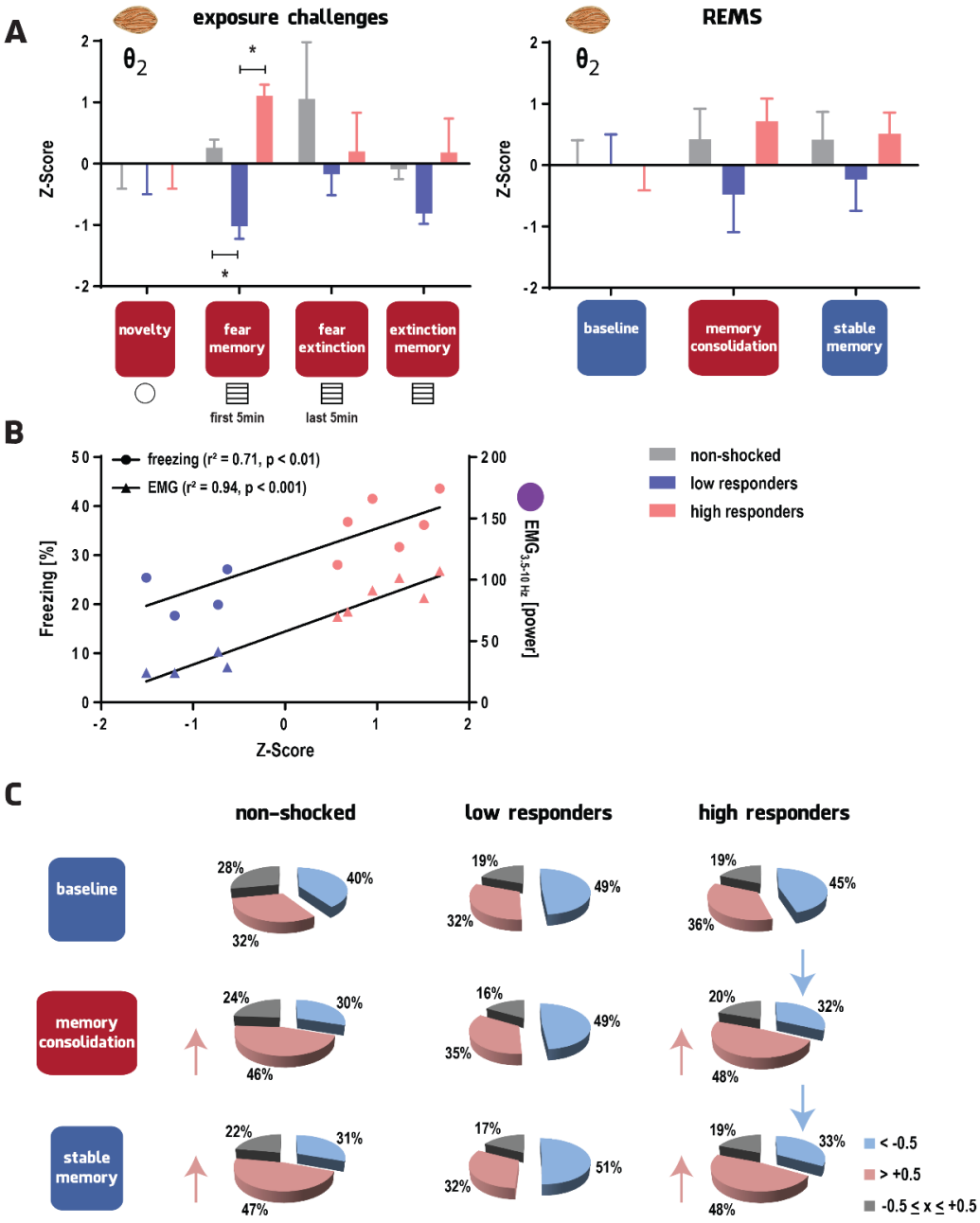

Figure 13 | Z-Score Based Characterization of REMS Episodes |

(A) Z-score calculated for amygdalar theta 2 power during exposure challenges and during REMS presented as mean +/- SEM. *p < 0.05 indicating a statistically significant difference between groups (2-way ANOVA). (B) Correlation between the z-score and the freezing behavior (circles) or the EMG activity (3.5-10 Hz; triangles) during testing of the fear memory in the shock context. Red: high responders, blue: low responders, gray: non-shocked animals. (C) REMS episodes were assigned to one of three categories according to the prevalent z-score: $REMS_{>0.5}$ (red), $REMS_{<-0.5}$ (blue) and $REMS_{others}$ (gray). The pie charts illustrate the mean percent distribution of REMS episodes within these categories for the three experimental groups. Arrows indicate an increase / decrease of a REMS category as compared to basal conditions.

Power Spectral Density Varies between REMS Episode Types and between Groups

Significant group effects could already be detected for **BASELINE** PSD in the BLA within the theta 2 band *[F(2,13) = 80.18, p < 0.001;* **FIGURE 14A***]* and in the CA1 within the theta 1 band *[F(2,13) = 20.76, p < 0.001;* **FIGURE 14B***]*. Basal measures also revealed that the episode type significantly affected CA1 power within the theta 2 *[F(2,26) = 27.41, p < 0.001]* and theta 1 *[F(2,26) = 13.19, p < 0.001]* frequency range independently of the group *[group x episode type;* θ_2*: F(4,26) = 1.40, p = 0.26;* θ_1*: F(4,26) = 0.28, p = 0.89]*. Basal hippocampal theta 2 (**FIGURE 14A**) power presented lowest for $REMS_{<-0.5}$ *[$REMS_{<-0.5}$ vs. $REMS_{>0.5}$: F(1,31) = 10.99, p < 0.001; $REMS_{<-0.5}$ vs. $REMS_{others}$: F(1,31) = 4.91, p < 0.01; $REMS_{>0.5}$ vs. $REMS_{others}$: F(1,31) = 6.09; p < 0.001]* whereas hippocampal theta 1 power (**FIGURE 14B**) appeared lowest for $REMS_{>0.5}$ *[$REMS_{<-0.5}$ vs. $REMS_{>0.5}$: F(1,31) = 7.34, p < 0.001; $REMS_{<-0.5}$ vs. $REMS_{others}$: F(1,31) = 3.41, p = 0.06; $REMS_{>0.5}$ vs. $REMS_{others}$: F(1,31) = 3.93; p < 0.05]*. In the amygdala, on the other hand, theta 2 (**FIGURE 14A**) was affected by the episode type *[F(2,26) = 408.8, p < 0.001]* as a function of the group *[group x episode type: F(4,26) = 6.46, p < 0.001]*, with significantly elevated power levels during $REMS_{>0.5}$ in all groups compared to both, $REMS_{<-0.5}$ and $REMS_{others}$ *(non-shocked: F(1,5) > 12.22, p < 0.001; high responders: F(1,5) > 9.41, p < 0.001; low responders: F(1,3) > 7.91, p < 0.001)*. Taken together, REMS episodes showed different spectral power characteristics under **BASELINE** conditions, with lowest hippocampal theta 1 and highest amygdalar and hippocampal theta 2 activity in the $REMS_{>0.5}$ episodes. Interestingly, general group differences could already be detected pre-shock.

Similarly, the group had an effect on theta 2 power in the BLA *[F(2,13) = 58.98, p < 0.001;* **FIGURE 15A***]* and theta 1 power in the CA1 *[F(2,13) = 15.90, p < 0.001;* **FIGURE 15D***]* when comparing the temporal development of $REMS_{>0.5}$. Independent of the day *[F(4,26) = 0.96, p = 0.45]*, high responding mice showed lower theta 2 power in the BLA compared to non-shocked and low responding animals on all three recording days (**FIGURE 15A**), i.e. before the shock *[high responders vs. non-shocked: F(1,11) = 2.42, p < 0.001 ; high responders vs. low responders: F(1,9) = 2.71, p < 0.001]*, during the **MEMORY CONSOLIDATION** phase *[high responders vs. non-shocked: F(1,11) = 2.42, p < 0.001 ; high responders vs. low responders: F(1,9) = 2.71, p < 0.05]* and after having built a **STABLE MEMORY** *[high responders vs. non-shocked: F(1,11) = 2.42, p < 0.001 ; high responders vs. low responders: F(1,9) = 2.71, p < 0.05]*. Contrarily, high responders displayed the strongest theta 1 power in the hippocampus on all days *[***FIGURE 15D***; baseline: high responders vs. non-shocked: F(1,11) = 7.82, p < 0.001 ; high responders vs. low responders: F(1,9) = 6.69, p < 0.001; memory*

consolidation: high responders vs. non-shocked: F(1,11) = 5.45, p < 0.01 ; high responders vs. low responders: F(1,9) = 4.42, p < 0.01; stable memory: high responders vs. non-shocked: F(1,11) = 4.12, p < 0.05 ; high responders vs. low responders: F(1,9) = 3.71, p < 0.05].

In summary of the REMS episode analysis so far, and also comparing these findings to the PSD results obtained during the exposure challenges (see **AMYGDALAR AND HIPPOCAMPAL POWER DURING THE EXPOSURE CHALLENGES, P.89** and **FIGURE 11**), high responders displayed an increased theta 2 power in the BLA when being re-exposed to the shock context (**FEAR MEMORY**) and during REMS after the shock in general (positive z-score). Furthermore, they spent more time in REMS episodes with an increased amygdalar theta 2 power (> 0.5). These $REMS_{>0.5}$ were generally shorter than other REMS episode types and were characterized not only by higher theta 2 power in the amygdala and the hippocampus, but also lower theta 1 power in the hippocampus. Although also non-shocked controls had more $REMS_{>0.5}$ episodes after the control exposure, in contrast to them and to low responders, high responders had lower theta 2 power levels in the BLA and higher theta 1 power levels in the CA1 before and after the shock. These results therefore could indicate that quantitative equivalence (i.e. more $REMS_{>0.5}$ episodes) in non-shocked and high responding animals was not paired with an analogy in qualitative power measures in amygdala (theta 2) and hippocampus (theta 1). In a next step, we evaluated REMS episode characteristics on the basis of three parameters measuring the relationship of amygdalar and hippocampal signals, the time lag, phase coherence and spectral coherence.

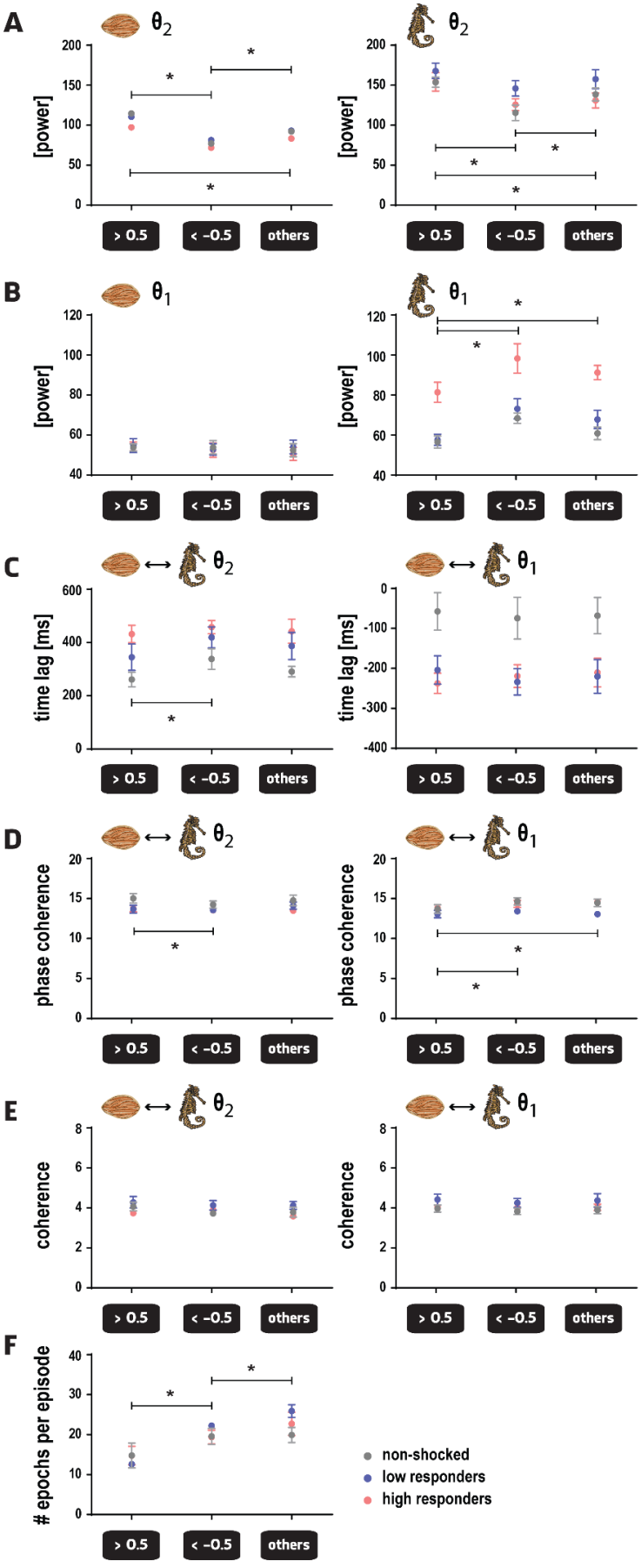
A
B
C
D
E
F
θ2
θ1
[power]
time lag [ms]
phase coherence
coherence
epochs per episode
> 0.5
< -0.5
others
non-shocked
low responders
high responders

Figure 14 | Basal Characteristics of REMS Episodes |
Characterization of the three REMS episode types $REMS_{>0.5}$, $REMS_{<-0.5}$ and $REMS_{others}$ under **BASELINE** conditions: amygdalar and hippocampal power in (**A**) theta 2 and (**B**) theta 1 frequencies, (**C**) time lag, (**D**) phase coherence and (**E**) coherence within theta 2 and theta 1 frequencies between BLA and CA1 and (**F**) the mean number of epochs per REMS episode. Data are presented as group mean +/- SEM. *p < 0.05 indicating a statistically significant difference between episode types (2 way ANOVA).

Time Lag between Amygdala and Hippocampus Varies dependent on Frequency Range

The analysis of the time lag between BLA and CA1 was used to extract information about the temporal relationship or offset between the two limbic structures. When inspecting the results, we first noticed contrary values for the analysis of the theta 2 and the theta 1 frequency range, with time lags in the theta 2 range always being positive and theta 1 time lags being always negative (**FIGURE 14C** and **FIGURE 16A, B**). This finding indicates that within the theta 2 frequency range, the signal of the hippocampus was temporally ahead the amygdala's signal, whereas the amygdalar signal was temporally leading the hippocampal signal within the theta 1 frequencies.

Time lags of both frequency ranges were affected by the group under **BASELINE** conditions *[θ_2: F(2,13) = 6.25, p < 0.05; θ_1: F(2,13) = 5.50, p < 0.05]* as well as over the temporal course *[θ_2: F(2,13) = 5.28, p < 0.05; θ_1: F(2,13) = 6.25, p < 0.05]*, but not during the exposure challenges *[θ_2: F(2,13) = 1.38, p = 0.29; θ_1: F(2,13) = 0.54, p = 0.60]*. During **BASELINE** measures, the theta 2 time lag (**FIGURE 14C**) was significantly lower in $REMS_{>0.5}$ compared to $REMS_{<-0.5}$ *[F(1,31) = 4.55, p < 0.01]* when comparing independently of the group *[group x episode type: F(4,26) = 0.50, p = 0.74; episode type: F(2,26) = 5.35, p < 0.05]*. On all recording days, high responders showed higher absolute time lags compared to non-shocked controls in the theta 2 *[***FIGURE 16A***; baseline: F(1,11) = 4.85, p < 0.01; memory consolidation: F(1,11) = 3.56, p < 0.05; stable memory: F(1,11) = 4.03, p < 0.05]* as well as the theta 1 band *[***FIGURE 16B***; baseline: F(1,11) = 4.68, p < 0.01; memory consolidation: F(1,11) = 4.32, p < 0.05; stable memory: F(1,11) = 4.93, p < 0.01]*. When being re-exposed to the shock chamber (**FEAR MEMORY** testing), an observed group x condition interaction effect for the theta 1 frequency range *[F(4,26) = 5.62, p < 0.01]* was based on a significantly lower absolute time lag in non-shocked compared to high responding animals in the **NOVEL CONTEXT** *[F(1,11) = 3.49, p < 0.05]* (**FIGURE 16B**).

We can summarize that $REMS_{>0.5}$ episodes in general depicted a smaller time lag between amygdala and hippocampus, with the amygdala leading the hippocampus within theta 1 frequencies and *vice versa* within the theta 2 frequency range. Also, the absolute time lag in the high responding group was always greater than in the non-shocked animals, before as well as after the shock. Therefore, another qualitative characteristic of augmented $REMS_{>0.5}$ episodes dissimilarly occurred in non-shocked and high responding animals, namely a larger temporal lag between hippocampal and amygdalar field potentials generated in the theta frequency range.

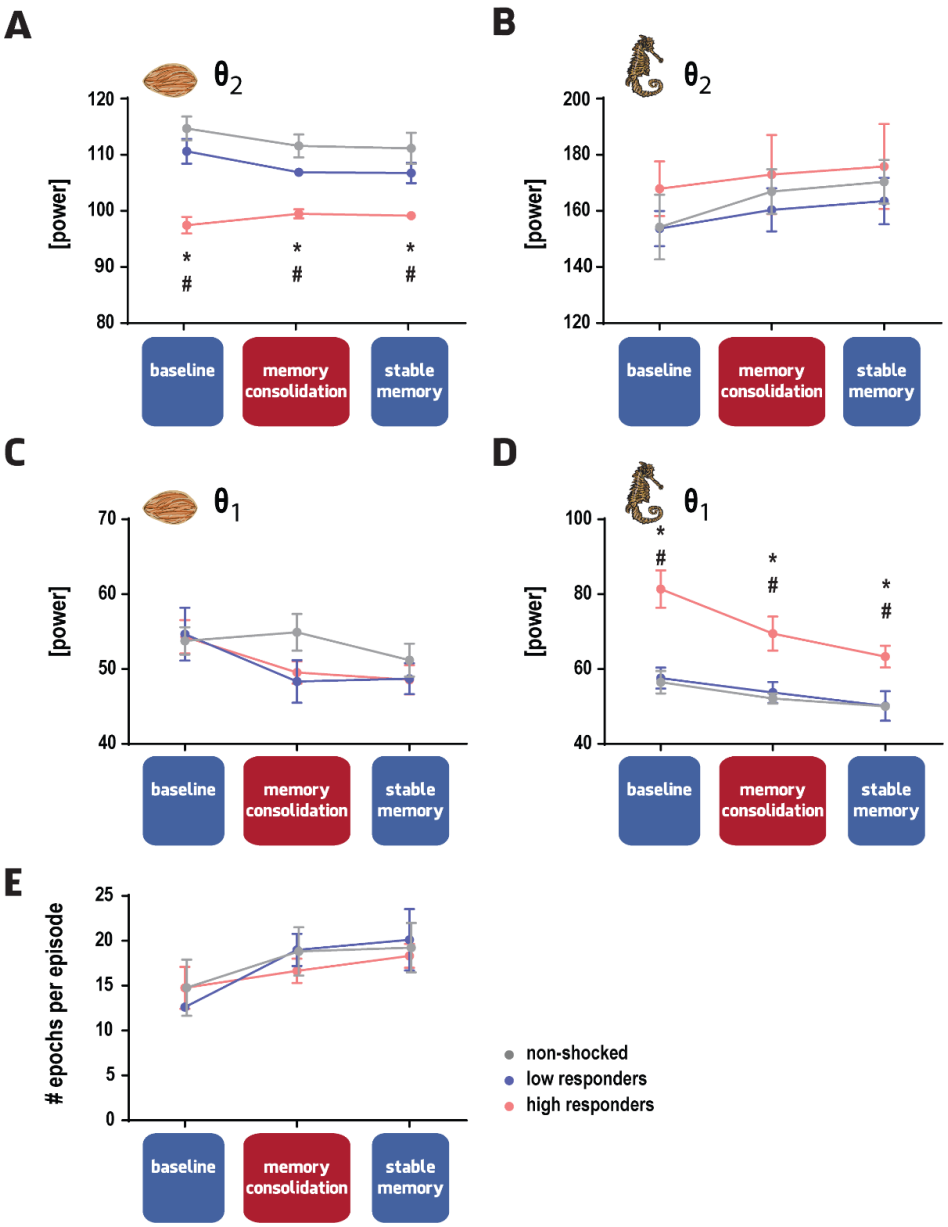

Figure 15 | Temporal Development of Characteristics of REMS Episodes with a Z-Score > 0.5 |

Integrated power (PSD) within the theta 2 and theta 1 frequency bands in BLA and CA1 during $REMS_{>0.5}$ episodes before and after the shock. All data are presented as group mean +/- SEM. Red: high responders; blue: low responders; gray: non-shocked animals. *p < 0.05 indicates a statistical significant difference between high (red) and low (blue) responders (2-way ANOVA). #p < 0.05 indicates a statistical significant difference between high responders (red) and non-shocked (gray) mice (2-way ANOVA).

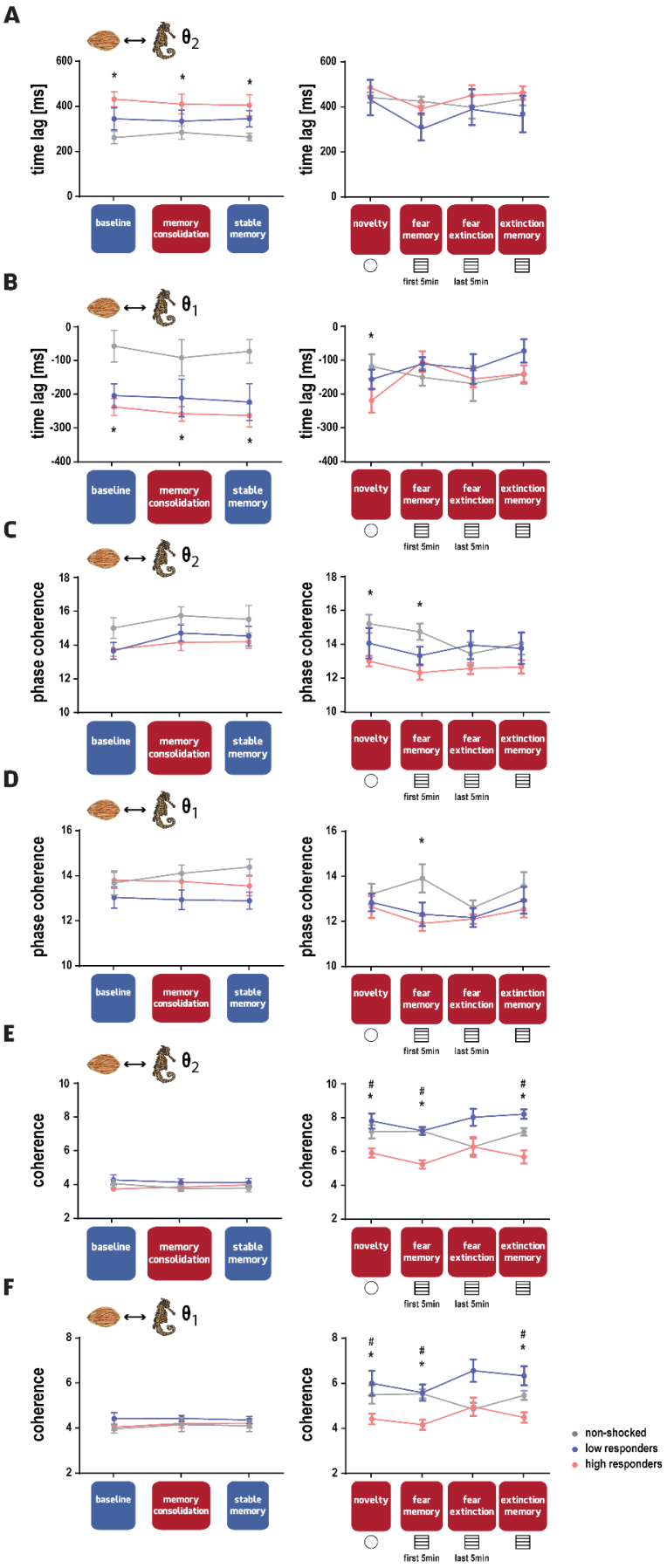
A
B
C
D
E
F
θ2
θ1
time lag [ms]
phase coherence
coherence
baseline
memory consolidation
stable memory
novelty
fear memory
fear extinction
extinction memory
first 5min
last 5min
non-shocked
low responders
high responders

Figure 16 | Temporal Development of Connectivity Parameters within REMS Episodes with a Z-Score > 0.5 and during Exposure Challenges |
Each parameter was analyzed for its temporal development during $REMS_{>0.5}$ (left column) and during different exposure challenges (right column): time lag between BLA and CA1 in the theta 2 (**A**) theta 1 (**B**) frequency range; phase coherence between BLA and CA1 in the theta 2 (**C**) theta 1 (**D**) frequency range; coherence between BLA and CA1 in the theta 2 (**E**) theta 1 (**F**) frequency range. All data are presented as group mean +/- SEM. Red: high responders; blue: low responders; gray: non-shocked animals. *p < 0.05 indicates a statistical significant difference between high responders (red) and non-shocked (gray) mice (2-way ANOVA).

Phase Coherence Varies dependent on Episode Type and Condition

In contrast to the time lag, the parameter of phase coherence was used to extract information not about the temporal relationship but about the strength of coupling between the two limbic structures regarding their phase. However, similarly to the time lag, also the investigation of the phase coherence between BLA and CA1 revealed a general distinction between $REMS_{>0.5}$ and $REMS_{<-0.5}$ episodes (**FIGURE 14D**). Independently of the group *[group x episode type: θ_2: F(4,26) = 1.80, p = 0.16; θ_1: F(4,26) = 0.84, p = 0.51; episode type: θ_2: F(2,26) = 3.45, p < 0.05; θ_1: F(2,26) = 4.64, p < 0.05]*, $REMS_{>0.5}$ were characterized with a stronger phase coupling between hippocampus and amygdala than $REMS_{<-0.5}$ for the theta 2 *[F(1,31) = 3.67, p < 0.05]* and theta 1 *[F(1,31) = 4.30, p < 0.05]* frequency bands. Theta 1 phase coherence was also generally increased compared to $REMS_{others}$ *[F(1,31) = 3.85, p < 0.05]*. Although a significant group effect could neither be detected for the theta 2, nor the theta 1 band under **BASELINE** conditions *[θ_2: F(2,13) = 1.94, p = 0.18; θ_1: F(2,13) = 2.26, p = 0.14]* or over days *[θ_2: F(2,13) = 2.08, p = 0.17; θ_1: F(2,13) = 1.86, p = 0.19]*, the group did significantly influence phase coherence during the exposure challenges in the theta 2 range *[F(2,13) = 4.68, p < 0.05]*, and dependent on the condition for theta 1 frequencies *[group x condition: F(4,26) = 3.69, p < 0.05]*. Non-shocked animals showed stronger theta 2 phase coupling than high responders in the **NOVELTY** *[F(1,11) = 4.19, p < 0.05]* and **FEAR MEMORY** tests *[F(1,11) = 4.59, p < 0.01;* **FIGURE 16C***]*; in the latter case also within the theta 1 band *[F(1,11) = 4.18, p < 0.05;* **FIGURE 16D***]*. No significant differences in phase coherence between groups were observed during $REMS_{>0.5}$ before or after the shock *(p > 0.05)*.

Taken together, the findings described above indicate that during $REMS_{>0.5}$ episodes, theta phase coupling between the amygdala and the

hippocampus was stronger than during the other REMS episode types. No statistically significant differences could be observed for $REMS_{>0.5}$ episodes between groups and *pre* to *post* shock. However, phase coupling in theta 2 and theta 1 bands was lower in the high responding animals, as compared to the non-shocked group upon re-exposure to the shock context. Last, we investigated whether similar observations could be made for the spectral coherence between the two limbic brain structures.

Similar Coherence within Different REMS Episode Types

In order to measure the strength of coupling between the two limbic structures not only regarding their phase, but also regarding their spectral activity, we examined the parameter of coherence. In contrast to all parameters described previously, no basal differences between REMS episode types were detected for spectral coherence between BLA and CA1 within the two theta frequency bands *[episode type: θ_2: F(2,26) = 1.87, p = 0.17; θ_1: F(2,26) = 1.10, p = 0.35;* **FIGURE 14E***]*. Moreover, no group or group interaction effect on REMS episode types under **BASELINE** conditions *[group: θ_2: F(2,13) = 1.69, p = 0.22; θ_1: F(2,13) = 1.57, p = 0.25; group x episode type: θ_2: F(4,26) = 1.35, p = 0.28; θ_1: F(4,26) = 0.16, p = 0.96]*, nor on the temporal development over days *[group: θ_2: F(2,13) = 0.89, p = 0.44; θ_1: F(2,13) = 0.73, p = 0.50; group x episode type: θ_2: F(4,26) = 1.69, p = 0.18; θ_1: F(4,26) = 0.18, p = 0.95]* were apparent (**FIGURE 16E, F**). Contrarily, the group significantly affected the coherence between amygdala and hippocampus during the exposure challenges *[θ_2: F(2,13) = 21.08, p < 0.001; θ_1: F(2,13) = 12.61, p < 0.001]*, with high responding animals displaying lower theta 2 (**FIGURE 16E**) and theta 1 coherence (**FIGURE 16F**) throughout the conditions compared to both, low responding *[novelty: θ_2: F(1,9) = 5.77, p < 0.001; θ_1: F(1,9) = 4.88, p < 0.01; fear memory: θ_2: F(1,9) = 6.04, p < 0.001; θ_1: F(1,9) = 4.39, p < 0.01; extinction memory: θ_2: F(1,9) = 7.70, p < 0.001; θ_1: F(1,9) = 5.69, p < 0.001]* and non-shocked animals *[novelty: θ_2: F(1,11) = 4.30, p < 0.05; θ_1: F(1,11) = 3.70, p < 0.05; fear memory: θ_2: F(1,11) = 6.68, p < 0.001; θ_1: F(1,11) = 4.72, p < 0.01; extinction memory: θ_2: F(1,11) = 5.02, p < 0.01; θ_1: F(1,11) = 3.39, p = 0.05]*. These findings indicate that spectral coherence between amygdala and hippocampus within the theta frequency range was affected by challenges during wakefulness only and independently of the shock.

Altogether, the analysis of three different REMS episode types, which were categorized based on theta 2 power measures in the BLA, revealed that **(I)** the electric foot shock, as well as the sole shock context exposure, lead to redistribution of the amount of time mice spent in different types of REMS episodes; **(II)** more specifically, non-shocked animals and shocked animals with particularly strong fear memory (severe fear phenotype) entered more REMS episodes where the amygdala showed greater theta 2 power as compared to basal levels; **(III)** these $REMS_{>0.5}$ episodes were generally shorter and were characterized by higher theta 2 activity in amygdala and hippocampus, lower theta 1 activity in the hippocampus, and a stronger coupling between the two limbic areas specifically in the theta 2 range (shorter time lag, stronger phase coherence); **(IV)** despite of quantitative equivalence between non-shocked and high responding animals (i.e. more $REMS_{>0.5}$ episodes in both groups), a qualitative analogy was not expressed, as power measures in amygdala (theta 2) and hippocampus (theta 1), as well as inter-limbic coupling, presented with divergent magnitude (power) and strength (temporal lag); **(V)** group differences appearing upon re-exposure to the shock context also emerged during $REMS_{>0.5}$ episodes with similar (power hippocampus, time lag) or contrarian tendency (power amygdala); **(VI)** many of these group divergences were present already before the shock, that is during REMS under basal conditions (theta 2 power BLA, theta 1 power CA1, time lag) and accordingly during wakefulness when challenged with a novel environment (theta 1 power BLA, power CA1, time lag, theta 2 phase coherence).

The presented findings might indicate that first, basal amygdalar and hippocampal activity inherently affected inter-individual shock-induced variations, and second that limbic activity was altered alike during REMS and wakefulness.

Chapter 4 | Iacta alea est.

Suetonius, Vita Divi Iuli

Within the scope of the present thesis, we aimed to investigate sleep-related behavioral and limbic bioelectrical activity changes after a traumatic experience in an animal model of PTSD. Mice underwent a singular contextual fear conditioning protocol with an intense foot shock (2x 1.5 mA, 2 s) as unconditioned stimulus. Behavioral testing one month *post* shock verified the development of a PTSD-like phenotype as exemplified by contextual fear, generalized fear, and hyperarousal indices. Increased amounts of REMS were found to represent early and long-lasting symptomatic alterations in the shocked animals. Also, sub-groups of high and low fear responders showed divergent limbic activity changes *post* shock, both during triggered fear in the former shock context and during REMS following the aversive experience. Activity changes during the shock context re-exposure during wakefulness resembled those seen during REMS within groups, potentially indicating a replay of the traumatic situation during sleep. Yet, distinct limbic activation patterns between groups occurred already under baseline conditions *before* the shock exposure, and also basal REMS fragmentation was found to be predictive of the strength of the subsequently emerging PTSD-like hyperaroused phenotype. In the presented studies, REMS properties were therefore found to constitute symptomatic, as well as prognostic hallmarks, and thus might unmask a risk for the development of PTSD, probably not only in the animal model. These findings, the potential underlying mechanisms, their meaning, relevance, and limitations are discussed in the following section.

A PTSD-like Phenotype in Mice

We used a well-characterized animal model of PTSD which is based on contextual fear conditioning in mice (Siegmund and Wotjak, 2006, 2007a). In comparison with other stressors used to model a traumatic event (e.g. under water holding, restrain stress, social defeat, predator stress/threat, see also **Animal Models of PTSD, p.37 ff.**), a clear advantage of electric shocks is: the possibility **i)** to vary the stressor intensity without the need to prolong or to repeat the stress, thus risking habituation or the induction of a rather depression-like phenotype of learned helplessness (Seligman and Beagley, 1975); and **ii)** to differentiate between trauma associative (conditioned) and non-associative (sensitized) fear memories (Siegmund and Wotjak, 2007a).

Contextual Fear

The delivery of a strong electric foot shock within a specific context (shock chamber) led to an elevated fear response (freezing) of the animals when re-exposed to the shock environment early (3 days, **Figure 2B**) or late (1 month, **Figure 8A**) after the shock. This is in accordance with our previous observations which showed that associative contextual fear emerges immediately after the fear conditioning and remains for several months (Siegmund and Wotjak, 2007a; Golub et al., 2009; Siegmund et al., 2009b; Pamplona et al., 2011). In general, fear responses seen in the present and earlier studies, using animals that underwent surgery (Siegmund and Wotjak, 2007b), are less pronounced than in non-operated mice (e.g. (Siegmund and Wotjak, 2007a; Golub et al., 2009, 2011)). We assume that the surgery *per se*, despite *intra*- and *post*-operative analgesia, already represents an aversive event for the animals, thus decreasing the aversive valence of the foot shock. Therefore, and in contrast to our previous studies, we chose to deliver a second foot shock, however within the same single exposure to the shock context with an inter-shock-interval of 1 min. As has been seen before (Golub et al., 2009), re-exposure to the original shock context for 30 min 3 days after the shock resulted in a decreased fear response upon re-testing on the next day, indicating successful fear extinction (**Figure 8A**). Accordingly, extinction training early (1 day) after the shock led to a long-lasting reduction of hyperarousal, contextual and generalized fear in the same model (Golub et al., 2009).

By contrast, re-exposure to the shock context one month after the shock for 3 min did not result in extinction of contextual fear, as assessed one week later (Thoeringer and Wotjak, 2013). Therefore, we doubt that in the current study a single re-exposure to the shock context for 3 min one month after the fear conditioning could have led to fear extinction, even when preceded by the exposure to other environments (novel context, context with reminding features of

the shock context). This circumstance is noteworthy, as sleep-wake behavior was investigated also 2 months after the shock, preceded by a behavioral testing 1 month *post* shock that included re-exposure to the shock context, but also testing for generalized fear in two other environments (see **EXPERIMENTAL DESIGN P.46 AND FIGURE 1A**).

Generalized fear

Generalized fear, resembling avoidance symptoms presented by PTSD patients (AMERICAN PSYCHIATRY ASSOCIATION, 2013), was expressed by the mice 1 month after the shock, as tested by exposing the animals to a novel, as well as a shock context-resembling environment (**FIGURE 2B**), but not before the animals had been conditioned (**NOVELTY**, **FIGURE 8A**). In contrast to contextual fear, generalized fear seems to develop after a latent period of one month (SIEGMUND AND WOTJAK, 2007A; PAMPLONA ET AL., 2011), probably as a consequence of forgetting specific stimulus attributes associated with the shock context (SAUERHÖFER ET AL., 2012). Similarly, PTSD patients present with inability to recall key features of the traumatic event (AMERICAN PSYCHIATRY ASSOCIATION, 2013). As mentioned before, there exist multiple levels of fear generalization (PAMPLONA ET AL., 2011; SAUERHÖFER ET AL., 2012). Even though testing in the novel context did not contain explicit context reminders (such as the metal grid floor used in the reminder context), it included more indirect environmental reminders (such as testing in the same setup, similar procedure by catching the mice and exposing them to the test context). These cues might be sufficient for inducing fear generalization. Although fear responses in the reminder context (**FIGURE 2B**, hexagon symbol) were presented at about the same level as in the original shock context in stressed mice, the difference between shocked and non-shocked individuals failed to reach statistical significance *($p = 0.06$)*, probably due to low statistical power. Although the order of testing (novel context, reminder context, shock context) introduces a deliberate bias towards more pronounced generalization during the first testing (novel context), 2-way ANOVA analysis with the factors "shock" and "context" for repeated measures (context) revealed a significant main effect of shock *[$F(1,14) = 10.70$, $p < 0.01$]*, independently of the context *[shock x context: ($F(2,28) = 2.35$; $p = 0.11$]*, thus confirming context generalization.

Hyperarousal

Similar to the exaggerated startle response in PTSD patients (AMERICAN PSYCHIATRY ASSOCIATION, 2013), a hyperaroused phenotype emerged in shocked mice, as verified by the acoustic startle response (**FIGURE 2A**) and the sensitized fear

response to a neutral tone in a novel context (**FIGURE 2B**, note symbol) 1 month after the shock. Particularly the severity of this hyperarousal phenotype, but not the amount of contextual fear, was associated with the degree of REMS fragmentation *pre* shock (**FIGURE 5**). Accordingly, we demonstrated that hyperarousal (non-associative) and contextual fear (associative) represent distinct and dissociable consequences of the strong foot shock stressor also used in this study (SIEGMUND AND WOTJAK, 2007B; GOLUB ET AL., 2009; SAUERHÖFER ET AL., 2012). The diagnostic manual DSM-V describes in PTSD the same symptom cluster comprising sleep alterations and an exaggerated startle response (**ALTERATIONS IN AROUSAL AND REACTIVITY**), while associative symptoms (**AVOIDANCE**, **INTRUSIONS**) constitute separate symptom classes (AMERICAN PSYCHIATRY ASSOCIATION, 2013).

Taken together, and in accordance with previous studies utilizing this animal model of PTSD, we observed a behavioral phenotype resembling major clinical manifestations in PTSD patients.

REMS Alterations

Extending the findings gathered within this mouse model so far, sleep-wake recordings in the early aftermath of the shock, but also after the development of a full PTSD-like phenotype (2 months *post* shock), showed that shocked mice spent significantly more time in REMS than non-shocked controls (**FIGURE 4**), although under basal conditions REMS amounts were indistinguishable between groups (**FIGURE 3** and see also (POLTA ET AL., 2013)). In comparison, polysomnographic studies performed in PTSD patients revealed divergent results regarding REMS-specific alterations. Observations range from decreased (ROSS ET AL., 1994A, 1994B; MELLMAN ET AL., 1995B; ENGDAHL ET AL., 2000), over unchanged (LAVIE ET AL., 1979; DOW ET AL., 1996; MELLMAN ET AL., 1997), to increased amounts of REMS (ROSS ET AL., 1994A, 1994B; MELLMAN ET AL., 1995B; ENGDAHL ET AL., 2000). However, REMS fragmentation (more awakenings from REMS), as well as an elevated REMS density (more eye movements during REMS) seem to constitute more frequently described PTSD-associated sleep alterations (GLAUBMAN ET AL., 1990; ROSS ET AL., 1994B, 1999, 1994A; MELLMAN ET AL., 1995B, 1997, 2002, 2007; DOW ET AL., 1996; HABUKAWA ET AL., 2007; KOBAYASHI ET AL., 2007; INSANA ET AL., 2012). Although nightmares occur during both, NREMS and REMS, in PTSD patients (VAN DER KOLK ET AL., 1984; WITTMANN ET AL., 2007), dreams of highly emotional content generally occur mainly during REMS (CARTWRIGHT ET AL., 1998; SCHREDL AND DOLL, 1998; SMITH ET AL., 2004; WAMSLEY ET AL., 2007), and REMS fragmentation and nightmares in the early aftermath of the trauma are related to PTSD symptom severity (FOA ET AL., 1995; MELLMAN ET AL., 2004, 2007; HABUKAWA ET AL., 2007). In contrast to the situation in the human disease, we did not detect a more pronounced REMS fragmentation in shocked as compared to non-shocked mice after the shock. Although a differential effect of an aversive event on REMS architecture in humans and rodents cannot be ruled out, it is likely

that the individual variability and naturally high degree of fragmentation in the rodent sleep-wake cycle might have "masked" an aggravation in REMS fragmentation. Contrary to the biphasic sleep-wake behavior of humans, rodents sleep in a rather polyphasic manner, with sleep episodes being interrupted by longer WAKE episodes, even during the inactive phase of the day (CAMPBELL AND TOBLER, 1984; WELSH ET AL., 1986; LO AND CHOU, 2004). In contrast to earlier reports describing increased amounts of sequential REMS episodes, indicative of a fragmented REMS architecture (DASILVA ET AL., 2011A, 2011B), our analysis did not differentiate between single and sequential REMS. Nevertheless, observations made in PTSD patients are in accordance with the present evidence of sleep alterations in shocked mice, as both affirm REMS-specific variations early, as well as late after the aversive experience.

Animal studies investigating the impact of different stressors on the sleep-wake behavior of rodents also confirm this potential REMS specificity (see CHAPTER 1 SLEEP ALTERATIONS IN ANIMAL MODELS, P.40 FF.; for review see (PAWLYK ET AL., 2008)). Most of the reports examining consequences of a fear conditioning paradigm, however, describe diminished, rather than elevated, REMS amounts after the application of an electric foot shock as a stressor (PALMA ET AL., 2000; SANFORD ET AL., 2003C, 2001, 2003A, 2003B; LIU ET AL., 2003, 2009, 2011; JHA ET AL., 2005; PAWLYK ET AL., 2005; WELLMAN ET AL., 2008, 2013; YANG ET AL., 2009, 2013; DESCHAUX ET AL., 2010). This is in contrast to the findings of our work, where we found increased REMS amounts. However, caution applies when comparing these results (SUCHECKI ET AL., 2012). First, most of the mentioned studies applied the shock during the inactive (light) diurnal phase and investigated the direct impact of the stress on sleep within the following hours. By contrast, delivery of the shock at the end of the active (dark) diurnal phase revealed elevated amounts of REMS (VAZQUEZ-PALACIOS AND VELAZQUEZ-MOCTEZUMA, 2000), similar to the findings described here. Second, the fear conditioning protocols vary considerably between studies. Most studies utilize several tone-shock pairings and are not considered as the representation of a trauma-like event in an animal model of PTSD. A report describing the long-term consequences of a single aversive event on the sleep-wake behavior of animals within an established model of PTSD is missing in the literature.

Although the REMS-specific effect after the shock seen in the first experiment was very strong (around 50% more REMS in shocked animals), we could not replicate this finding in the second experiment. However, it has to be noted that recording environments and conditions differed between the two experiments. While EEG signals in mice of the same experimental group were recorded in the same environment, and recordings in all mice were performed simultaneously in experiment 1, animals in experiment 2 passed sequentially through the experimental schedule. Only one animal was housed in the recording environment at a time, with non-shocked animals sequentially following the shocked group. Therefore, we could not control for seasonal or breeding factors, as mice came from different litters and underwent surgeries and recordings during different

seasons distributed over the period of 1.5 years. Still, mice were at approximately the same age (~10-12 weeks) when undergoing surgery, and timing of the experimental protocol (light-dark rhythm, start of recordings, time of shock application, and time of behavioral testing) was preserved between animals. Nevertheless, animals in experiment 1 in total slept around 10% less than the individually recorded mice in experiment 2. We believe that, since in the second experiment (i) the recording took place within a sound-attenuated box, and (ii) mice were kept singly in this recording box, they were deprived of auditory and olfactory input from conspecifics. Thus, they might have been less engaged and spent more time sleeping than animals in experiment 1, where 8 individuals were kept in the same room. In general, it is known that animals kept in captivity, in safe confined cages with unlimited access to food and water, within an unchanging and non-challenging environment, spend more time asleep than their conspecifics living in the wild (Lima et al., 2005; Rattenborg et al., 2008; Lesku et al., 2009). This extra sleep might constitute a "time filling default" (Horne, 2013). Thus, discrepancies in the holding conditions during recordings between the two experiments and potential multi-causal inter-individual sleep-wake variations (Bittman et al., 2013) might explain the lack of reproducibility. The issue of alternated sleep-wake behavior under safe conditions constitutes incidentally a difficulty of sleep recordings also in humans or patients. For example, a few generations ago, human slept rather polyphasic than strictly biphasic, probably due to the daily vexations people underwent in those days (Horne, 2013). Also, when PTSD patients are brought to the sleep laboratory, in order to verify reports of sleep difficulties by polysomnographic monitoring, many of them fail to show sleep problems anymore, have no nightmares, are less stressed and less anxious than at their home (Domhoff and Kamiya, 1964; Woodward et al., 2000; Schredl, 2003). This seems to be an artefact of the perceived safety of the environment in the presence of physicians, or even the solely polysomnographic setup, and the knowledge of being observed and not alone (Spoormaker et al., 2006; Wittmann et al., 2007; Spoormaker and Montgomery, 2008).

The question remains, why sleep alterations in PTSD patients, and animal models, seem to affect particularly REMS. In general, it is difficult to judge from animal models of psychiatric disorders, whether behavioral alterations are adaptive or maladaptive (Polta et al., 2013). In order to draw conclusions, consideration of the environmental context (*How does the developed phenotype change the survival prospects of the animal?*) and the evolutionary perspective (*How does the developed phenotype influence the reproductive success of the animal?*) are indispensable. Direct interference of the evolving REMS increase, e.g. by pharmacological, genetic or optogenetic manipulations, could shed light on the beneficial *vs.* harmful nature of these sleep changes. In favor of an adaptive, beneficial effect of the observed REMS increase, pharmacological and behavioral treatments targeting sleep disturbances (Maher et al., 2006) revealed REMS-specific changes in PTSD patients (Germain, 2013). Treatment with prazosin (an adrenergic alpha-1 receptor

antagonist) or imagery rehearsal therapy, the two recommended treatment options for nightmares and insomnia in PTSD (AURORA ET AL., 2010), were found to be paired with greater REMS amounts, longer REMS duration, elevated REMS density and shorter REMS latency, together with improvements in nightmares, sleep complaints and daytime symptoms of PTSD ((GERMAIN AND NIELSEN, 2003A; TAYLOR ET AL., 2008); but see (GERMAIN ET AL., 2012)). Although the neurobiological mechanisms of this effect are unknown, several explanations of the REMS-specific increase after the shock in this study can be proposed on the basis of the manifold findings regarding REMS and emotional (memory) processing detailed in **CHAPTER 1 (P.1 FF.)**.

It has been hypothesized that, whereas NREMS, or more specifically SWS, seems to fulfill the function of recovery, REMS might rather be involved in preparing the individual for the ensuing WAKE period (HORNE, 2013). For example, the presentation of fear and anxiety during dreams and REMS might help to recognize and adequately respond to threatening stimuli during wakefulness (REVONSUO, 2000; VALLI ET AL., 2005). Similarly, REMS and dreaming have been proposed to act as emotion regulators by "resetting" the affect associated with an emotional memory (CARTWRIGHT ET AL., 1998; MANCIA, 2004; NIELSEN AND LEVIN, 2007; WALKER, 2009, 2010; GUJAR ET AL., 2011A; VAN DER HELM ET AL., 2011; DELIENS ET AL., 2013A). An increase in REMS after the experience of an aversive event might therefore indicate an impaired emotional down-regulation during REMS, which potentially projects to PTSD, where deficits in emotion regulation are found (VANDEKERCKHOVE AND CLUYDTS, 2010; JOVANOVIC AND NORRHOLM, 2011; HAYES ET AL., 2012B; PITMAN ET AL., 2012). Thus, elevated REMS amounts might represent a defensive attempt to "de-tag" the shock experience from its highly emotional meaning, by prolonging the functionally important sleep period. The failure to achieve this down-regulation of the emotional tone is likely reflected by the persistent maintenance of contextual fear in the shock context, but also by the development of generalized fear after an elapsed latent period.

Another potential role of the shock-induced REMS increase might be the formation of a very adherent fear memory. According to the **ACTIVE SYSTEM CONSOLIDATION HYPOTHESIS** (for review see (RIBEIRO AND NICOLELIS, 2004; ELLENBOGEN ET AL., 2007; RASCH AND BORN, 2007, 2008, 2013; DIEKELMANN AND BORN, 2010; WALKER, 2010; WANG ET AL., 2011; LEWIS AND DURRANT, 2011; MÖLLE AND BORN, 2011; BORN AND WILHELM, 2012; RIBEIRO, 2012; INOSTROZA AND BORN, 2013)), transfer of recently acquired memories from a temporary hippocampal into cortical long-term storage sites (system consolidation), by coordinated activity in the hippocampo-thalamo-cortical network during SWS, might be strengthened (synaptic consolidation) during subsequent REMS (DUDAI, 2012). Spending more time in this memory reinforcing sleep period, a particularly strong fear memory of the shock event may be preserved. The finding that REMS percentages in shocked mice were still elevated, even two months after the shock, seems to be in disagreement with this theory though, as consolidation processes are thought to be accomplished within 24 hours or after a few days the latest (DIEKELMANN ET AL., 2009). However, if the

observed increase in REMS percentage was accompanied by an increased incidence of aversive memory replay, these long-lasting REMS alterations might represent reconsolidation of recalled memories rather than consolidation of freshly acquired memories. Thus, recurrent replay of the traumatic situation during sleep might, similarly to the recall of a memory during wakefulness, bring the memory back into a fragile state demanding for reconsolidation. However, since replay studies have shown that the amount of re-activation during NREMS and REMS correlated with the strength of the resulting memory (e.g. (GUERRIEN ET AL., 1989; PEIGNEUX ET AL., 2004; DEUKER ET AL., 2013) and see **CHAPTER 1 SELECTIVE RE-ACTIVATION DURING SWS, P.24 FF., SELECTIVE RE-ACTIVATION DURING REMS, P.27 FF.**), this interpretation appears rather unlikely.

Taken together, it seems conceivable that the documented REMS increase in shocked mice represents a perpetual neuronal replay of the shock situation during REMS, serving the formation of a persistent aversive memory ("over-consolidation" or "mis-consolidation"), and/or a constant effort to down-regulate the emotional component associated with this memory (impaired emotional "de-tagging"). However, we should stress once more that it remains unclear whether the proposed mechanisms define a maladaptive disease-like state or rather a beneficial, adaptive response to the shock.

RESILIENT OR BAD LEARNER?

Cautious interpretation is also advised with regard to the changes in behavior and brain activity in the three fear responder groups of low responders, high responders and non-shocked controls. The classification of these three groups was based on the fear response of the animals when placed back into the original shock context, as assessed by freezing behavior and EMG power measures (**FIGURE 8**), and was not *a priori* expected, nor defined. Here, high responders, in contrast to low responders and non-shocked mice, expressed exaggerated fear responses that were associated with increased electromyographic activity from the neck muscle (EMG). We inferred that the EMG can be used as a real-time freezing detector in mice, differentiating voluntary immobility from fear-related freezing (KÄFER, 2013). By this means, two sub-groups of shocked animals could be identified upon recall of a conditioned fear memory in the conditioning context. In contrast to mere freezing scoring by eye, which has a poor temporal resolution due to reaction time delays implicated by the scorer, this measure allowed to investigate real-time associations between fearful behavior and brain activity, as recorded by local field potentials (LFP).

Variability in Inbred Animals

The animals used in this study, and also in previous work from our group, were inbred mice. Among different inbred mouse strains, BL6 mice appear to be particularly vulnerable to developing a fearful phenotype and thus to model the human disease of PTSD (Szklarczyk et al., 2012). Comparisons of different BL6 strains confirmed that C57BL/6N mice (used in the present study) are particularly susceptible for developing PTSD-like symptoms in terms of both, associative and non-associative memories (Siegmund et al., 2005; Siegmund and Wotjak, 2007a; Dahlhoff et al., 2010). Although a genetic impact on individual responses can be excluded here, we distinguished subgroups of animals that seemed to be more vulnerable or more resilient towards the shock, depending, among others, on maternal inexperience (Siegmund et al., 2009a). Also in humans, not every individual develops PTSD after the experience of a traumatic situation (Breslau et al., 1991; Bryant, 2006; Foa et al., 2006). Depending on the type of trauma and its intensity (North et al., 2012), the proportion of individuals who develop PTSD varies greatly (for a general discussion of risk factors for PTSD see **We are what we dream?, p.129 ff.** below). The differentiation between high responders and low responders, or resilient vs. vulnerable individuals respectively, has also been applied to other animal models of PTSD. For example, only a subpopulation of rats (25 % in Sprague-Dawley rats, 50 % in Lewis rats) exposed to a cat urine predator scent stressor for 10 min, displays extreme behavioral (PTSD-like) responses on the basis of anxiety and startle measures, whereas others show minimal or intermediate responses (Cohen and Zohar, 2004; Cohen et al., 2012a). This is in accordance with the human situation where about 10-20 % of individuals exposed to a severe stressful situation will develop PTSD (Breslau et al., 1991, 1998; Kessler et al., 1995, 2005; Breslau and Kessler, 2001). Here, apart from the re-exposure to the shock context, we did not apply other behavioral tests like the elevated plus maze or the startle response immediately following the shock. Thus, we cannot argue about the general emotionality level of high and low responding animals (e.g. regarding anxiety, generalized fear or arousal). Still, we observed differential limbic activity changes *post* shock during REMS when comparing the two subgroups; however, whether the present subgroups reflect resilience *vs.* vulnerability remains to be examined.

Low Responders vs. High Responders - The Search for Resilience?

It has to be pointed out that, when discussing the findings of our second experiment, two possible interpretations can be considered. **i) "traumatized" mice:** The first intuitive view specifies high responders as the highly vulnerable,

PTSD-resembling phenotype group, while mice of the low responding group are considered more resilient. In this scenario, high responders develop, for example due to over-consolidation, a PTSD-like phenotype (strong fear response) that is paired with certain activity changes within and between limbic areas in the brain, also during REMS. By contrast, resilient mice (low fear response) react by distinct limbic activity patterns, although having been exposed to the same stressor, and, thus, are resistant to the development of a PTSD-like symptomatology. The alternative view postulates a split-up into **II) BAD LEARNERS AND GOOD LEARNERS**: As we did not assess other behavioral endpoints (anxiety, generalized fear, hyperarousal, mood, cognitive functions *etc.*), we cannot rule out that the animals may differ solely in their capacity to acquire and/or consolidate contextual fear memory. Thus, low responders might merely have formed a poor context-shock association (insufficient contextual processing) and/or consolidated the fear memory less efficiently than high responding mice. In other words, high responders and low responders may denote good and bad learners, rather than "symptomatic" and "healthy" cases.

Another aspect worth consideration, is the potential variability in the non-shocked animals which were originally intended as a mere control group. First, these mice were not left completely undisturbed but exposed to the non-familiar shock context (albeit without delivery of a shock), which might have induced some learning processes as well. Second, also within this group a variance of the inherent emotional phenotype and individual susceptibility to develop any long-lasting fear-related behavioral alterations, is likely. Therefore, we consider the comparison between low responders and high responders more meaningful and significant than the contrast to non-shocked mice which experienced an unlike situation (novelty exposure). Nevertheless, in order to control for the impact of the shock *per se*, a non-shocked control group was certainly essential.

FEAR-RELATED REPLAY DURING REMS?

When comparing limbic theta activity changes between the three subgroups after the shock (or novelty exposure in the non-shocked animals), we observed differential profiles in high and low responding mice. Interestingly, these changes were similar during WAKE (**FIGURE 11**), upon re-exposure to the shock context (**FEAR MEMORY**), and during REMS (**FIGURE 12**), especially during the **MEMORY CONSOLIDATION** phase. Particularly theta 2 power in the amygdala (BLA) and the hippocampus (CA1) increased in high responders during re-exposure and REMS *post* shock in comparison to low responding animals. Since only amygdalar theta 2 power was not distinguishable between groups upon the exposure to a novel

environment *pre* shock, but was altered by the day x group interaction during REMS *post* shock, we calculated the z-score for this parameter which exposed explicitly the similarity between WAKE and REMS developments (**FIGURE 13**). This approach allowed for comparing the change in magnitude of theta 2 power between WAKE and REMS, where absolute power levels are strikingly different and prohibit direct comparison. In addition, z-scores were used to objectively classify different REMS episodes with regard to theta 2 power in the BLA (see **ALL REMS IS NOT THE SAME, P.125 F.**), the electrophysiological parameter that was most prominently affected in high *vs.* low responding animals.

All Theta is not the same

Our findings of differential effects of the shock on theta 2 and theta 1 during WAKE and REMS are in accordance with previous studies characterizing these frequency bands. For instance, the two types of theta frequencies not only vary in their pharmacological profile (atropine resistant *vs.* susceptible; (KRAMIS ET AL., 1975; VANDERWOLF, 1975; BLAND, 1986)) but also in the behaviors they have been associated with. While theta 1 is predominant during voluntary movement and exploration, theta 2 is dominant during aroused immobility and in the presence of predators (KRAMIS ET AL., 1975; VANDERWOLF, 1975; BLAND, 1986; SAINSBURY ET AL., 1987A, 1987B). Also, while the application of a foot shock increased theta 2 activity in the hippocampus, disruption of theta 2 oscillations reduced anxiety levels induced by the shock in rats, as tested in the elevated plus maze (HSIAO ET AL., 2012, 2013). Consistently, within this study, during re-exposure to the original shock context, theta 2 power in the BLA was increased in high responders as compared to novelty exposure levels, whereas mice expressing low degrees of freezing showed rather decreased amygdalar and hippocampal theta 2 activity. Theta 1 power, contrarily, was not affected by the shock, in neither BLA nor in CA1, but rather defined group differences already *pre* shock, i.e. under baseline conditions upon testing in a novel context (**FIGURE 11**).

Theta oscillations have been related to memory consolidation (e.g. (BUZSÁKI AND DRAGUHN, 2004; KAHANA, 2006; ROBBE AND BUZSÁKI, 2009; HYMAN ET AL., 2010; JUTRAS AND BUFFALO, 2010; RUTISHAUSER ET AL., 2010; KIM ET AL., 2011; LIEBE ET AL., 2012)), plasticity (e.g. (ORR ET AL., 2001; HYMAN ET AL., 2003)) emotional processing (e.g. (PARÉ ET AL., 2002; SEIDENBECHER ET AL., 2003; PAPE ET AL., 2005; MITCHELL ET AL., 2008)), innate anxiety (GORDON ET AL., 2005; ADHIKARI ET AL., 2010, 2011; JACINTO ET AL., 2013) as well as novelty-induced fear (JEEWAJEE ET AL., 2008; LEVER ET AL., 2010; JACINTO ET AL., 2013; WELLS ET AL., 2013; LIKHTIK ET AL., 2014), and have been proposed as a sorting mechanism for memories pending consolidation (BENCHENANE ET AL., 2010, 2011). Accordingly, disruption of theta waves impaired for example learning of a spatial task (MCNAUGHTON ET AL., 2006) as well as contextual fear (BISSIERE ET AL., 2011) in rats, while theta recovery reinstalled learning capabilities (MCNAUGHTON ET AL., 2006).

Theta oscillations are inhibited by anxiolytic drugs, and thus have been considered as a neurophysiological marker of anxiolytic drug efficacy (McNaughton et al., 2007; Engin et al., 2008). Similarly to the results reported here, the amount of theta activity has been shown to correlate with the strength of a contextual fear memory (Landfield et al., 1972). However, in the latter study, theta oscillations had been extracted from EEG measures and while animals were awake. A more recent study in rats has shown that theta synchrony between hippocampus and amygdala during REMS was associated with the strength of the consolidated conditioned fear memory (Popa et al., 2010). However, in this study no differentiation between low (theta 2) and high (theta 1) theta frequencies had been considered. Here, we expand the previous findings described above by demonstrating that **first**, after a contextual fear conditioning high responders (strong fear memory) and low responders (weak fear memory) displayed opposite changes in theta (particularly theta 2) power during consecutive REMS and following re-exposure to the shock context during WAKE a few days later; **second**, amygdalar alterations in theta power were related to the fear phenotype of the animals (high vs. low freezing/EMG power); and **third**, within groups theta activity changes during awake re-exposure and asleep REMS fairly resembled each other.

Based on these findings, and in accordance with the literature, we hypothesize that increased theta activity in general is indicative of an innate agitated, hyper-responsive (and potentially more vulnerable) phenotype, as high responders showed elevated theta power when being exposed to a novel context prior to the shock (**Figure 11**). Furthermore, excessive theta 2 activity in the BLA seems to be indicative of a highly fearful state: fear responses were strongly correlated with amygdalar power in this frequency range (**Figure 13B**). We consider analogous changes in limbic activation during WAKE and REMS after the shock as a presumable sign of re-activation of neuronal activity patterns that had been active during the shock event. Although we did not perform LFP recordings during the actual fear conditioning procedure (due to disturbing electrical noise generated by the shock device), we assume that upon recall of the conditioned fear memory similar neuronal circuits might become activated in the amygdala (Gross and Canteras, 2012). At this time point (3 days after the fear conditioning), memory consolidation presumably had not been completed yet, thus resulting in a hippocampus-dependent recall (Kim and Fanselow, 1992; Kitamura et al., 2009). Since in contrast to previous replay studies (see **chapter 1 Selective Re-activation during SWS, Selective Re-activation during REMS, p.24 ff.**) electrophysiological recordings from single cells were not performed in our investigation, examination of re-activated spike sequences in CA1 and BLA was not possible and thus, power changes as obtained from LFP recordings may only indicate a recurrence of limbic activity patterns but cannot provide a proof of replay.

Re-activation of temporal sequences of patterned neuronal activity, present during the acquisition of new information during wakefulness, has been shown to occur during both, NREMS and REMS. Brain regions, for which the occurrence of neuronal replay in animals has been confirmed so far, include the hippocampus (Pavlides and Winson, 1989; Poe et al., 2000; Sutherland and McNaughton, 2000; Louie and Wilson, 2001; O'Neill et al., 2010), the striatum (Pennartz et al., 2004; Lansink et al., 2008, 2009), and the cortex (Qin et al., 1997; Euston et al., 2007; Ji and Wilson, 2007; Peyrache et al., 2009; Johnson et al., 2010). To our best knowledge, spontaneous replay of fear memory related activity in the amygdala has not been investigated yet. However, cueing studies in animals and humans have provided strong evidence that triggered replay during sleep is beneficial for the consolidation of the cue-coded memory, likewise for spatial (Rasch et al., 2007; Rudoy et al., 2009; Bendor and Wilson, 2012), other declarative (Guerrien et al., 1989; Smith and Weeden, 1990; Antony et al., 2012), non-declarative (Ritter et al., 2012; Schönauer et al., 2014), as well as fear memories (Hars et al., 1985; Maho et al., 1991; Hauner et al., 2013; Rolls et al., 2013). Importantly, the presentation of an auditory cue, which was paired with a shock during previous fear conditioning, has been shown to result in elevated neuronal responses in the lateral amygdala (LA) during REMS (Hennevin et al., 1998). The lateral part of the amygdala receives sensory input from the thalamus and the cortex, thus coding of an auditory cue-shock association relies on neurons in this region (LeDoux, 2000; Maren, 2001; Fanselow and Poulos, 2005; Wotjak and Pape, 2013). Contextual information as provided by the hippocampus, on the other hand, was found to be paired with the shock information (coded in the LA) rather in the basolateral part of the amygdala (Calandreau et al., 2005, 2006; Barot et al., 2009; Flavell and Lee, 2012; Wotjak and Pape, 2013). Similar observations have also been reported in humans (Alvarez et al., 2008). Here we show that similar activation of the BLA occurs during REMS as during awake recall of a contextual fear conditioning memory. Thus, replay of emotional memory might arise within subparts of the amygdala depending on the form of the learned emotional association.

The similarity of electrophysiological characteristics between the vigilance states WAKE and REMS (Horne, 2000) supports the notion that awake experiences are replayed during this specific sleep stage. EEG recordings during REMS and alert wakefulness, for example, are almost indistinguishable as both are characterized by theta oscillations and a low amplitude signal, which coined the name of "paradoxical sleep" (awake-like EEG while being asleep) (Horne, 2013). Similarly, in humans REMS has also been referred to as "ascending stage 1 sleep" due to its EEG resemblance with drowsiness (Corsi-Cabrera et al., 2006; Horne, 2013). Although, as compared to WAKE, enhanced activation of emotion-related circuits and decreased activation of higher cortical areas characterize REMS, a global level of activation is very similar between WAKE and REMS (Dang-Vu et al., 2010). In

contrast to NREMS, sensory awareness is preserved during REMS. Sensory stimuli even seem to be evaluated by their potential risk during this sleep stage allowing the animal to arouse much more rapidly and to react to the stimulus, if necessary (Morrison et al., 2000; Horne, 2013). This function of emotional "tagging" is ascribed to the amygdala (Morrison et al., 2000), also during WAKE (Jacobs et al., 2012). Thus the gating of emotions by the amygdala leads only then to arousal, if it is demanded by an endangering situation, and thereby protects REMS continuity. Another similarity between REMS and WAKE is the potential pseudo-motor output that is provided during REMS. When entering REMS, muscle tonus of the face and neck is lost, while postural muscles are paralyzed although the actual muscle tonus is preserved (Morrison, 1988). However, when muscle paralysis is prevented, stereotypic behaviors can be expressed during REMS in the absence of external stimuli (Jouvet, 1979; Morrison, 1988). In cats such behaviors range from staring, head raising, searching, reaching and grasping to apparently stalking imaginary pray, aggression, attacks and other flight or fight behaviors, thus being presumably related to dreaming and replay of awake behavior.

In summary, as vigilance states of REMS and WAKE, but not NREMS, share several characteristics, and emotions and alertness are controlled by the amygdala during both stages, REMS seems to constitute an appropriate condition for the replay of particularly emotional memory. Investigations of replay functionality during dreaming, by activation measurements paired with assessment of dream occurrence, rely on dream reports from subjects, which represent a highly variable and subjective endpoint. Such experiments cannot be extrapolated to animals. Dreaming itself has been shown to be supportive of memory consolidation in humans (Wamsley et al., 2010a, 2010b; Blagrove et al., 2011) and spontaneous as well as cued replay studies in both, humans and animals, have confirmed the beneficial effect of neuronal activity replay as presented during an awake experience (e.g. (Deuker et al., 2013; Rolls et al., 2013) and see **chapter 1 Selective Re-activation during SWS, Selective Re-activation during REMS, p.24 ff.**). In PTSD patients, nightmares before and after the trauma (i.e. the re-experience of the traumatic situation during sleep) have been related to the later PTSD symptom severity (Foa et al., 1995; Mellman et al., 1995a; Koren et al., 2002; Kobayashi et al., 2008; Wright et al., 2011; van Liempt, 2012; van Liempt et al., 2013). We hypothesize that the observed re-activation of amygdalar activity during REMS in this study might strengthen the consolidation of the context-shock association, thus leading to an enhanced fear memory in high responders (PTSD-like phenotype), as compared to low responders (resilient phenotype).

All REMS is not the same

We observed a very strict separation between the behavioral subgroups of high and low responders according to their amygdalar theta 2 power during the

re-exposure testing. While all high responders displayed increased theta 2 activity in the BLA, i.e. a calculated z-score that was greater than +0.5 standard deviations, all low responders showed decreased amygdalar theta 2 activation that was at least -0.5 standard deviations smaller than during the novelty exposure challenge. As theta 2 frequencies are present during threatening situations (KRAMIS ET AL., 1975; VANDERWOLF, 1975; BLAND, 1986; SAINSBURY ET AL., 1987A, 1987B) and amygdalar theta 2 power was associated with a highly fearful state in the present study, we used the theta 2 z-score to define REMS episodes characterized by elevated *vs.* decreased theta 2 power in the BLA, as compared to baseline.

This classification allowed for an objective subdivision of all REMS episodes which were highly variable in terms of duration and amygdalar and hippocampal power. In rodents, like in humans, REMS characteristics seem to diverge in their characteristics across the sleeping period. For example, in humans REMS amount and episode durations increase during the second half of the night. REMS can be divided into tonic and phasic states, the latter being characterized by bursts of rapid eye movements accompanied by pontine-geniculate-occipital activity (PGO waves) which have been shown to facilitate learning and memory processes in animals (DATTA, 2000; DATTA ET AL., 2005, 2008; DATTA AND O'MALLEY, 2013). Human PGO waves have been associated with increased activity, amongst others, in the amygdala (MIYAUCHI ET AL., 2009), and electrical stimulation of the amygdala resulted in elevated PGO activity during REMS in rats (DATTA, 2000). Human studies have further shown that the replay of a learned morse code or of a ticking sound, that had been paired with the learning of complex rules, during phasic REMS (as opposed to tonic REMS or no presentation), resulted in a better performance on the next day (GUERRIEN ET AL., 1989) and 1 week later (SMITH AND WEEDEN, 1990). Together these findings suggest that strengthening of learned associations might occur during specific REMS episodes characterized by high amygdalar activation. Likewise, neuronal experience-related activity patterns are probably not replayed during every REMS episode. In accordance with this theory, dream reports are prevalent particularly during phasic REMS (WEHRLE ET AL., 2007), suggesting that not every REMS episode is paired with dreaming (at least with dreams that are remembered upon awakening). Among PTSD patients, about 50% report their dreams to be exact replications of the traumatic event (WITTMANN ET AL., 2007), with a tendency of this dream to reoccur (SCHREUDER ET AL., 1998). Based on the observations described above, we hypothesize that REMS episodes of high theta 2 power ($REMS_{>0.5}$) may be paired with re-activation of neuronal activity associated with the aversive shock experience, thus leading to a stronger memory of the traumatic event.

The comparison of the three REMS episode types under baseline conditions (**FIGURE 14**) congruently showed that $REMS_{>0.5}$ comprised the episodes of highest theta 2 activity in CA1 and BLA, lowest theta 1 activity in CA1 and the strongest coupling between hippocampus and amygdala (highest phase coherence, lowest time lag). The observed hippocampal power characteristics of $REMS_{>0.5}$ are in line

with the assumption that frequency bands specifically associated with fear-related (theta 2), but not exploratory (theta 1) behavior, are activated during this REMS episode type. Stronger coupling between amygdala and hippocampus during REMS has been described as an indicator of fear memory strength in an earlier study (POPA ET AL., 2010). Interestingly, here we saw that $REMS_{>0.5}$ presented a stronger limbic coupling especially within the theta 2 frequency range, in which the hippocampus was found to "lead" the amygdala (positive time lag; **FIGURE 14C** and see **CHAPTER 3 TIME LAG BETWEEN AMYGDALA AND HIPPOCAMPUS, P.103 FF.**). In accordance with this finding and in support of the idea that replay and strengthening of the shock memory might have occured particularly during $REMS_{>0.5}$, replay studies in rodents have revealed that the hippocampus has a guiding role during re-activation of later strengthened memory, since hippocampal replay was found to precede replay in cortical and striatal regions (LANSINK ET AL., 2008, 2009; PEYRACHE ET AL., 2009). Thus, $REMS_{>0.5}$ episodes might represent a suitable state for the strengthening of especially emotional memories as **I)** amygdalar and hippocampal theta 2 activity were specifically elevated during this episode type, and **II)** interplay between the amygdala and the hippocampus in the theta 2 frequency range was predominant within these REMS periods.

The more, the better?

Although we did not find an overall increase of REMS amounts in the second experiment (as discussed above, **REMS ALTERATIONS, P.115 FF.**), high responding mice, but not low responders, displayed more REMS episodes characterized by high amygdalar theta 2 power ($REMS_{>0.5}$) *post* shock as compared to basal measures. Based on the reports from replay studies, where the effective replay of several kinds of acquired information has been shown to benefit the capacity for remembering (GUERRIEN ET AL., 1989; SMITH AND WEEDEN, 1990; RASCH ET AL., 2007; RUDOY ET AL., 2009; ANTONY ET AL., 2012; RITTER ET AL., 2012; VAN DONGEN ET AL., 2012; DEUKER ET AL., 2013; RIHM ET AL., 2014; SCHÖNAUER ET AL., 2014), more $REMS_{>0.5}$ might also imply more situational replay in high responding animals, thus leading to a better (over-consolidated) fear memory and an elevated fear response upon re-exposure to the shock environment. Potentially, the observed increase in time that shocked mice spent in REMS in experiment 1 (**FIGURE 4**) consequently represents a gain of "replay-suitable" $REMS_{>0.5}$ episodes.

Recordings under baseline conditions revealed that the duration of $REMS_{>0.5}$ episodes was generally shorter than that of the other two REMS episode types (**FIGURE 14F**). Therefore, an elevated number of shorter REMS periods in high responders may denote a more fragmented REMS pattern in these PTSD-like phenotype expressing animals, as compared to low responders. REMS fragmentation has not only been described as a prevalent symptom in PTSD patients (GLAUBMAN ET AL., 1990; MELLMAN ET AL., 1995B, 2002, 2007; HABUKAWA ET AL.,

2007; INSANA ET AL., 2012) but was also found to be related to the severity of trauma-related nightmare complaints (HABUKAWA ET AL., 2007) and to an increased risk and severity of PTSD (MELLMAN ET AL., 2002, 2004, 2007). In humans, REMS fragmentation implies more brief arousals from REMS (MELLMAN ET AL., 1995B; BRESLAU ET AL., 2004; HABUKAWA ET AL., 2007). As REMS episodes in rodents are typically followed by a brief arousal under "unchallenged" conditions (HORNE, 2013), we did not investigate this aspect here. However, as detailed above (**REMS ALTERATIONS, P.115 FF.** and **CHAPTER 2 SYMPTOMATIC VALUE OF REMS P.58 FF.**), the differentiation between microarousals and longer awake periods in experiment 1 revealed no significant changes in the duration of awakenings succeeding REMS *post* shock. Nevertheless, similar to the findings in PTSD patients (MELLMAN ET AL., 2002, 2004, 2007), REMS fragmentation under basal conditions predicted the severity of a hyperaroused PTSD-like phenotype expressed 1 month after the aversive experience (**FIGURE 5A**).

Like high responding animals, non-shocked mice displayed an unexpected increase of $REMS_{>0.5}$ after the exposure to the unfamiliar shock context. That is, the confrontation with the mere "shock context" resulted in an elevation in REMS episode types characterized by stronger amygdalar theta 2 activation. Although one possible explanation of this finding is that the amygdala might tag the novel experience with an emotional value and strengthen the memory of this situation, we would like to stress that the two conditions in shocked and non-shocked animals are hardly comparable. Re-exposure to the shock context presumably was paired with the expression of two different neuronal activation patterns in mice that received the shock (aversive experience) *vs.* mice that merely explored a novel context (novelty experience). While in the former case, re-exposure to the shock context induced fearful behavior and possibly remembering of the traumatic situation, recognition of a previously explored environment which was not associated with a fearful experience and did not elicit fear behavior (**FIGURE 8**), was not accompanied by a fear-related neuronal activation pattern (**FIGURE 11**). Accordingly, z-score calculations in the non-shocked group did not reveal a strong trend towards altered amygdalar theta 2 power (**FIGURE 13A**). Thus, even if the observed increase of $REMS_{>0.5}$ in the non-shocked mice was paired with more replay events, the replayed situation, its emotional value, and the related neuronal activation would presumably be different between groups. This aspect underlines the question of the appropriate control group in this experiment, as discussed above (see **LOW RESPONDERS VS. HIGH RESPONDERS - THE SEARCH FOR RESILIENCE?, P. 120 F.**).

WE ARE WHAT WE DREAM? - RISK VS. RESILIENCE FACTORS IN POST-TRAUMATIC STRESS DISORDER

The analysis of amygdalar activity changes as compared to baseline measures (z-score calculation) and the resulting classification of REMS episodes into three subtypes of strongly increased ($REMS_{>0.5}$), strongly decreased ($REMS_{<-0.5}$) and almost unchanged ($REMS_{others}$) power in the BLA in the present study revealed that high responders, but not low responders, spent more time in $REMS_{>0.5}$ *post* shock, at the expense of the number of $REMS_{<-0.5}$ episodes (**FIGURE 13C**). When we inspected particularly these $REMS_{>0.5}$ episodes with regard to changes of episode features from *pre* to *post* shock, we found that differences between groups were already present under baseline conditions. That is, limbic activation (amygdalar theta 2 and hippocampal theta 1 power, **FIGURE 15**) during $REMS_{>0.5}$ episodes differed between prospective low and high responding mice already before the shock. Similarly, REMS architecture (fragmentation) *pre* shock predicted the severity of the developed hyperaroused PTSD-like phenotype in experiment 1 (**FIGURE 5**) (POLTA ET AL., 2013). Thus, limbic activation patterns, especially during REMS episodes of amygdalar hyperactivity, might be associated with the probability of high *vs.* low consolidation of the traumatic experience, i.e. a vulnerable *vs.* resilient individual might be predefined on the basis of its REMS quality under basal conditions.

In a psychiatric-pathological context, as discussed in this thesis, vulnerability refers to the inability of an individual to adequately and successfully adapt to an acute stress, trauma, or chronic adverse condition. Resilience on the other hand is understood as the ability to cope with such stressful or traumatic situations (CHARNEY, 2004; FEDER ET AL., 2009). Still, resilience constitutes not only the absence of pathological responses as presented by susceptible individuals (passive resilience). Rather, resilience is mediated by active adaptive processes promoting healthy behavioral function (active resilience) (RUSSO ET AL., 2012). Although the development of PTSD by definition is induced by the exposure to a traumatic event, biological abnormalities that are found in PTSD patients must not necessarily be caused by the trauma (PITMAN ET AL., 2012). Potential risk factors might facilitate the development of the disease and its symptomatology. With the help of such vulnerability markers, populations at risk could be monitored on a regular basis and early detection and prevention of PTSD by pharmacological or behavioral treatment could be achieved. Previous studies in humans, and animal models, have revealed a broad spectrum of potential risk and resilience factors, comprising genetic, epigenetic, environmental, psychophysiological, psychosocial, neuroendocrine, neurostructural, neurophysiological and neurocircuit-related aspects (SCHMIDT ET AL., 2013B).

Genetic studies so far have focused on the identification of potential candidate genes that determine the risk or resilience to develop psychiatric

disorders induced by a highly stressful event (e.g. *FKBP5* (Binder et al., 2008), *NPY* (Zhou et al., 2008)). However, the described associations are rather weak and their role far from being understood (Pitman et al., 2012; Russo et al., 2012). Similarly, epigenetic mechanisms, such as DNA methylation or histone modifications, have been suggested to influence the development of PTSD (for review see (Feder et al., 2009; Pitman et al., 2012; Zovkic and Sweatt, 2012; Raabe and Spengler, 2013)). Importantly, environmental factors, such as early life experiences and stress exposure, strongly interact with epigenetic mechanisms and can lead to sustained dysregulation of homeostatic mechanisms (Patchev et al., 2014). Epigenetic effects might explain the occurrence of resilient and vulnerable responses towards stress also in genetically identical animals under controlled environmental conditions and histories. As mice presenting as high and low responders in our study originated from different litters born over 1.5 years, the influence of environmental factors might be more substantial. It is noteworthy that "individuality" and "personality" are displayed also by inbred animals, and are shaped by social experience from the prenatal phase throughout adolescence and beyond through behavioral and neuroendocrine processes (Lewejohann et al., 2011; Freund et al., 2013; Sachser et al., 2013). Similar gene-environment interactions explain the development of different personalities in human monozygotic twins.

Psychosocial factors promoting successful adaptation to stress have been addressed mainly in human studies, however some behavioral aspects in animals could also be implied in this category of resilience/vulnerability markers (for review see (Feder et al., 2009)). In humans, identified resilience factors include for example optimism and positive emotions, social competence and openness to social support, a sense of purpose in life, spirituality, cognitive reappraisal, facing fears and active coping strategies. The latter can be matched with "fight or flight" responses in animals, i.e. active responses like attempts to escape or aggression, or passive responses, like freezing and submission, which might characterize a rather vulnerable individual (Korte et al., 2005), although both can be considered as adaptive with regard to the particular situation (Feder et al., 2009). In the present study, only one behavioral endpoint, i.e. fear behavior upon the exposure to a novel context, was assessed before the shock, where prospective high and low responders showed similarly low freezing responses (**Figure 8**). Within the same mouse model, however, maternal inexperience has been determined as a risk factor for the development of PTSD-like symptoms after the shock experience (Siegmund et al., 2009a). Nurturing maternal behavior has also been described as a risk/vulnerability factor in rats, not only influencing anxious and later nurturing behavior of the pups but also inducing epigenetic and endocrine stress-related changes (Weaver et al., 2004; Meaney and Szyf, 2005).

Neuroendocrine responses to stress in general constitute prominent factors underlying the variability in stress- and trauma-resilience (Russo et al., 2012). The main mediator of the impact of stress on brain and behavior is the hypothalamic-pituitary-adrenal (HPA) axis which, upon activation, induces a variety

of hormonal, neurochemical and physiological alterations influencing behavior. In PTSD patients, hyper-reactivity of the sympathetic nervous system has been suggested as a symptomatic aspect of the disease and, at least in part, as a risk factor for the disorder (YEHUDA, 2009). Hypocortisolemia has not been consistently replicated as a hallmark in PTSD patients (MEEWISSE ET AL., 2007), and in contrast to a state of chronic stress or depression, PTSD does not seem to be accompanied by tonically increased cortisol levels (YEHUDA, 2002). Animal models of PTSD support the notion of altered neuroendocrine responses as risk factors for the development of a PTSD-like phenotype. Increased hippocampal glucocorticoid receptor levels have e.g. been found in a single prolonged stress (LIBERZON ET AL., 1999A; ZHE ET AL., 2008) and a predator stress (KOZLOVSKY ET AL., 2009) model of PTSD where treatment with a glucocorticoid receptor antagonist (ADAMEC ET AL., 2007; KOHDA ET AL., 2007) as well as a high dose corticosterone (COHEN ET AL., 2008) prevented behavioral and plasticity changes induced by the stress. Although in previous studies we have not observed alterations in corticosterone in our fear-conditioning mouse model (UNPUBLISHED DATA), we cannot rule out HPA-axis dysregulation as a potential risk factor for the observed low and high responding phenotypes, as stress-related endocrine responses have not been measured within this thesis. Taken together, although the HPA axis is essential for a physiological, adaptive stress response, its impact on resilience/risk to develop PTSD remains to be investigated. Other neuroendocrine processes influencing HPA axis activity have been identified as potential resilience/risk factors, including, amongst others, dehydroepiandrosterone (DHEA), testosterone and neuropeptide Y, although further studies need to replicate these findings and confirm their interpretations (PITMAN ET AL., 2012; RUSSO ET AL., 2012).

Psychophysiological responses like elevated emotional reactivity, exaggerated startle response, and poor fear extinction, as measured by heart rate, skin conductance, and facial EMG, have further been hypothesized as potential risk factors in PTSD (PITMAN ET AL., 2012). Whereas increased heart rate and startle responses seem to represent rather acquired features of the disorder (SHALEV ET AL., 2000; ORR ET AL., 2003; GRIFFIN, 2008; METZGER ET AL., 2008), i.e. induced by the trauma, prospective studies have found that elevated skin conductance and eye-blink responses (GUTHRIE AND BRYANT, 2005), as well as slower extinction of fear conditioned facial EMG responses (GUTHRIE AND BRYANT, N.D.; ORR ET AL., 2012) and slower habituation of auditory startle responses (POLE ET AL., 2009) predicted PTSD symptom severity. Contradicting findings from twin studies suggest that poor extinction or extinction retention, like enhanced heart rate and startle reactivity, rather represent symptomatic factors (MILAD ET AL., 2008).

Although no measures of autonomic stress responses have been obtained in the present study, we replicate the observation of a hyperaroused PTSD-like phenotype in our animal model (SIEGMUND AND WOTJAK, 2007A, 2007B) and further show a strong association between elevated startle responses *post* and REMS architecture *pre* shock (POLTA ET AL., 2013). Accordingly, sleep-related risk factors for

the development of PTSD have been described in humans. REMS disturbances or REMS fragmentation (MELLMAN ET AL., 2002, 2004, 2007), nightmares and disturbed sleep due to nightmares (MELLMAN ET AL., 1995A; VAN LIEMPT, 2012; VAN LIEMPT ET AL., 2013) have been implicated in this context. We hypothesize that variations in limbic activity patterns during REMS before a traumatic experience, as observed in the present work, might identify vulnerable *vs*. resilient individuals on the basis of qualitative aspects of REMS.

In accordance with the results presented here, neurostructural and connectivity studies in PTSD patients and animal models point towards changes in emotion-processing structures, like the amygdala and the hippocampus, as potential vulnerability markers. Although the status of hippocampal diminution as an acquired *vs*. pre-existing risk factor in PTSD patients is debated (BREMNER, 2001; GILBERTSON ET AL., 2002; KASAI ET AL., 2008; WOON ET AL., 2010; SEKIGUCHI ET AL., 2013), we have shown in a previous study that low hippocampal levels of N-acetyl-aspartate predict the development of PTSD-like symptoms in the mouse (SIEGMUND ET AL., 2009B). Also decreased amygdalar volume was considered as a potential risk factor in humans (MOREY ET AL., 2012). Furthermore, correspondingly to a proposed vulnerability due to a hyper-reactive sympathetic nervous system, hyper-activation of the amygdala (ADMON ET AL., 2009, 2013A; MOREY ET AL., 2012) and the dorsal anterior cingulate cortex (dACC) (SHIN ET AL., 2009, 2011; SCHULZ-HEIK ET AL., 2011) have been hypothesized to increase the risk of developing PTSD after a traumatic experience. Variations in activity and connectivity between emotion-related structures have additionally been shown to correlate with individual anxiety levels in humans (KIM ET AL., 2010; CORNWELL ET AL., 2012) and animals (GORDON ET AL., 2005; ADHIKARI ET AL., 2010, 2011; JACINTO ET AL., 2013). Congruent findings have been obtained in our study, as high and low responders displayed certain differences in amygdalar and hippocampal activity (theta 1 power, **FIGURE 11**) and connectivity (theta coherence, **FIGURE 16**) already at the time before the shock, when exposed to a novel environment. Importantly, a recent study performed in humans found subgroups varying in baseline sleep characteristics that reacted differentially towards an emotionally distressing film in terms of emotional responsiveness and subsequent sleep behavior. Individuals with a strong emotional response to the distressing stimulus spent more time in REMS during the preceding (baseline) night than individuals with a moderate emotional reaction. The authors suggest a coupling of certain emotion and sleep traits into distinct emotional sleep types (TALAMINI ET AL., 2013). In consistence with this notion, pre-trauma difficulties with emotional control have been shown to predict the development of post-traumatic stress symptoms following exposure to a mass shooting (BARDEEN ET AL., 2013). Thus, the ability to cope with emotionally distressing experience might depend on emotional, as well as certain sleep-related traits. In this vein, in the present study limbic activity patterns during REMS episodes with a potentially high emotional value ($REMS_{>0.5}$) denoted the two subgroups of high and low fear responding mice already under baseline conditions (**FIGURE 15**). Also, baseline REMS architecture

predicted the severity of the *post* shock developed PTSD-like hyperarousal (**FIGURE 5**). As suggested before (GERMAIN, 2013), regular sleep monitoring in high-risk populations/occupations might facilitate early intervention or rather the enhancement of resilience by preventive treatment. However, the performance of prospective and longitudinal studies in high-risk individuals is strongly required in order to understand how emotional sleep traits contribute to vulnerability (or also resilience) towards PTSD development after the experience of a traumatic situation.

TECHNICAL ISSUES AND LIMITATIONS OF THE STUDY

„Wer viel misst, misst viel Mist."

General saying in the electrophysiological field

This saying, stated here in German, is commonly expressed in the community of electrophysiologists and literally translated means "recording a lot, produces a lot of rubbish". At this point we would like to stress with this quote that in general, one should critically scrutinize the used recording techniques and methods, the signals obtained, the parameters applied to the recorded signals, and the interpretations and conclusions drawn from the results. Thus, in this paragraph we would like to point out and discuss the limitations of the present study including several methodological as well as interpretational aspects.

Paradoxically, a major strength of this study represents also its most prominent weakness. When designing the second experiment of the present study, we did not expect the appearance of such strongly diverging subgroups of high and low responding animals. Indeed, we had observed differentially strong fear responses of the used inbred mouse strain already before (SIEGMUND AND WOTJAK, 2007A; SIEGMUND ET AL., 2009B), however we did not predict such pronounced distributions with respect to the recorded limbic activity patterns, ranging down to levels of the non-shocked controls. The subdivision of the shocked group resulted not only in diminished statistical power (n=6 *vs.* n=4), creating several only marginally significant effects or trends and making correction for multiple comparisons (multiple potentially dependent parameters) unsuitable. Also the adequacy of the control group of non-shocked animals proved rather unsatisfactory (see also **LOW RESPONDERS VS. HIGH RESPONDERS - THE SEARCH FOR RESILIENCE?, P.120 F.**). Due to infrastructural limitations, recordings had to be performed in a serial manner over 1.5 years, thus impact of

seasonal/environmental/maternal factors (different litters) cannot be excluded. However, the resulting "individuality" also constitutes a merit of the study, as basal REMS characteristics were shown to be potentially related to emotional vulnerability. Future studies are needed to confirm this interpretation by the use of larger experimental group sizes and preceding *pre* shock classifications of high *vs*. low responders on the basis of behavioral endpoints (e.g. anxiety measures in the open field test, on the elevated plus maze, as done in other animal models of PTSD (COHEN AND ZOHAR, 2004; COHEN ET AL., 2012A)).

It is pertinent to highlight that epidemiological studies suggest the risk for developing PTSD to be twofold higher in women than in men (TOLIN AND FOA, 2006; OLFF ET AL., 2007). Similarly, male rodents seem to be more resilient towards chronic stress than females (LAPLANT ET AL., 2009). The biological source of this prevalence for PTSD in females might be explained by stronger brainstem activation to threat stimuli (FELMINGHAM ET AL., 2010) and by physiological fluctuation of ovarian hormones, as indicated by rodent studies (BOWMAN ET AL., 2002; LAPLANT ET AL., 2009). In the present study, only male mice were used, with the aim to avoid cyclic hormone fluctuations. However, in future studies it would be intriguing to examine whether gender differences are paired with the differential occurrence of REMS-specific replay of the traumatic situation or fear-related REMS episode *per se*.

With respect to the electrophysiological method used here, the extracellular recording of electric potentials in the form of cortical EEGs and local field potentials (LFP), through deep electrodes in the region of the BLA and the CA1, potentially holds certain limitations. Electric potentials in the brain basically constitute voltage fluctuation arising from a summation of ionic currents across cellular membranes generated from several sources (see (BUZSÁKI ET AL., 2012) for extensive review). All transmembrane currents from spines, dendrites, somas, or axons etc., superimpose and form the potential we record with our electrodes. Magnitude, sign, spatial as well as temporal distribution (synchrony) of these currents shape the extracellular field, and thus, the recorded electric potential. Sodium spikes (generating action potentials), calcium spikes, neuronal burst induced hyperpolarizations, intrinsic voltage-dependent oscillations, and synaptic activity (inhibitory and excitatory post-synaptic potentials) all contribute as current sources to the fluctuations of LFP/EEG to a varying degree (MONTGOMERY, 2009; BUZSÁKI ET AL., 2012). Since in this study we did not obtain simultaneous (multi-) unit recordings from the BLA and the CA1 region in addition to LFP, we cannot exclude the probability that the recorded electric field potentials are "contaminated" by volume conduction. As "*verification of the local nature of the signal always requires the demonstration of a correlation between the LFP and local neuronal firing*" (BUZSÁKI ET AL., 2012), we cannot rule out that observed changes in the relationship between the hippocampal and the amygdalar signal (time lag, coherence, phase coherence) are due to volume conduction. Nevertheless, interpretations of our findings are based mainly on results from behavioral and amygdalar power measures, and not on

inter-limbic activity relations. The observation of a replay-like phenomenon during REMS, as well as the differentiations between high and low responders related to REMS characteristics under baseline conditions, are consistent, even if all recorded activity might have been biased by volume conduction. Confirmation of the local nature of the measured limbic signals and verification of the observed re-activation of limbic activity patterns during REMS requires further studies on a single-cell recording level.

LFP recordings in the present study have been performed in the BLA and the CA1 region of the dorsal hippocampus (dHPC). First observations of a cued fear conditioning-induced alteration in synchronized theta activity between the hippocampus and the amygdala had been based on LFP recordings from the lateral amygdala (LA) and the CA1 of the dHPC in mice (SEIDENBECHER ET AL., 2003). Since our mouse model comprises a contextual, instead of a cued, fear conditioning paradigm for mimicking the traumatic experience, and the dHPC is mainly implicated in the learning of spatial information (MOSER ET AL., 1993, 1995; HOCK AND BUNSEY, 1998; BANNERMAN ET AL., 1999, 2002; POTHUIZEN ET AL., 2004), we opted to place one of the LFP electrodes within the CA1 region of this dorsal part of the hippocampus. The amygdala, as the brain region most implicated in fear (GROSS AND CANTERAS, 2012), was targeted in its basolateral part, since contextual information is most likely paired with information about the shock stimulus in the BLA (CALANDREAU ET AL., 2005, 2006; ALVAREZ ET AL., 2008; BAROT ET AL., 2009; FLAVELL AND LEE, 2012; WOTJAK AND PAPE, 2013). However, direct projections between the hippocampus and the basolateral amygdala have only been confirmed for the ventral hippocampus so far (MAREN AND FANSELOW, 1995; PITKÄNEN ET AL., 2000; PETROVICH ET AL., 2001). Thus discrepant findings between the current study and the literature regarding inter-limbic parameters might be accounted for by the lack of direct communication between the dorsal CA1 and the BLA. For example, while theta coherence between hippocampus and amygdala during REMS was associated with the strength of the conditioned fear memory in rats (POPA ET AL., 2010), here we found no variations in theta coherence during REMS *post* shock when comparing low and high responders. Since spatial processing seems to involve the interaction of vHPC and dHPC (ADHIKARI ET AL., 2010; ROYER ET AL., 2010; SCHMIDT ET AL., 2013A; WANG ET AL., 2013), information flow from the dHPC to the amygdala might pass indirectly, though the vHPC, as hypothesized also for information passage to the mPFC (O'NEILL ET AL., 2013). Nonetheless, studies in PTSD patients reported negative impacts of the disease on specifically the posterior (dorsal) part of the hippocampus (BONNE ET AL., 2008; CHEN AND ETKIN, 2013) and the induction of a PTSD-like phenotype in mice has been observed after the infusion of glucocorticoids into the dHPC (KAOUANE ET AL., 2012). Taken together, further studies are needed to scrutinize the precise projections between different parts of the hippocampus and the amygdala. Although connections between the regions of CA1 and BLA might be indirect, re-occurring activation of these brain areas during REMS nevertheless likely carries spatial and emotional information that had

been associated during fear conditioning. Also, dHPC-BLA synchrony, albeit possibly guided by the vHPC, might still inform about the strength of amygdalar-hippocampal communication.

In summary, despite the discussed limitations, we consider the methods applied in this study as solid and adequate, and consider our findings as valid and important for this field of research engaged with the objectives of fear, anxiety, memory, sleep and dreams. Thus, they might advance our knowledge and inspire further research with regards to fear-related mnemonic processes during sleep which might also contribute to the development of psychiatric diseases, like PTSD.

QUOD ESSET DEMONSTRANDUM – AN OUTLOOK

To be afraid or fearful, in humans, refers to the feeling that arises when we experience our wellbeing, if not survival, to be threatened. The relation between the feeling of fear and the physiological responses that accompany or underlie this feeling, however, remains debatable. This philosophical controversy (see also the Mind-Body-Problem (LEDOUX, 2003)) obviously needs to be met by a reasonable compromise when studying fear-related aspects in animals. Therefore, the terms "fear" and "fear responses" in animals refer to behavioral and physiological responses presented by the animal in potentially threatening situation (GROSS AND CANTERAS, 2012).

In the present work, for example, the behavioral response of freezing and enhanced amygdalar activity had been used to indicate such fear-related states. Although the amygdala is the brain region most often implicated in fear-related conditions (e.g. fear of conditioned stimuli or contexts, predator fear, fear of aggressive conspecifics, novelty induced fear, *etc.*), fear-related phenomena during sleep and their relation to amygdalar activity have so far been studied extensively only in humans. The amygdala is highly active during sleep, also in animals, and its activity has been shown to be associated with bad dreams and nightmares in humans (see **CHAPTER 1 SLEEPING YOUR WORRIES AWAY, P.6 FF.**). In order to provide additional proof that signs of amygdalar hyper-activity during REMS are indicative of fear in animals, future studies will need to implement additional simultaneous measures, for example, of autonomic responses like heart rate or heart rate variability (STIEDL ET AL., 2009; LIU ET AL., 2013). Not only have arrhythmias been shown to be more evident during REMS (HOLTY AND GUILLEMINAULT, 2011). Also heart rate variability was reported to be positively correlated with regional cerebral blood flow in the right amygdala during REMS (DESSEILLES ET AL., 2006) and seems to be implicated in the development of PTSD (MELLMAN ET AL., 2004). Additional measures of fluctuating corticosterone levels during sleep may supplement the insights which

can be drawn from brain activity and heart rate responses, since changes in cortisol might explain the nature of dreams across the sleep cycle in humans (PAYNE AND NADEL, 2004). As dreaming and nightmares are not restricted to REMS, i.e. REMS can occur without dreaming but also dreaming can occur without REMS (DE GENNARO ET AL., 2012), and replay of awake experiences has been intensively studied also during NREMS (see **CHAPTER 1 SELECTIVE RE-ACTIVATION DURING SWS, P.24 FF.**), comparing NREMS and REMS episodes will yield further insight on the REMS-specificity of emotional replay.

Besides nightmares occurring during sleep, flashbacks during WAKE constitute another negative symptom affecting daily life in PTSD patients, where the concerned person is thrown back into the traumatic situation and re-experiences the horror over and over again. Mental imagery studies have reported that similar regions activated during the processing of real sensory stimuli are also involved in the imaginary equivalent (DASELAAR ET AL., 2010). Several studies in humans and animals have revealed that activity patterns of newly encoded information are also re-activated during subsequent episodes of WAKE (CARR ET AL., 2011; DIEKELMANN ET AL., 2011; RASCH AND BORN, 2013). Thus, the replay of fear-related memory during WAKE could be an interesting subject of future studies in combination with the above described physiological measures of fear. One of the challenges here will be that theta rhythms are present during an immense variety of behaviors during WAKE, thus detection of fear, unless paired with obvious fearful behavior, might be complicated with respect to amygdalar activity.

Importantly however, independently of the vigilance state during which a re-experiencing-like phenomenon could be observed, the validation of the involvement of this process in the somehow disturbed processing of an aversive experience in this PTSD model is absolutely essential and has yet to be examined in future studies by, for example, pharmacological or optogenetic approaches. Thus, the treatment with sleep-improving (e.g. Prazosin) or PTSD-symptom diminishing (e.g. antidepressants) drugs, the optogenetic switching-on and -off of REMS (to e.g. induce REMS fragmentation), or the alteration of REMS quality (by prohibiting e.g. theta oscillations with anxiolytic drugs), *pre* or *post* shock will extend our knowledge about the symptomatic and/or prognostic role of REMS in PTSD. REMS, in all its facets, also related to dreaming, thus remains one of the most promising starting points for future research on PTSD, or, to quote a hypothesis formulated already 25 years ago, REMS disturbances might constitute "the hallmark of PTSD" (ROSS ET AL., 1989).

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LIST OF PUBLICATIONS

Publications

Polta SA, Fenzl T, Jakubcakova V, Kimura M, Yassouridis A, Wotjak CT (2013) Prognostic and symptomatic aspects of rapid eye movement sleep in a mouse model of posttraumatic stress disorder. Frontiers in Behavioral Neuroscience 7:1–13

Stepan J, Dine J, Fenzl T, Polta SA, Wolff G von, Wotjak CT, Eder M (2012) Entorhinal theta-frequency input to the dentate gyrus trisynaptically evokes hippocampal CA1 LTP. Frontiers in Neural Circuits 6:1–13

Michalakis S, Kleppisch T, Polta SA, Wotjak CT, Koch S, Rammes G, Matt L, Becirovic E, Biel M (2011) Altered synaptic plasticity and behavioral abnormalities in CNGA3-deficient mice. Genes, brain, and behavior 10:137–48

Kreuzer M, Polta SA, Fenzl T (2014) Straight forward and automated sleep scoring tool using electroencephalographic recordings in mice. *in prep*.

Conference contributions

Society for Neuroscience 43rd Annual Meeting, San Diego, 2013
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Kreuzer M, Polta S, Kochs EF, Fenzl T (2013) Straight forward and automated sleep scoring tool using electroencephalographic recordings in mice: 7AP4-4. Eur J Anaesthesiol 30.

Federation of European Neuroscience Societies Forum, Barcelona, 2012
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EIDESSTATTLICHE VERSICHERUNG/AFFIDAVIT

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation „The Architecture and Limbic Activity Characteristics of Rapid Eye Movement Sleep as Symptomatic and Prognostic Factors in an Animal Model of Post-Traumatic Stress Disorder“ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation “The Architecture and Limbic Activity Characteristics of Rapid Eye Movement Sleep as Symptomatic and Prognostic Factors in an Animal Model of Post-Traumatic Stress Disorder” is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, November 2014

Stephanie Patchev

CONTRIBUTIONS

The author of the present thesis contributed to the first experiment by conceiving of the experimental questions and hypotheses, designing the experimental schedule, conducting the experiment (including surgeries, recording of electrophysiological data, behavioral tests) and analyzing its data (sleep scoring, behavioral readout, statistical analysis). She also wrote the manuscript and designed figures and tables of the resulting publication in "Frontiers in Behavioral Neuroscience" (POLTA ET AL., 2013).

The author of the present thesis contributed to the second experiment by conceiving of the experimental questions and hypotheses, designing the experimental schedule, conducting the experiment (including surgeries, recording of electrophysiological data, behavioral tests) and analyzing its data (signal processing, sleep scoring, behavioral readout, signal analysis, statistical analysis). She also wrote the program routines in MATLAB® for the processing and analysis of the electrophysiological data.

Herewith the author of this thesis confirms her contributions to the present study as specified above.

München, November 2014

Stephanie Anna Patchev

Herewith I confirm the contributions of Ms. Stephanie Polta to the present study as specified above.

München, November 2014

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