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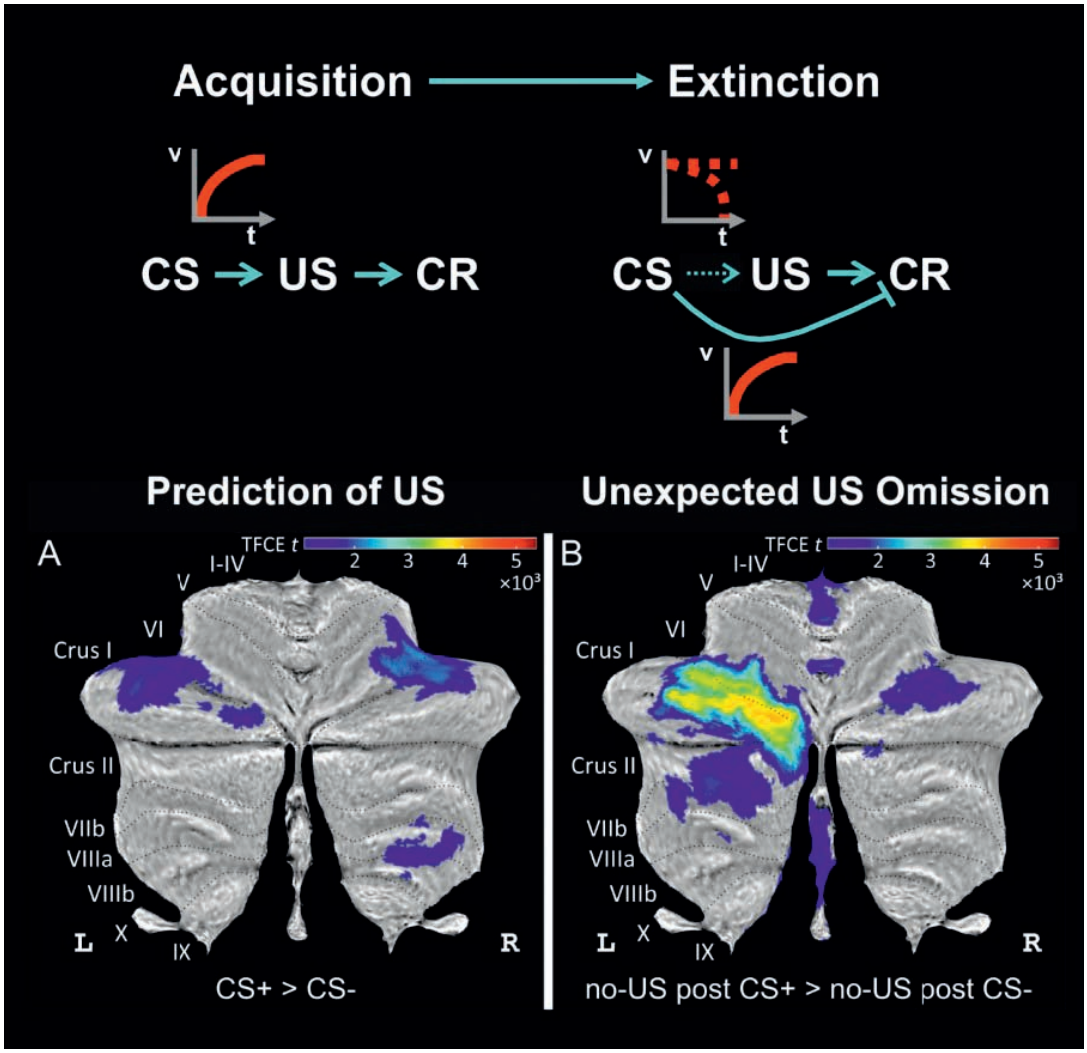

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COVER ILLUSTRATION Differential cerebellar activations during fear acquisition. (A) Cerebellar activations related to the prediction of the US (contrast CS+ > CS−) are shown as cerebellar flatmap (Diedrichsen and Zotow, 2015). (B) Cerebellar activations related to the unexpected of the omission of the US (contrast no-US after CS+ > no-US after CS−). Cerebellar activation is abolished during extinction. All contrasts calculated using TFCE and familywise error correction ($p < 0.05$). CS, conditioned stimulus; L, left; R, right; TFCE, threshold-free cluster enhancement; US, unconditioned stimulus. Adapted from Figure 3 in the study by Ernst et al. (2019). Cover figure provided by Onur Güntürkün et al., Beyond the classic extinction network: a wider, comparative view (nf-2020-0009, pp. 161–169 in this issue).

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Inhalt

Review articles

Presentation of scientific institutions

Nachrichten aus der Gesellschaft

Onur Güntürkün*

Editorial

https://doi.org/10.1515/nf-2020-0020

During our lifetime we make countless experiences. The memories of these events enable us to make better predictions of the outcomes of future actions. Unfortunately, the world is constantly changing and, consequently, our memories have to be modified every time a prediction turns out to be wrong. When the discrepancy between prediction and reality is small, it is sufficient to just slightly modify our memory. If, however, our expectation about our choice's outcome turns out to be grossly wrong, mere modifications of our memory aren't sufficient. Instead, a second, new memory of this situation is established that competes with the old one. This, in short, describes the process of extinction learning.

Let me make my point clear by giving you an example from classic fear conditioning paradigms in rodents. Here, a mouse first learns that an auditory signal (conditioned stimulus; CS) is always followed by a painful foot shock (unconditioned stimulus; US). If this is repeated a few times, the animal starts to freeze when it hears the CS. Thus, the animal has learned the association between CS and US and expects the shock after hearing the tone. After this acquisition is established, we start the extinction paradigm. Now, the CS is delivered but is not followed by a US. So, to the surprise of the mouse, its fearful expectation turned out to be utterly wrong. If we repeat the "CS → no US" sequence for a while, the mouse ceases to freeze after hearing the CS: it seems to feel safe. Did it forget that once the tone was followed by shock? No, it didn't; at least not completely. Instead, the animal has acquired two memories: one in which the mouse fears the consequences of the tone and another one in which it doesn't. These two memories compete with each other and minute changes of the experimental conditions or the context can produce either feelings of safety or an instant return of fear.

So, extinction learning is a far more complex than the initial acquisition learning. And it is easy to see how important the potential clinical consequences of extinction learning are: When extinguished responses are not simply erased but can come back anytime, they can easily constitute invasive components of psychopathological disorders. Therefore, the Research Unit FOR 1581 and its subsequently established SFB 1280 decided to study the behavioral, neural, and clinical aspects of extinction in a concerted way and in series of complementary experiments. This special issue of Neuroforum gives an overview of the insights gathered during this period. Since some studies of FOR 1581 were finalized during the first funding period of SFB 1280, we have also included these results.

In the first paper, Meir Drexler et al. ask the question if the glucocorticoid cortisol, a major player in the development of stress-related psychopathology, can also be used for the augmentation of extinction-based psychotherapies, like, e.g., exposure therapy. In their review, they first present the role of stress and cortisol in the development of maladaptive emotional memories. Then, they describe the mechanisms that may account for the cortisol-induced augmentation of extinction-based psychotherapy. This is especially due to the enhancement of extinction memory consolidation and the reduction of the contextual dependency of the extinction memory. Finally, the authors discuss several considerations and limitations for the use of cortisol in psychotherapy, focusing on the possible adverse effects of cortisol in a reconsolidation-based (as opposed to extinction-based) intervention.

Zlomuzica et al. study extinction learning from a clinical perspective. Exposure is the most effective therapy option for Anxiety disorders (ADs). Nevertheless, some patients show poor treatment responses as well as a heightened vulnerability for relapse after treatment completion. Hence, significant research effort needs to be devoted to improve the long-term effectiveness of exposure effects. Recent attempts to increase exposure therapy efficacy utilize strategies aimed at promoting the acquisition and retrieval of extinction memories. The review of the authors illustrates the value and limitations of such extinction-based therapy approaches. They present and discuss recent findings from translational studies using cortisol and self-efficacy enhancement as an add-on to exposure therapy. In addition, they illustrate how the integration of findings from experimental research on fear extinction learning and self-efficacy could advance the development of more optimized treatments for ADs.

Uengoer et al. aim to broaden the successful but inevitably narrow focus of fear extinction paradigms in rodents by studying appetitive settings in humans and rodents. They thereby use the renewal procedure in which the subject acquires an association in context A,

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extinguishes it in context B and is then tested again in context A. In such a condition, the extinguished behavior suddenly reappears due to the final switch to context A. The authors show that the impact of context-dependent learning crucially depends on mechanisms of selective attention and receptor-specific dopaminergic, noradrenergic, and glutamatergic transmission. At the systems-level, the authors reveal that ventromedial prefrontal cortex (vmPFC), hippocampus, and amygdala play a role in extinction of appetitive learning, similar to their role in aversive extinction accounts. Most importantly, the activity of hippocampus and vmPFC is discovered to be a predictor of the occurrence of renewal.

Güntürkün et al. broaden the field of the neural substrates of extinction learning both at the phylogenetic and the systems level. For the phylogenetic analysis they study extinction in pigeons, a species that since 300 million years undergoes a separate evolution from mammals. They discover that the avian extinction pathway is not identical, but highly similar to that of mammals. Thus, we are possibly dealing with a rather ancient network that has not changed much in this long period of time. Then, the authors go on and ask if the human cerebellum should be included into the core extinction circuit. The answer is a strong 'yes' since the cerebellum processes prediction errors – a key element that drives extinction learning and that contributes to context-related effects of extinction.

Elsenbruch et al. summarize the current knowledge on the formation, extinction, and return of pain-related memories with a focus on visceral pain. Indeed, it is increasingly recognized that pain-related fear learning and memory processes are conceptually embedded within the fear avoidance model of chronic pain. The unique biological salience of interoceptive, visceral pain with its cognitive, emotional, and motivational facets has a strong capacity to foster associative learning. The downside of this capacity is that conditioned fear can turn maladaptive and then contributes to hypervigilance and hyperalgesia in chronic pain. In their review the authors provide a conceptual background, describe experimental approaches, and summarize findings on behavioral and neural mechanisms in healthy humans and patients with chronic pain. Future directions underscore the potential of refining knowledge on the role of associative learning in the pathophysiology and treatment of chronic visceral pain in disorders of gut-brain interactions such as irritable bowel syndrome.

Hadamitzky et al. subsequently turn gears and study the extinction of conditioned immunosuppressive responses. This is based on previous studies that demonstrated that immune functions can be modulated by associative learning. The authors have established a conditioned taste avoidance (CTA) paradigm in rats by pairing a novel taste (conditioned stimulus, CS) with an injection of the immunosuppressive drug cyclosporine A (CsA; unconditioned stimulus, US). Re-exposure to the CS results in a pronounced CTA and, more importantly, in a selective suppression of specific T cell functions, mimicking the drugs' effects. To provide a basis for employing learned immunosuppressive strategies in clinical situations, the authors investigate the neurobiological mechanisms underlying the extinction of conditioned immunosuppressive responses and the generalizability of these findings to other immunomodulatory drugs.

All together, we thank the German Neuroscience Society as well as the editorial board of Neuroforum for having invited us to compile this special issue on this fascinating subject. We hope that our readers will share our enthusiasm for the behavioral, neural, and clinical fundaments of extinction learning.

Review article

Shira Meir Drexler, Christian J. Merz, Valerie L. Jentsch and Oliver T. Wolf*

Stress modulation of fear and extinction in psychopathology and treatment

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Abstract: The glucocorticoid cortisol, a major player in the development of stress-related psychopathology, can also be used for the augmentation of extinction-based psychotherapies (e.g., exposure therapy). Substantial evidence supports its beneficial effects in the treatment of post-traumatic stress disorder and specific phobias. In this review, we first present the role of stress and cortisol in the development of maladaptive emotional memories. Then, we describe the mechanisms that may account for the cortisol-induced augmentation of exposure, namely, the enhancement of extinction memory consolidation and the reduction of the contextual dependency of the extinction memory. Finally, we discuss several considerations and limitations for the use of cortisol in psychotherapy, focusing on the possible adverse effects of cortisol in a reconsolidation-based (as opposed to extinction-based) intervention.

Keywords: cortisol; exposure therapy; extinction learning; fear conditioning; reconsolidation.

Zusammenfassung: Das Glucocorticoid Cortisol ist beteiligt an der Entwicklung von stress-assoziierten Psychopathologien, kann aber auch benutzt werden um die extinktionsbasierte Psychotherapie (z.B. Exposition) zu verbessern. Substanzielle Befunde unterstützen seine vorteilhaften Effekte bei der Behandlung der Posttraumatischen Belastungsstörung und Phobien. Überblicksartig erläutern wir zuerst die Rolle von Stress und Cortisol bei der Entwicklung von maladaptiven emotionalen Erinnerungen. Danach beschreiben wir die Mechanismen, die für die Cortisol-induzierte Verbesserung der Expositionstherapie verantwortlich sein könnten, nämlich die Verstärkung der Konsolidierung und die Reduktion der Kontextabhängigkeit des Extinktionsgedächtnisses. Zuletzt diskutieren wir die Einbindung des Cortisols in die Psychotherapie mit einem Fokus auf mögliche negative Auswirkungen einer Cortisolgabe im Rahmen einer Rekonsolidierungsbasierten (im Gegensatz zu einer extinktionsbasierten) Intervention.

Schlüsselwörter: Cortisol; Expositionstherapie; Extinktionslernen; Furchtkonditionierung; Rekonsolidierung.

Stress and the strength of emotional memories

Unusually challenging physical or psychological events may lead to stress, a subjective state of tension that is difficult to manage or endure (Colman, 2001). Two neuroendocrine systems come into play to promote an adaptive response to a stressful situation (see Figure 1): the sympathetic nervous system (SNS), mainly through the release of adrenaline and noradrenaline, and the hypothalamus-pituitary-adrenocortical (HPA) axis, mainly through the release of the glucocorticoid (GC) cortisol. The SNS is responsible for the fast and short-term responses occurring in the initial phase of the stressful event (e.g., elevated heart rate and breathing, increased arousal), whereas the HPA axis responds slower and has long-lasting effects (e.g., increase in blood sugar, suppression of the immune system) that promote the response to the stressor and the subsequent return to homeostasis (McCarty, 2016; McEwen, 2019). The effects of the SNS and HPA axis are not limited to responding to present events; through their ability to modulate learning and memory processes, they influence the response to future events as well (Joëls et al., 2006).

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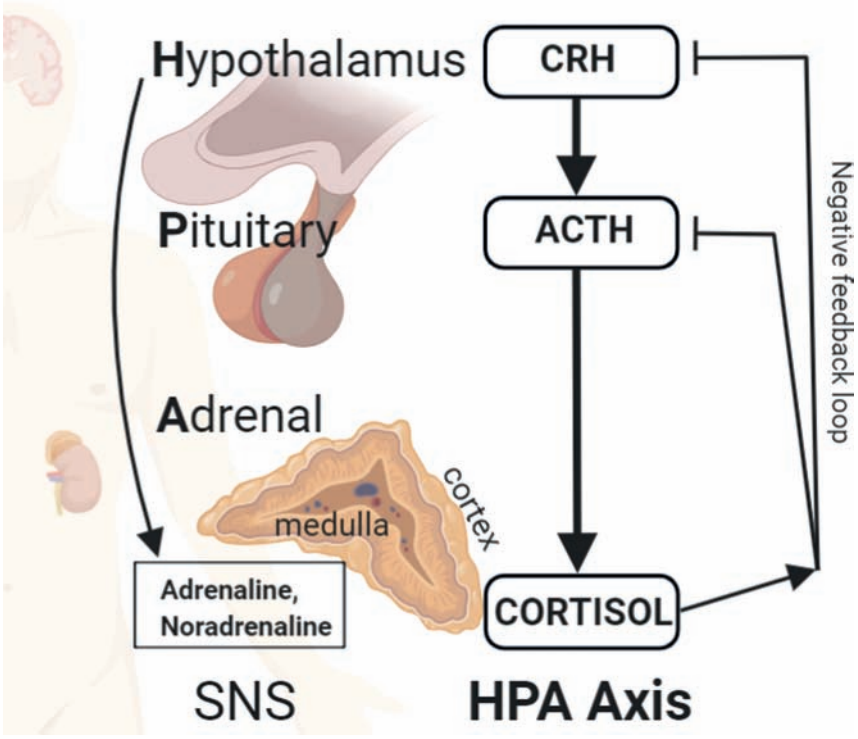

Figure 1: The stress response. Two systems come into play to promote an adaptive response to a stressful situation: the sympathetic nervous system (SNS; mainly through the secretion of adrenaline and noradrenaline) and the hypothalamus-pituitary-adrenocortical (HPA) axis (mainly through the secretion of the glucocorticoid cortisol). Cortisol is also involved in a negative feedback loop, affecting the HPA axis. ACTH: adrenocorticotropic hormone; CRH: corticotrophin-releasing hormone. The figure was created with BioRender.com.

The effects of stress of learning and memory processes depend on various modulating factors, such as intensity and duration of stress, the characteristics of the learning task, and individual differences, such as age, sex, and personality traits (Meir Drexler and Wolf, 2017a; Shields et al., 2017). Another significant modulating factor is the timing of stress in relation to the task: Did learning occur before stress or after it has subsided or did an older or unrelated memory have to be recalled during or after the stressful episode itself? In general, cortisol (through interaction with noradrenaline) promotes the consolidation of emotional or arousing memories but at the same time impairs the retrieval of previously consolidated memories (de Quervain et al., 2017; Roozendaal, 2002). For this reason, a stressed student might have difficulties recalling the learning material during an exam, but the memory of the stressful exam experience itself might be easily recalled later.

In addition to enhancing emotional memory consolidation, stress also affects the contextualization of memories. Because stress can disrupt the context dependency of memories (Schwabe et al., 2009), emotional memories are often not only stronger but also more easily generalized from the original learning context to other contexts. In extreme cases, strong and generalized emotional memories will not fade over time and might become overpowering and maladaptive. Strong maladaptive memories underlie post-traumatic stress disorder (PTSD), phobias (Merz et al., 2016), and chronic pain (Elsenbruch and Wolf, 2015).

Exposure therapy and the problem of relapse

Exposure therapy is a type of cognitive behavioral treatment, which is often used for the treatment of PTSD and phobias (Craske et al., 2018). One of the possible underlying mechanisms of exposure therapy is extinction learning, which involves repeated confrontation with the conditioned stimulus (CS; e.g., dog) in the absence of the unconditioned stimulus (UCS; e.g., dog bite), typically resulting in a decrement of conditioned responses (e.g., fear). Extinction learning depends on the formation of a new inhibitory (i.e., safety) memory and does not erase the original (i.e., fear) memory (Bouton, 2014). Following extinction, the original and the extinction memory will compete against one another for the control over behavior. The challenge for exposure therapy stems from the differences in the strength and context dependency of both memories. The original memory is often robust, is not bound to a specific context, and is thus more easily generalized (e.g., generalizing the fear of dogs from the park, where a dog attack had happened, to other places). Extinction memory, in contrast, is not the first association that is learned about a stimulus and as such is encoded as a conditional (e.g., context-dependent) exception to the rule (for instance, feeling safe despite the presence of a dog but only while being at the clinic).

As a result, relapse (or "return of fear") may occur under various conditions: after an exposure to an aversive stimulus ("reinstatement"), after a change in context ("renewal"), or just by the passage of time ("spontaneous recovery"; Bouton, 2014). This significant challenge to the long-term success of exposure therapy has led many research groups to investigate various (e.g., cognitive, pharmacological) methods of extinction augmentation (Craske et al., 2018; Ressler et al., 2004). Growing knowledge on the role of stress and cortisol in learning and memory has shown that cortisol can act as an adjuvant in extinction-based therapy (de Quervain et al., 2017).

What is the mechanism of cortisol-induced extinction augmentation?

Recently, we suggested the STaR model (the initials of which stand for "Stress Timing affects Relapse"; see Figure 2) to illustrate the consequences of stress timing on the strength and context dependency of extinction memories, resulting in either relapse or not (Meir Drexler et al., 2019a). These findings are based on several studies in which we used exposure to laboratory stress or a pharmacological cortisol administration at different times: before extinction learning (i.e., to affect the encoding and consolidation of the extinction memory), after extinction learning (i.e., to affect extinction memory consolidation only), or before extinction retrieval.

We found that exposure to stress or cortisol administration before extinction learning promotes extinction memory consolidation in a context-independent way (Meir Drexler et al., 2017, 2018; but see: Merz et al., 2018), making extinction memory more resistant to relapse after context change (see similar GCs-related contextual impairments in other tasks: McGlade et al., 2019; Schwabe et al., 2009; van Ast et al., 2013). In contrast, exposure to stress/cortisol after extinction leads to an enhanced, but context-dependent, extinction memory trace (Hamacher-Dang et al., 2013, 2015), making extinction retrieval more likely, but only in the context in which it had been learned (see GCs-related context-dependency in other tasks: van Ast et al., 2013). Finally, we found that when stress or cortisol is given before a retrieval test, extinction retrieval is impaired (Hamacher-Dang et al., 2013; Kinner et al., 2016, 2018; but see: Merz et al., 2014), making relapse more likely to occur (see GC-related retrieval deficit in other tasks: Shields et al., 2017).

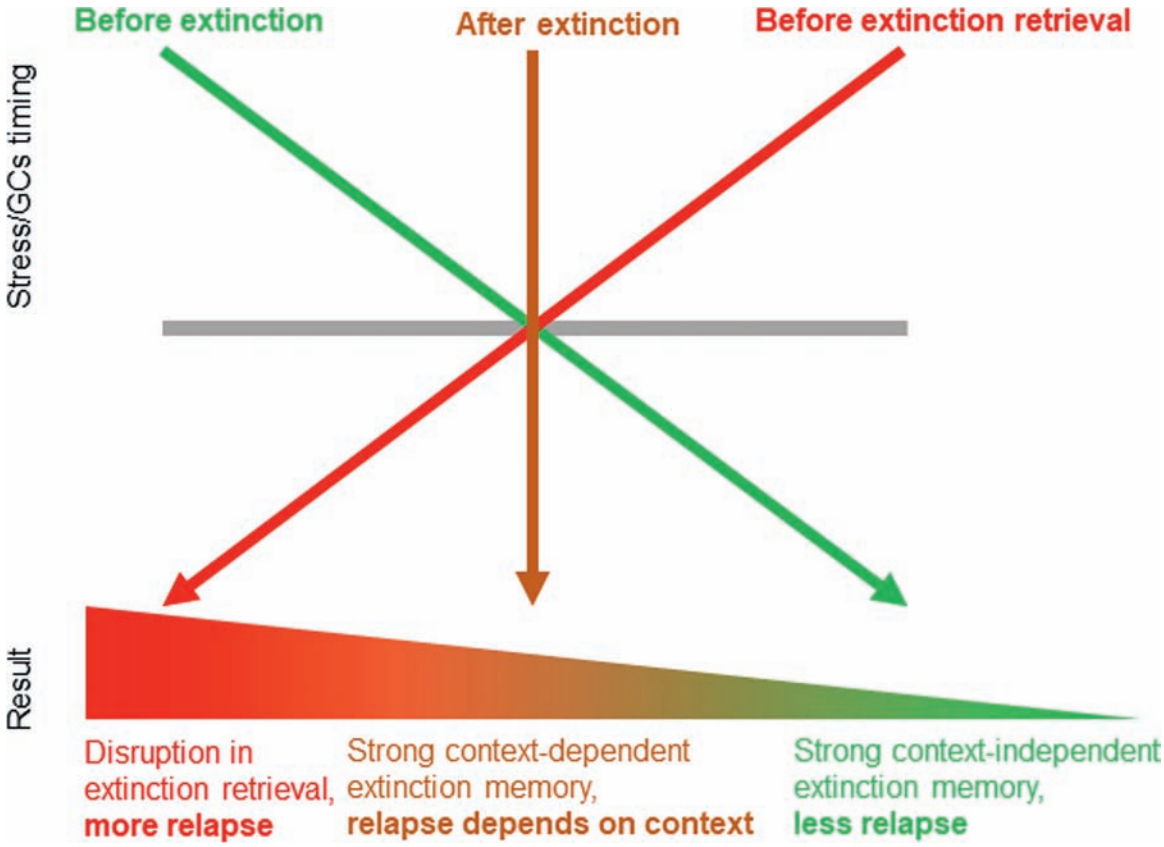

Figure 2: The STaR (Stress Timing affects Relapse) model represents the timing-dependent modulation of extinction and relapse by stress/glucocorticoids (GCs). Stress or GCs before extinction promote memory consolidation in a context-independent manner, making extinction memory more generalized and thus resistant to relapse after context change. Stress or GCs after extinction also enhance extinction consolidation, but in a context-bound manner, thus making extinction retrieval more likely only in the context in which it had been learned. In contrast, stress or GCs before an extinction retrieval test impair extinction retrieval and promote relapse. Reprinted from Meir Drexler et al. (2019a), Copyright (2019), with permission from Elsevier.

At the neural level (as illustrated in Figure 3), we could show that the timing-dependent effects of stress/cortisol on extinction memories are modulated by alterations in the amygdala, the hippocampal complex, the prefrontal cortex, and their communication with other brain regions (Meir Drexler et al., 2019a). In line with evidence from previous works on animals and humans (Milad and Quirk, 2012), our findings suggest that the ventromedial prefrontal cortex (vmPFC) and the hippocampus are activated and determine, based on the given context, whether or not extinction memory is expressed under nonstressful conditions. However, if cortisol was administered before extinction learning, activity of the hippocampus and its functional connectivity to the vmPFC increases in a later retrieval task, leading to enhanced extinction retrieval and thus reduced fear (Merz et al., 2018). In contrast, exposure to cortisol before the retrieval task itself suppresses vmPFC activation and its connectivity with the parahippocampal gyrus, enhances activation of the amygdala, and leads to impaired extinction retrieval and thus enhanced fear (Kinner et al., 2016, 2018).

Our findings provide additional support for the beneficial (time-specific) use of cortisol in psychotherapy (de Quervain et al., 2017). By focusing on the contextual factor, which is a crucial element not only in renewal but also in other relapse phenomena (Bouton, 2014), these findings may help in developing more efficient interventions. In particular, our data suggest that the use of cortisol or stress should be promoted shortly before and avoided after extinction-based psychotherapy, taking into account possible factors that can affect cortisol concentrations (e.g., sex, sex hormones, and medication including hormonal contraceptives; see Kudielka et al., 2009; Merz and Wolf, 2017; Raeder et al., 2019). In cases wherein cortisol administration is not feasible, behavioral interventions might promote the desired moderate and time-limited cortisol response (Lass-Hennemann and Michael, 2014; Meir Drexler et al., 2017, 2018).

Cortisol and memory reconsolidation

While repeated presentations of conditioned cues usually lead to the formation of a new memory trace (i.e., extinction learning, as discussed previously), a single brief presentation of the CS triggers a reconsolidation process, resulting in an alteration or update of the original memory itself (Merlo et al., 2014). It was suggested that the strength of the prediction error (i.e., the discrepancy between a predicted and an actual outcome) in each case leads to either an update of the old memory when the prediction error is moderate or a formation of a new memory altogether when a stronger prediction error occurs (Gershman et al., 2017).

Much like newly acquired memories, reactivated memories are sensitive to various (e.g., behavioral, pharmacological) manipulations that can be designed to weaken or strengthen the memory until its reconsolidation is complete (Josselyn and Tonegawa, 2020). Among these are stress and cortisol manipulations (Akirav and Maroun, 2013), yet the direction of the effect is still debated (Meir Drexler and Wolf, 2017c, 2018; Shields et al., 2017). These conflicting findings may result from methodological differences that are common in the general reconsolidation field (Meir Drexler and Wolf, 2017c), such as variations in the type or age of the memory, study sample, or the manipulation itself. For instance, although we previously found an enhancing effect of cortisol on fear memory reconsolidation in men (Meir Drexler et al., 2015), we found no effect in women (possibly owing to interactions with female sex hormones: Meir Drexler et al., 2016). In contrast, exposure to mild stress led to a fear memory impairment in men (possibly through an interruption of memory reconsolidation: Meir Drexler and Wolf, 2017b). Moreover, while the previous studies used the commonly used CS-based reconsolidation paradigm (i.e., reactivation by a single unreinforced CS presentation), in an alternative UCS-based reconsolidation paradigm (i.e., through a single weaker UCS presentation), the reactivation method itself prevented the return of fear regardless of the pharmacological (cortisol or placebo) treatment (Meir Drexler et al., 2019b).

As these findings demonstrate, one has to bear in mind that a given behavioral or pharmacological manipulation can lead to different behavioral outcomes when paired with either extinction (e.g., less fear: Meir Drexler et al., 2019a) or reconsolidation (e.g., more fear, at least in men: Meir Drexler et al., 2015). Unlike cortisol, more promising targets for future reconsolidation-based therapies may include the GC receptor antagonist mifepristone (Nikzad et al., 2011; Pitman et al., 2011), the noradrenergic β-blocker

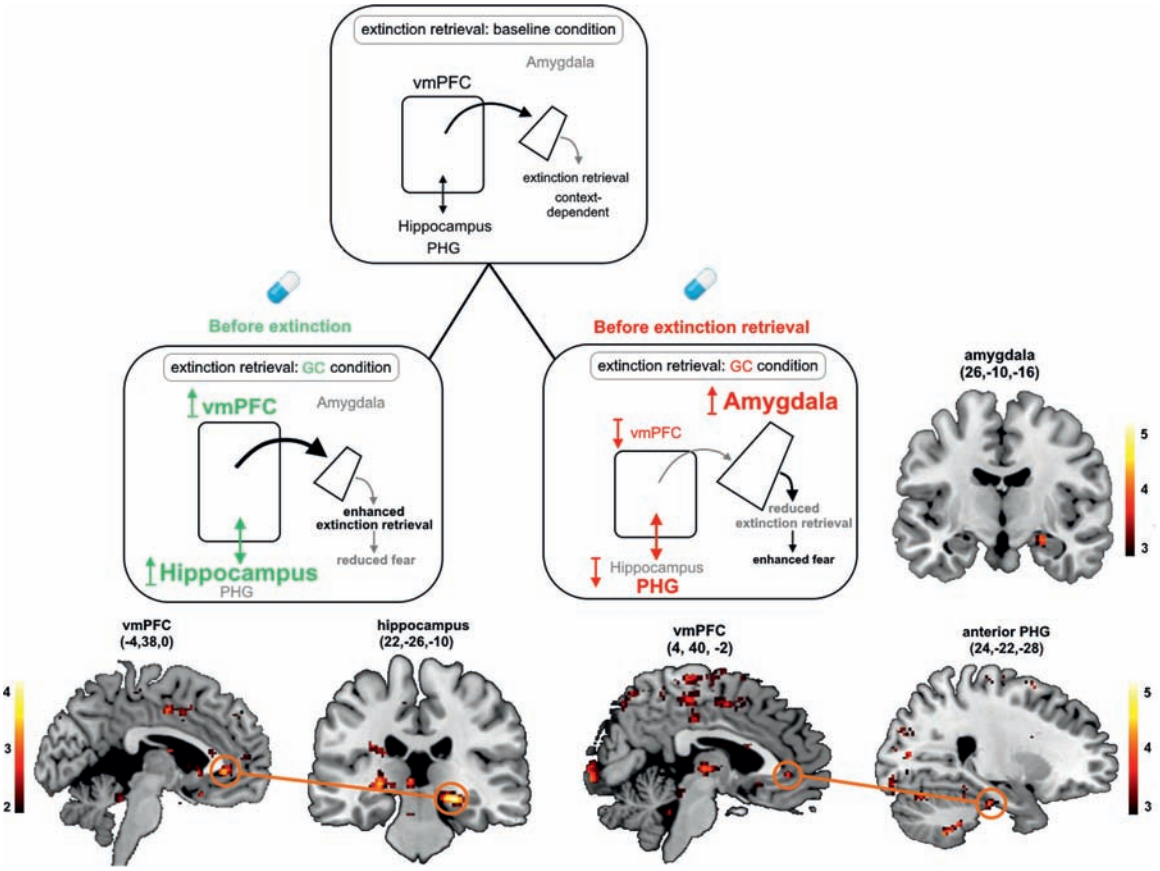

Figure 3: Simplified scheme of the neural network mediating extinction retrieval under baseline conditions (upper panel) and the proposed neural mechanisms underlying the effects of glucocorticoids (GCs) on this network, when administered before extinction learning (lower left panel) or before extinction retrieval (lower right panel). Neural activation and functional connectivity are additionally shown for the comparison between conditioned stimuli in the respective brain regions. The ventromedial prefrontal cortex (vmPFC) and the hippocampus are activated and determine, based on the given context, whether or not extinction memory is expressed under nonstressful (baseline) conditions. However, if cortisol was administered before extinction learning, activity of the hippocampus and its functional connectivity to the vmPFC increases in a later retrieval task, leading to enhanced extinction retrieval and thus reduced fear. In contrast, exposure to cortisol before the retrieval task itself suppresses vmPFC activation and its connectivity with the parahippocampal gyrus (PHG), enhances activation of the amygdala, and leads to impaired extinction retrieval and thus enhanced fear. The size of the structures indicates activation dominance. The colors of the arrows depict the proposed modulating influence (black = modulation; gray = reduced modulation by GCs; green = enhancing GC effects; red = impairing GC effects). Reprinted from Meir Drexler et al. (2019), Copyright (2019), with permission from Elsevier.

propranolol (Soeter and Kindt, 2015), or cognitive techniques for memory updating (Josselyn and Tonegawa, 2020; Meir Drexler and Wolf, 2017b, 2018), but more evidence in clinical populations is needed.

Conclusion

Cortisol, a GC involved in the development of maladaptive memories, can also be used as a pharmacological agent for the augmentation of exposure therapy. We suggest that the beneficial effect of cortisol in exposure-based psychotherapy results from its modulation of extinction processes, in particular the enhancement of extinction memory consolidation and the reduction of its contextual dependence. When used in a reconsolidation paradigm, however, cortisol may lead to an enhancement of the original fear memory and, thus, to adverse effects. The current findings encourage further investigation of the clinical use of cortisol in extinction-based (but not reconsolidation-based) interventions.

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References

Akirav, I. and Maroun, M. (2013). Stress modulation of reconsolidation. Psychopharmacology *226*, 747–761.

Bouton, M.E. (2014). Why behavior change is difficult to sustain. Prev. Med. *68*, 29–36.

Colman, A.M. (2001). Oxford Dictionary of Psychology (Oxford, UK: Oxford University Press).

Craske, M.G., Hermans, D., and Vervliet, B. (2018). State-of-the-art and future directions for extinction as a translational model for fear and anxiety. Philos. Trans. R. Soc. Lond. B Biol. Sci. *373*, 20170.

de Quervain, D.J.F., Schwabe, L., and Roozendaal, B. (2017). Stress, glucocorticoids and memory: implications for treating fear-related disorders. Nat. Rev. Neurosci. *18*, 7–19.

Elsenbruch, S., and Wolf, O.T. (2015). Could stress contribute to pain-related fear in chronic pain?. Front. Behav. Neurosci. *9*, 1–8.

Gershman, S.J., Monfils, M.H., Norman, K.A., and Niv, Y. (2017). The computational nature of memory modification. ELife *6*, 1–48.

Hamacher-Dang, T.C., Engler, H., Schedlowski, M., and Wolf, O. T. (2013). Stress enhances the consolidation of extinction memory in a predictive learning task. Front. Behav. Neurosci. *7*, 1–8.

Hamacher-Dang, T.C., Üngör, M., and Wolf, O.T. (2013). Stress impairs retrieval of extinguished and unextinguished associations in a predictive learning task. Neurobiol. Learn. Mem. *104*, 1–8.

Hamacher-Dang, T.C., Merz, C.J., and Wolf, O.T. (2015). Stress following extinction learning leads to a context-dependent return of fear. Psychophysiology *52*, 489–498.

Joëls, M., Pu, Z., Wiegert, O., Oitzl, M.S., and Krugers, H.J. (2006). Learning under stress: how does it work?. Trends Cognit. Sci. *10*, 152–158.

Josselyn, S.A., and Tonegawa, S. (2020). Memory engrams: Recalling the past and imagining the future. Science *367*, eaaw4325.

Kinner, V.L., Merz, C.J., Lissek, S., and Wolf, O.T. (2016). Cortisol disrupts the neural correlates of extinction recall. NeuroImage *133*, 233–243.

Kinner, V.L., Wolf, O.T., and Merz, C.J. (2018). Cortisol increases the return of fear by strengthening amygdala signaling in men. Psychoneuroendocrinology *91*, 79–85.

Kudielka, B.M., Hellhammer, D.H., and Wüst, S. (2009). Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. Psychoneuroendocrinology *34*, 2–18.

Lass-Hennemann, J., and Michael, T. (2014). Endogenous cortisol levels influence exposure therapy in spider phobia. Behav. Res. Ther. *60*, 39–45.

McCarty, R. (2016). The fight-or-flight response: A cornerstone of stress research. Stress: Concepts, Cognition, Emotion, and Behavior: Handbook of Stress (Elsevier Inc), https://doi.org/10.1016/B978-0-12-800951-2.00004-2.

McEwen, B.S. (2019). What is the confusion with cortisol?. Chronic Stress *3*, 1–3.

McGlade, A., Zbozinek, T.D., Treanor, M., and Craske, M.G. (2019). Pilot for novel context generalization paradigm. J. Behav. Ther. Exp. Psychiatr. *62*, 49–56.

Meir Drexler, S., and Wolf, O.T. (2017a). Stress and memory consolidation. In Cognitive Neuroscience of Memory Consolidation. N. Axmacher and B. Rasch, eds. (Cham, Switzerland: Springer), pp. 285–300, https://doi.org/10.1007/978-3-319-45066-7_17.

Meir Drexler, S., and Wolf, O.T. (2017b). Stress disrupts the reconsolidation of fear memories in men. Psychoneuroendocrinology *77*, 95–104.

Meir Drexler, S., and Wolf, O.T. (2017c). The role of glucocorticoids in emotional memory reconsolidation. Neurobiol. Learn. Mem. *142*, 126–134.

Meir Drexler, S., and Wolf, O.T. (2018). Behavioral disruption of memory reconsolidation: From bench to bedside and back again. Behav. Neurosci. *132*, 13–22.

Meir Drexler, S., Merz, C.J., Hamacher-Dang, T.C., Tegenthoff, M., and Wolf, O.T. (2015). Effects of cortisol on reconsolidation of reactivated fear memories. Neuropsychopharmacology *40*, 3036–3043.

Meir Drexler, S., Merz, C.J., Hamacher-Dang, T.C., and Wolf, O.T. (2016). Cortisol effects on fear memory reconsolidation in women. Psychopharmacology *233*, 2687–2697.

Meir Drexler, S., Hamacher-Dang, T.C., and Wolf, O.T. (2017). Stress before extinction learning enhances and generalizes extinction memory in a predictive learning task. Neurobiol. Learn. Mem. *141*, 143–149.

Meir Drexler, S., Merz, C.J., and Wolf, O.T. (2018). Preextinction stress prevents context-related renewal of fear. Behav. Ther. *49*, 1008–1019.

Meir Drexler, S., Merz, C.J., Jentsch, V.L., and Wolf, O.T. (2019a). How stress and glucocorticoids timing-dependently affect extinction and relapse. Neurosci. Biobehav. Rev. *98*, 145–153.

Meir Drexler, S., Merz, C.J., Lissek, S., Tegenthoff, M., and Wolf, O.T. (2019b). Reactivation of the unconditioned stimulus inhibits the return of fear independent of cortisol. Front. Behav. Neurosci. *13*, https://doi.org/10.3389/fnbeh.2019.00254.

Merlo, E., Milton, A.L., Goozee, Z.Y., Theobald, D.E., and Everitt, B.J. (2014). Reconsolidation and extinction are dissociable and mutually exclusive processes: behavioral and molecular evidence. J. Neurosci. *34*, 2422–2431.

Merz, C.J., and Wolf, O.T. (2017). Sex differences in stress effects on emotional learning. J. Neurosci. Res. *95*, 93–105.

Merz, C.J., Hamacher-Dang, T.C., and Wolf, O.T. (2014). Exposure to stress attenuates fear retrieval in healthy men. Psychoneuroendocrinology *41*, 89–96.

Merz, C.J., Elzinga, B.M., and Schwabe, L. (2016). Stress, fear, and memory in healthy individuals. In Post-traumatic Stress Disorder: From Neurobiology to Treatment. J. D. Bremner, ed. (Malden, MA: Wiley-Blackwell), https://doi.org/10.1002/9781118356142.ch8.

Merz, C.J., Hamacher-Dang, T.C., Stark, R., Wolf, O.T., and Hermann, A. (2018). Neural underpinnings of cortisol effects on fear extinction. Neuropsychopharmacology *43*, 384–392.

Milad, M.R., and Quirk, G.J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. Annu. Rev. Psychol. *63*, 129–151.

Nikzad, S., Vafaei, A.A., Rashidy-Pour, A., and Haghighi, S. (2011). Systemic and intrahippocampal administrations of the glucocorticoid receptor antagonist RU38486 impairs fear memory reconsolidation in rats. Stress-Int. J. Biol. Stress *14*, 459–464.

Pitman, R.K., Milad, M.R., Igoe, S.A., Vangel, M.G., Orr, S.P., Tsareva, A., Gamache, K., Nader, K. (2011). Systemic mifepristone blocks reconsolidation of cue-conditioned fear; propranolol prevents this effect. Behav. Neurosci. *125*, 632–638.

Raeder, F., Heidemann, F., Schedlowski, M., Margraf, J., and Zlomuzica, A. (2019). No pills, more skills: The adverse effect of hormonal contraceptive use on exposure therapy benefit. J. Psychiatr. Res. *119*, 95–101.

Ressler, K.J., Rothbaum, B.O., Tannenbaum, L., Anderson, P., Graap, K., Zimand, E., Hodges, L., and Davis, M. (2004). Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch. Gen. Psychiatr. *61*, 1136–1144.

Roozendaal, B. (2002). Stress and memory: Opposing effects of glucocorticoids on memory consolidation and memory retrieval. Neurobiol. Learn. Mem. *78*, 578–595.

Schwabe, L., Böhringer, A., and Wolf, O.T. (2009). Stress disrupts context-dependent memory. Learn. Mem. *16*, 110–113.

Shields, G.S.S., Sazma, M.A.A., McCullough, A.M.M., and Yonelinas, A.P.P. (2017). The effects of acute stress on episodic memory: A meta-analysis and integrative review. Psychol. Bull. *143*, 636–675.

Soeter, M., and Kindt, M. (2015). An abrupt transformation of phobic behavior after a post-retrieval amnesic agent. Biol. Psychiatr. *78*, 880–886.

van Ast, V.A., Cornelisse, S., Meeter, M., Joëls, M., and Kindt, M. (2013). Time-dependent effects of cortisol on the contextualization of emotional memories. Biol. Psychiatr. *74*, 809–816.

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Review article

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Clinical implications of fear extinction in anxiety disorders

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Abstract: Anxiety disorders (ADs) are characterized by increased chronicity and comorbidity with other ADs. Although exposure is the most effective therapy option for ADs, some patients show poor treatment response and a heightened vulnerability for relapse after treatment completion. Hence, significant research effort needs to be devoted to improve the long-term effectiveness of exposure effects. Recent attempts to increase exposure therapy efficacy use strategies aimed at promoting the acquisition and retrieval of extinction memories. The present review illustrates the value and limitations of such extinction-based therapy approaches. We present and discuss recent findings from translational studies using cortisol and self-efficacy enhancement as an add-on to exposure therapy. We illustrate how the integration of findings from experimental research on fear extinction learning and self-efficacy could advance the development of more optimized treatments for ADs.

Keywords: cortisol; exposure therapy; fear extinction; self-efficacy; therapy generalization.

Zusammenfassung: Angststörungen zeichnen sich durch eine erhöhte Chronizität und Komorbidität mit anderen Angststörungen aus. Obwohl die Exposition eine effektive Therapieoption für Angststörungen darstellt, profitieren einige Patienten nicht von dieser Intervention und/oder zeigen eine erhöhte Anfälligkeit für Rückfälle nach Therapieabschluss. Es gibt daher zunehmend Forschungsbedarf zur Verbesserung der Langzeiteffektivität von Exposition. Kürzliche Ansätze zur Erhöhung der Expositionsthe-rapieeffektivität beinhalten Strategien zur Verbesserung des Extinktionslernens. In dieser Übersichtsarbeit werden die Vorteile und Limitationen dieser extinktions-basierten Strategien näher beleuchtet. Wir präsentieren und diskutieren die neusten Befunde aus translationalen Studien zu Effekten von Cortisol und Erhöhung der Selbstwirksamkeitserwartung als potenzielle Strategien zur Verbesserung der Expositionstherapieeffekte. Wir illustrieren wie die Integration der experimentellen Befunde zum Extinktionslernen und Selbstwirksamkeitserwartung die Entwicklung optimierter Therapien für Angststörungen vorantreiben kann.

Schlüsselwörter: Furchtextinktion; Generalisierungseffekte; Kortisol; Selbstwirksamkeit; Konfrontationstherapie.

Anxiety disorders (ADs) belong to the most prevalent mental disorders (Bandelow and Michaelis, 2015). Chronicity and comorbidities with other ADs affect the disease course of ADs (Bandelow and Michaelis, 2015). Cognitive behavioral therapy (CBT) is both highly efficient and effective in the treatment of ADs (Otte, 2011). CBT involves a set of cognitive and behavioral interventions such as exposure. Although exposure is the most effective therapeutic tool for ADs, some patients fail to exhibit significant symptom improvement or show recovery of fear and avoidance after completion of exposure (Hoffmann and Smits, 2008; Norton and Price, 2007). Current knowledge on the mechanisms governing the beneficial effects of exposure has been largely influenced by the general propositions of the inhibitory learning and inhibitory regulation models (Craske et al., 2006, 2008). Here, fear extinction is considered a central candidate to explain the beneficial effects of exposure as well as relapse phenomena after successful treatment (Craske and Mystkowski, 2006).

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The association between fear extinction and exposure therapy

From an inhibitory learning perspective (Craske and Mystkowski, 2006, 2008), interindividual variability in exposure treatment outcome (Norton and Price, 2007) may be explained by the level of interindividual differences in fear extinction learning. In line with this idea, initial studies demonstrated that differences in extinction learning performance during a differential fear conditioning task were associated with variability in CBT outcomes in phobic children (Waters and Pine, 2016) and with the level of treatment gains during an exposure therapy analog in spider phobia (Forcadell et al., 2017). Likewise, anxiety reductions after exposure in patients with social anxiety could be predicted on the basis of extinction learning performance (Ball et al., 2017). Work from our group indicates that interindividual differences in fear extinction learning might also influence the patient's general ability to complete an exposure task within one or two sessions (Raeder et al., 2020). We showed that spider-phobic participants who were able to complete exposure within two 60-min sessions (i.e., completers) exhibited more pronounced short- and long-term therapy benefit than non-completers. Most importantly, fear extinction performance is linked to the ability to complete the exposure. Completers showed more pronounced fear extinction (retrieval) relative to noncompleters. This finding indicates that one subgroup of patients with specific phobia (non-completers) failed to accomplish exposure in a predetermined time possibly owing to deficient fear extinction.

These results bear important implications for the implementation of exposure in routine care. The inability of some patients to accomplish exposure in a predetermined time might be at odds with the specific regularities of routine care (Gunther and Whittal, 2010). To conclude, research on fear extinction might not only explain the variability in exposure treatment efficacy across patients but also bear specific implications for the implementation of exposure to routine care (Richter et al., 2017).

Pharmacological enhancement of exposure therapy efficacy: lessons from studies using cortisol as an add-on to exposure therapy

Studying exposure treatment processes from the perspective of the fear extinction model might provide valuable information on how to optimize exposure treatment efficacy (Craske et al., 2018). A great number of studies showed alterations in fear acquisition (Mosig et al., 2014) and/or deficits in fear extinction in ADs (Lissek et al., 2005). Fortunately, research on cognitive and neurobiological mechanisms of extinction produced a great wealth of meaningful results on how fear extinction can be selectively enhanced (Craske et al., 2018). For instance, data from animal and human work suggest that stress and cortisol can modulate the acquisition, consolidation, and retrieval of extinction memories (de Quervain et al., 2017; Stockhorst and Antov, 2016). Accordingly, the translation of these findings to the context of exposure therapy has received great interest. Systemic administration of glucocorticoids (i.e., cortisol) before exposure has been shown to enhance the efficacy of exposure-based treatments (for a review, see de Quervain et al., 2017). However, possible timing-dependent effects of cortisol on exposure outcome have been neglected in clinical studies. This is surprising given that the effects of stress and cortisol on (extinction) memory processes are not ubiquitous but might depend on the exact timing of administration (Stockhorst and Antov, 2016). Likewise, existing clinical studies rarely considered the possible impact of cortisol on the generalization of therapy effects across contexts. Given the existence of context-specific effects of cortisol on fear extinction (Meir Drexler et al., 2019), cortisol might affect the generalization of exposure treatment effects from the treatment context to other unfamiliar contexts. In other words, owing to the impact of cortisol on context specificity of fear extinction, the pharmacological enhancement of exposure with cortisol can possibly aggravate or dampen the return of fear after successful treatment. In the therapy setting, return of fear can be observed when patients encounter their feared object in an unfamiliar context, for example, seeing a spider in the basement instead of the room in which the exposure therapy took place – termed as fear renewal (Craske and Mystkowski, 2006, 2008).

Raeder et al. (2019a) conducted the first study that examined the effect of cortisol on both exposure efficacy and fear renewal after exposure. We showed that the administration of cortisol after exposure did not enhance the efficacy of exposure therapy in spider phobia. We further observed a detrimental effect on context-dependent return of fear (fear renewal) in the long term in participants who received cortisol relative to placebo-treated participants. In light of previous clinical studies in this field (de Quervain et al., 2017), our findings indicate that cortisol may boost exposure therapy efficacy only when given before (rather than after) exposure. Furthermore, the exact timing of cortisol administration seems to be critical when attempting to increase the generalization of therapeutic effects across contexts (Meir Drexler et al., 2019). Accordingly, post-exposure

administration of cortisol might be a less well-suited augmentation strategy because it may lead to an increase in fear renewal in the long term.

Exposure treatment efficacy: mediators and moderators

Some important mediators/moderators need to be taken into consideration when conducting clinical studies assessing the putative role of cognitive enhancers in exposure therapy. ADs are more frequent in women (Kessler et al., 2005). There is a gender-dependent effect in fear extinction (Merz et al., 2018). The sex hormone estrogen may affect the short- and long-term processing of extinction memories (Maeng and Milad, 2015). The use of oral contraceptives (OCs) affects endogenous estrogen secretion in women. Women using OCs show impaired fear extinction learning (Merz et al., 2012, 2018). Considering the influence of OC use and the variations in estrogen levels during the menstrual cycle in the context of exposure treatment in women might therefore be highly valuable. In support of this proposition, work from our laboratory (Raeder et al., 2019c) and that from others (Graham et al., 2018) indicate that hormonal contraceptive use in women has an impact on the immediate and long-term effects of exposure. Precisely, free-cycling women and women using hormonal contraceptives showed different response profiles to exposure therapy (Raeder et al., 2019c). Spider-phobic women using hormonal contraceptives exhibited less fear reduction and symptom improvement from pre-treatment to post-treatment and at six-week follow-up than their free-cycling counterparts.

The aforementioned findings suggest that the implementation of hormonal measurements and the systematic assessment of contraceptive use, which itself affects variability in exposure outcome, is important to derive a complete picture on the possible effects of cognitive enhancers in exposure therapy. This is especially true with regard to the effects of cortisol because OC use alters the effects of cortisol on fear learning (Merz et al., 2012, 2018). Interestingly, the Stress Timing affects Relapse (STAR) model has been proposed as a valuable framework to stimulate future clinical studies on the interaction between cortisol and sex hormones on extinction memories (Meir Drexler et al., 2019).

Exposure: is it more than fear extinction?

The rationale behind exposure therapy is to assist patients in overcoming their anxiety by creating a safe environment in which they encounter feared or avoided scenarios. Thus, a central goal of exposure is to induce positive mastery experiences that are ideally accompanied by substantial decrements of fear and avoidance in treated patients. According to Bandura (1988), positive mastery experiences lead to an increase in self-efficacy beliefs, which might constitute a prerequisite for a successful CBT. Several studies showed a positive association between increased self-efficacy and therapy outcome in patients with ADs (Bouchard et al., 2007; Gallagher et al., 2013). Given the mutual relationship between exposure and self-efficacy, the selective modulation of perceived self-efficacy might be effective to promote key processes (i.e., fear extinction learning) of exposure. In line with this, we showed that an increase in perceived self-efficacy (induced by false-positive verbal feedback) affects the acquisition and retrieval of extinction memories. Healthy participants with an increased self-efficacy showed better fear extinction learning and retrieval in a differential fear conditioning task (Zlomuzica et al., 2015).

Promoting self-efficacy might also represent an effective strategy to increase exposure efficacy. Raeder et al. (2019b) recently showed that increasing self-efficacy via the active rehearsal of personal mastery experiences is suitable to promote exposure outcome in patients with height phobia. In particular, self-efficacy enhancement led to more pronounced reductions in fear and avoidance after one session of standardized exposure in virtual reality (Raeder et al., 2019b). The mechanisms underlying the beneficial effect of an increased self-efficacy on fear extinction remain to be explored. Increased self-efficacy might lead to changes in the processing of extinguished memories (Zlomuzica et al., 2015). Alternatively, the utilization of positive personal experiences might affect the way how subjects perceive and cope with future challenges (Margraf and Zlomuzica, 2015; Zlomuzica et al., 2018). Since an adaptive processing of mastery experiences is fundamental to self-efficacy (Bandura, 1988), a better understanding of mechanisms underlying the storage and retrieval of personally relevant memories in patients with ADs would be highly valuable (Zlomuzica et al., 2014, 2016).

Generalization of exposure therapy effects

The comorbidity of ADs with other ADs is common (Bandelow and Michaelis, 2015). For instance, phobic individuals tend to suffer from multiple fears at the same time

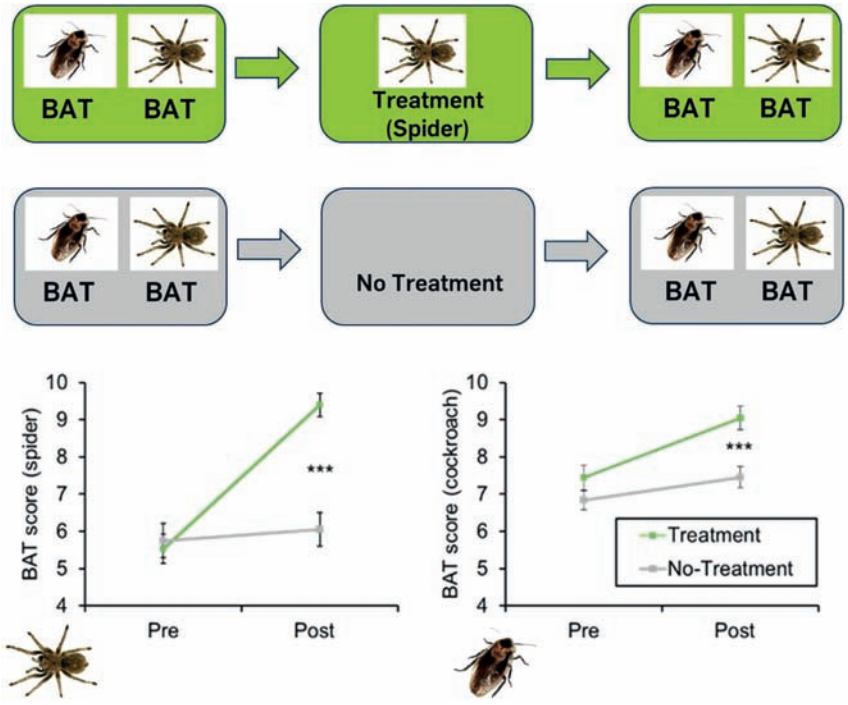

Figure 1: Participants with spider and cockroach phobia were subjected to exposure (Treatment) or a waiting control condition (No-Treatment). In addition to a Behavioral Approach Test (BAT) for spiders, the participants from both groups were subjected to a BAT for cockroaches before and after the assessment. Participants in the Treatment condition were subjected to a standardized *in vivo* exposure treatment for spider phobia. Cockroaches were not presented during the Treatment or No-Treatment condition. In contrast to the participants in the No-Treatment condition, those in the Treatment condition showed significantly less avoidance and fear during the BAT for spiders (left panel) and cockroaches (right panel).

(Davey, 1991; Matchett and Davey, 1991). Individuals with fear of spiders tend to fear other similar insects (e.g., cockroaches) and/ or small animals (e.g., rats). Such multiple fears might even be functionally related and lead to an increase in psychopathological symptoms (Rachman and Lopatka, 1986a, b). Surprisingly, recommendations on how to systematically treat multiple fears and/or comorbid anxieties do not exist. Likewise, there is no therapeutic tool that can induce a generalization of therapeutic effects for different functionally related fears. Notwithstanding, we have recently shown that exposure might lead to a generalization of therapeutic effects to untreated fear stimuli.

In particular, Preusser et al. (2017) demonstrated that exposure-induced reduction in fear and avoidance can also be observed for untreated stimuli, that is, those that bear feature overlap with treated stimuli but do not belong to the same category of fear stimuli (Figure 1).

These findings, which present to our knowledge the first study on this research gap, indicate that exposure effects are not restricted to the specific fear stimulus used during exposure (Preusser et al., 2017). Interestingly, such a generalization of clinical exposure treatment was recently also demonstrated in other fears (Hollander et al., 2020). How can we explain such generalization of exposure therapy effects? Findings from basic research on fear generalization (in particular, extinction generalization) (Dymond et al. 2015; Pittig et al., 2018) cannot fully account for the generalization of exposure effects to untreated fear stimuli. Alternatively, the self-efficacy concept of Bandura offers a more parsimonious account for the generalization of mastery experiences across different related (fear) domains (Bandura, 1988). Nevertheless, studying the generalization of therapeutic effects in ADs represents an important but neglected research field (Pittig et al., 2018).

Conclusions

Fear extinction might be a central candidate to explain exposure therapy benefit. The formation of personal mastery experiences during exposure leads to an increased self-efficacy, which might constitute another important element of a successful therapy for ADs. Attempts to promote fear extinction learning (e.g., via pharmacological modulation with cognitive enhancers) and to increase self-efficacy represent promising strategies to enhance exposure treatment efficacy and increase generalization of therapeutic effects.

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References

Ball, T.M., Knapp, S.E., Paulus, M.P., and Stein, M.B. (2017). Brain activation during fear extinction predicts exposure success. Depress. Anxiety *34*, 257–266.

Bandelow, B. and Michaelis S. (2015). Epidemiology of anxiety disorders in the 21st century. Dialogues Clin. Neurosci. *17*, 327–335.

Bandura, A. (1988). Self-efficacy conception of anxiety. Anxiety. Res. *1*, 77–98.

Bouchard, S., Gauthier, J., Nouwen, A., Ivers, H., Vallieres, A., Simard, S., and Fournier, T. (2007). Temporal relationship between dysfunctional beliefs, self-efficacy and panic apprehension in the treatment of panic disorder with agoraphobia. J. Behav. Ther. Exp. Psy. *38*, 275–292.

Craske, M.G. and Mystkowski, J. (2006). Exposure therapy and extinction: Clinical studies. Fear and Learning: From Basic Processes to Clinical Implications. M.G. Craske, D. Hermans, and D. Vansteenwegen, eds. (Washington, DC: American Psychological Association), pp. 217–233.

Craske, M.G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., and Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. Behav Res Ther. *46*, 5–27.

Craske, M.G., Hermans, D., and Vervliet, B. (2018). State-of-the-art and future directions for extinction as a translational model for fear and anxiety. Philos. Trans. R. Soc. Lond. B Biol. Sci. *373*, 20170.

Davey, G.C. (1991). Characteristics of individuals with fear of spiders. Anxiety Res. *4*, 299–314.

de Quervain, D.J.-F., Schwabe, L., and Roozendaal, B. (2017). Stress, glucocorticoids and memory: implications for treating fear-related disorders. Nat. Rev. Neurosci. *18*, 7–19.

Dymond, S., Dunsmoor, J. E., Vervliet, B., Roche, B., and Hermans, D. (2015). Fear generalization in humans: systematic review and implications for anxiety disorder research. Behav. Ther. *46*, 561–582.

Forcadell, E., Torrents-Rodas, D., Vervliet, B., Leiva, D., Tortella-Feliu, M., Fullana, M.A. (2017). Does fear extinction in the laboratory predict outcomes of exposure therapy? A treatment analog study. Int J Psychophysiol. *121*, 63–71.

Gallagher, M.W., Payne, L.A., White, K.S., Shear, K.M., Woods, S.W., Gorman, J.M., and Barlow, D.H. (2013). Mechanisms of change in cognitive behavioral therapy for panic disorder: The unique effects of self-efficacy and anxiety sensitivity. Behav. Res. Ther. *51*, 767–777.

Graham, B.M., Li, S.H., Black, M.J., and Öst, L.-G. (2018). The association between estradiol levels, hormonal contraceptive use, and responsiveness to one-session-treatment for spider phobia in women. Psychoneuroendocrinology *90*, 134–140.

Gunter, R.W. and Whittal, M.L. (2010). Dissemination of cognitive-behavioral treatments for anxiety disorders: Overcoming barriers and improving patient access. Clin. Psychol. Rev. *30*, 194–202.

Hofmann, S.G. and Smits, J.A.J. (2008). Cognitive-behavioral therapy for adult anxiety disorders: A meta-analysis of randomized placebo-controlled trials. J. Clin. Psychiatr. *69*, 621–632.

Hollander, M.D., de Jong, J., Onghena, P., and Vlaeyen, J.W.S. (2020). Generalization of exposure in vivo in complex regional pain syndrome type I. Behav. Res. Ther. *124*, 103511.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., and Walters, E.E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch. Gen. Psychiatry *62*, 593–602.

Lissek, S., Powers, A.S., McClure, E.B., Phelps, E.A., Woldehawariat, G., Grillon, C., and Pine, D.S. (2005). Classical fear conditioning in the anxiety disorders: a meta-analysis. Behav. Res. Ther. *43*, 1391–1424.

Maeng, L.Y. and Milad, M.R. (2015). Sex differences in anxiety disorders: Interactions between fear, stress, and gonadal hormones. Horm. Behav. *76*, 106–117.

Margraf, J. and Zlomuzica, A. (2015). Changing the future, not the past: a translational paradigm shift in treating anxiety. EMBO Rep. *16*, 259–260.

Matchett, G. and Davey, G.C. (1991). A test of a disease-avoidance model of animal phobias. Behav. Res. Ther. *29*, 91–94.

Meir Drexler, S., Merz, C.J., Jentsch, V.L., and Wolf, O.T. (2019). How stress and glucocorticoids timing-dependently affect extinction and relapse. Neurosci. Biobehav. Rev. *98*, 145–153.

Merz C.J., Tabbert, K., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., and Wolf, O.T. (2012). Oral contraceptive usage alters the effects of cortisol on implicit fear learning. Horm. Behav. *62*, 531–538.

Merz, C.J., Kinner, V.L., and Wolf, O.T. (2018). Let's talk about sex… differences in human fear conditioning. Curr. Opin. Behav. Sci. *23*, 7–12.

Mosig, C., Merz, C.J., Mohr, C., Adolph, D., Wolf, O.T., Schneider, S., Margraf, J., and Zlomuzica, A. (2014). Enhanced discriminative fear learning of phobia-irrelevant stimuli in spider-fearful individuals. Front. Behav. Neurosci. *8*, 328.

Norton, P.J. and Price E.C. (2007). A meta-analytic review of adult cognitive-behavioral treatment outcome across the anxiety disorders. J. Nerv. Ment. Dis. *195*, 521–531.

Otte, C. (2011). Cognitive behavioral therapy in anxiety disorders: current state of the evidence. Dialogues Clin. Neurosci. *13*, 413–421.

Pittig, A., Treanor, M., LeBeau, R.T., and Craske, M.G. (2018). The role of associative fear and avoidance learning in anxiety disorders: Gaps and directions for future research. Neurosci. Biobehav. Rev. *88*, 117–140.

Preusser, F., Margraf, J., and Zlomuzica, A. (2017). Generalization of extinguished fear to untreated fear stimuli after exposure. Neuropsychopharmacology, *42*, 2545.

Rachman, S., and Lopatka, C. (1986a). Do fears summate?—III. Behav. Res. Ther. *24*, 653–660.

Rachman, S., and Lopatka, C. (1986b). A simple method for determining the functional independence of two or more fears—IV. Behav. Res. Ther. *24* 661–664.

Raeder, F., Merz, C.J., Tegenthoff, M., Wolf, O.T., Margraf, J., and Zlomuzica, A. (2019a). Post-exposure cortisol administration does not augment the success of exposure therapy: A randomized placebo-controlled study. Psychoneuroendocrinology *99*, 174–182.

Raeder, F., Woud, M. L., Schneider, S., Totzeck, C., Adolph, D., Margraf, J., et al. (2019b). Reactivation and evaluation of mastery experiences promotes exposure benefit in height phobia. Cognit. Ther. Res. *43*, 948–958. https://doi.org/10.1007/s10608-019-10018-x. In press.

Raeder, F., Heidemann, F., Schedlowski, M., Margraf, J., Zlomuzica, A. (2019c). No pills, more skills: The adverse effect of hormonal

contraceptive use on exposure therapy benefit. J Psychiatr Res. *119*, 95–101.
Raeder, F., Merz, C.J., Margraf, J., Zlomuzica, A. (2020). The association between fear extinction, the ability to accomplish exposure and exposure therapy outcome in specific phobia. Sci. Rep. *10*, 4288. https://doi.org/10.1038/s41598-020-61004-3. In press.
Richter, J., Pittig, A., Hollandt, M., and Lueken, U. (2017). Bridging the gaps between basic science and cognitive-behavioral treatments for anxiety disorders in routine Care. Z. für Psychol. *225*, 252–267.
Stockhorst, U. and Antov, M.I. (2016). Modulation of fear extinction by stress, stress hormones and estradiol: A review. Front Behav. Neurosci. *9*, 359.
Waters, A.M. and Pine, D.S. (2016). Evaluating differences in Pavlovian fear acquisition and extinction as predictors of outcome from cognitive behavioural therapy for anxious children. J. Child Psychol. Psychiatry *57*, 869–876.
Zlomuzica, A., Dere, D., Machulska, A., Adolph, D., Dere, E., Margraf, J. (2014). Episodic memories in anxiety disorders: Clinical implications. Front. Behav. Neurosci. *8*, 131.
Zlomuzica, A., Preusser, F., Schneider, S., and Margraf, J. (2015). Increased perceived self-efficacy facilitates the extinction of fear in healthy participants. Front. Behav. Neurosci. *9*, 270.
Zlomuzica, A., Preusser, F., Totzeck, C., Dere, E., and Margraf, J. (2016). The impact of different emotional states on the memory for what, where and when features of specific events. Behav. Brain Res. *298*, 181–187.
Zlomuzica, A., Woud, M.L., Machulska, A., Kleimt, K., Dietrich, L., Wolf, O.T., Assion, H.J., Huston, J.P., Silva, M.A.D.S., and Dere, E. (2018). Deficits in episodic memory and mental time travel in patients with post-traumatic stress disorder. Prog. Neuro Psychopharmacol. Biol. Psychiatr. *83*, 42–54.

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Review article

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Principles of extinction learning of nonaversive experience

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Abstract: This review outlines behavioral and neurobiological aspects of extinction learning, with a focus on nonaversive experience. The extinction of acquired behavior is crucial for readaptation to our environment and plays a central role in therapeutic interventions. However, behavior that has been extinguished can reappear owing to context changes. In the first part of the article, we examine experimental strategies aimed at reducing behavioral recovery after extinction of nonaversive experience, focusing on extinction learning in multiple contexts, reminder cues, and the informational value of contexts. In the second part, we report findings from human imaging studies and studies with rodents on the neural correlates of extinction and response recovery in nonaversive learning, with a focus on ventromedial prefrontal cortex, hippocampus, and neurotransmitter systems.

Keywords: associative learning; context; renewal.

Zusammenfassung: Dieser Artikel gibt einen Überblick über verhaltens- und neurobiologische Aspekte der Verhaltenslöschung (Extinktion) mit einem Schwerpunkt auf nicht-aversive Lernerfahrungen. Die Löschung gelernten Verhaltens ist entscheidend für Wiederanpassungsleistungen an unsere Umwelt und spielt eine zentrale Rolle bei therapeutischen Interventionen. Gelöschtes Verhalten kann jedoch aufgrund von Kontextänderungen wieder auftreten. Im ersten Teil des Artikels stellen wir experimentelle Strategien vor, die darauf abzielen, das Wiedererstarken gelöschten Verhaltens zu reduzieren. Dabei stehen im Mittelpunkt die Extinktion in multiplen Kontexten, Erinnerungsreize und der Informationswert von Kontexten. Der zweite Teil liefert eine Übersicht über unsere Erkenntnisse zu neuronalen Korrelaten von Extinktion und Reaktionserholung, welche auf Studien zur Bildgebung beim Menschen und Studien mit Nagetieren beruhen. Hierbei liegt unser Schwerpunkt auf dem ventromedialen präfrontalen Kortex, dem Hippocampus und verschiedenen Neurotransmittersystemen.

Schlüsselwörter: Assoziatives Lernen; Kontext; Erneuerungseffekt.

Extinction and the role of context

Our environment is usually quite predictable: it does not rain when there is a cloudless sky; tasting your morning coffee is preceded by visual and olfactory perceptions of the beverage. Thus, certain events are related and often occur in a particular order. Humans and other animals are able to learn about event relationships, which allows us to predict future events based on the presence of preceding stimuli or actions (Lachnit et al., 2004; Melchers et al., 2005). This ability for associative learning is a considerable advantage for adaption and survival.

Classical conditioning and instrumental conditioning are two basic forms of associative learning. In classical conditioning (Pavlov, 1927), a neutral stimulus is repeatedly presented before a motivationally relevant outcome. As a result of these pairings, the neutral stimulus comes to elicit a response that indicates anticipation of the outcome. Consider Pavlov's dog who salivated when hearing a bell that had been repeatedly presented before feeding. Instrumental conditioning (Skinner, 1938) reflects our ability to learn about the consequences of our actions. Reward or punishment that follows a behavior increases or decreases the probability with which that behavior will occur in the future.

Classical conditioning and instrumental conditioning are crucial for successful interactions with our environment.

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However, they are also involved in the development of maladaptive behavior. Both forms of associative learning play key roles for a variety of psychopathological disorders, including phobias, eating disorders, and drug abuse. Many therapeutic treatments aimed at overcoming maladaptive behavior are based on the principle of extinction learning (Craske et al., 2014; Podlesnik et al., 2017). When a stimulus or an action is no longer followed by the expected outcome, we will cease the acquired behavior: Pavlov's dog will eventually stop salivating in response to the bell when subsequent feeding is repeatedly omitted; a patient's fear of spiders will decrease significantly when repeatedly exposed to spiders in the absence of actual danger.

However, extinction of acquired behavior does not always endure. Rather, acquired responses have been observed to reappear after extinction under various conditions (Bouton, 1993; Bouton et al., 2012). An intriguing example is the renewal effect, which refers to the finding that changing the context in which a behavior was extinguished can restore (renew) the original response. In a typical renewal experiment, the conditioned response is first established in a particular context. Then, the acquired behavior is extinguished in a different context. During a final test, it has been observed that the original response reoccurs either when the individual is shifted to the context of initial conditioning or when the individual is exposed to a third, novel context (Bouton and Bolles, 1979). Renewal has also been observed when behavioral acquisition and extinction take place in the same context, but testing occurs in a different context (Bouton and Ricker, 1994). Analogous results have been reported for human associative learning with motivationally insignificant stimuli (Rosas and Callejas-Aguilera, 2006; Üngör and Lachnit, 2006, 2008). Thus, the absence of the context of extinction learning appears to be sufficient to induce a recovery of acquired behavior.

The renewal effect has rather challenging implications for therapeutic treatments involving extinction learning. It suggests that full expression of therapeutic success may be limited to the therapeutic environment: the likelihood of relapse increases outside the therapeutic setting.

Basic research has revealed several experimental strategies that reduce or even prevent the renewal effect. These findings may provide important insights for improving the long-term success of therapeutic interventions. One experimental strategy that has received considerable attention comprises extinction learning in multiple contexts (Craske et al., 2014; Laborda et al., 2011). However, experiments involving human associative learning (Bustamante et al., 2016b) and instrumental conditioning in rats (Bernal-Gamboa et al., 2017) have indicated that the impact of this strategy may depend on the type of renewal procedure: extinction in multiple contexts resulted in weaker response recovery than extinction in a single context, when testing for renewal occurred in a novel context. However, when the test took place in the context in which the response had been originally acquired, extinction in multiple contexts exerted no attenuating effect on renewal (Bernal-Gamboa et al., 2017; Bustamante et al., 2016b).

Another experimental strategy aimed to counter the renewal effect is the application of so-called reminder cues, which refer to discrete stimuli that are repeatedly presented during the extinction of a response. Using visual reminder cues in human associative learning (Bustamante et al., 2016a) and auditory reminder cues in instrumental conditioning with rats (Nieto et al., 2020), experiments have shown that the application of reminder cues during renewal testing in a novel context completely prevented the recovery of acquired responding. Although this level of effectiveness is not reached when testing occurs in the context of initial acquisition, reminder cues weaken the degree of response recovery in this test situation (Nieto et al., 2017).

The renewal effect is also influenced by experimental manipulations that target the informational value of contexts. For many cases, contexts have low informational value, in the sense that they are irrelevant for the relationship between events – the delicious taste after biting into an apple occurs regardless of whether you are at home or in your workplace. However, in other cases, the relationship between events varies across contexts – having a lively conversation is welcomed at a party, but the same behavior is considered inappropriate in a library. Thus, contexts can carry relevant information about the current relationship between events. Studies of human associative learning have revealed that response recovery after extinction is weaker when initial acquisition (Lucke et al., 2013) or extinction (Lucke et al., 2014) was conducted in a context that had been trained as being irrelevant for other stimulus-outcome relationships, compared with a context trained as being relevant. Measures of eye-gaze behavior (Lucke et al., 2013) and other experimental approaches (Uengoer et al., 2018) suggest that the impact of context information on context-dependent learning is based on processes of selective attention.

Brain regions involved in extinction and renewal of nonaversive experience

Extinction learning can comprise aversive/maladaptive (fear, phobias, addiction) or benign/appetitive elements.

Extinction of aversive and maladaptive behavior has received the greatest degree of scrutiny to date, and it has become apparent that structures such as the amygdala, prefrontal cortex, and hippocampus play important roles in the processing of context in human subjects and in rodents during extinction of fear responses (Kalisch, 2006; Lang et al., 2009; Lingawi et al., 2019; Marek et al., 2019; Milad et al., 2007) and in fear renewal (Hermann et al., 2016). Extinction of appetitive, or nonaversive, learning in humans (Lissek et al., 2013) and rodents (Mendez-Couz et al., 2019) also involves the hippocampus.

Imaging studies investigating extinction related to nonaversive learning in humans (Figure 1) have demonstrated that the hippocampus and ventromedial prefrontal cortex (vmPFC) mediate renewal of acquired behavior (Lissek et al., 2013). Both regions showed higher activation in participants who exhibited renewal than in those who did not: the hippocampus encoded context information during extinction, displaying even higher activation in response to a stimulus presented in a novel context, while the vmPFC retrieved this information during renewal testing to decide upon response recovery. Recent studies on rats have demonstrated that information processing in discrete hippocampal subfields contribute to specific elements of context-dependent acquisition, extinction, and renewal in an appetitive spatial learning task (Mendez-Couz et al., 2019; see Figure 1), indicating that the hippocampus may be intrinsically involved in determining the specificity of the learned response.

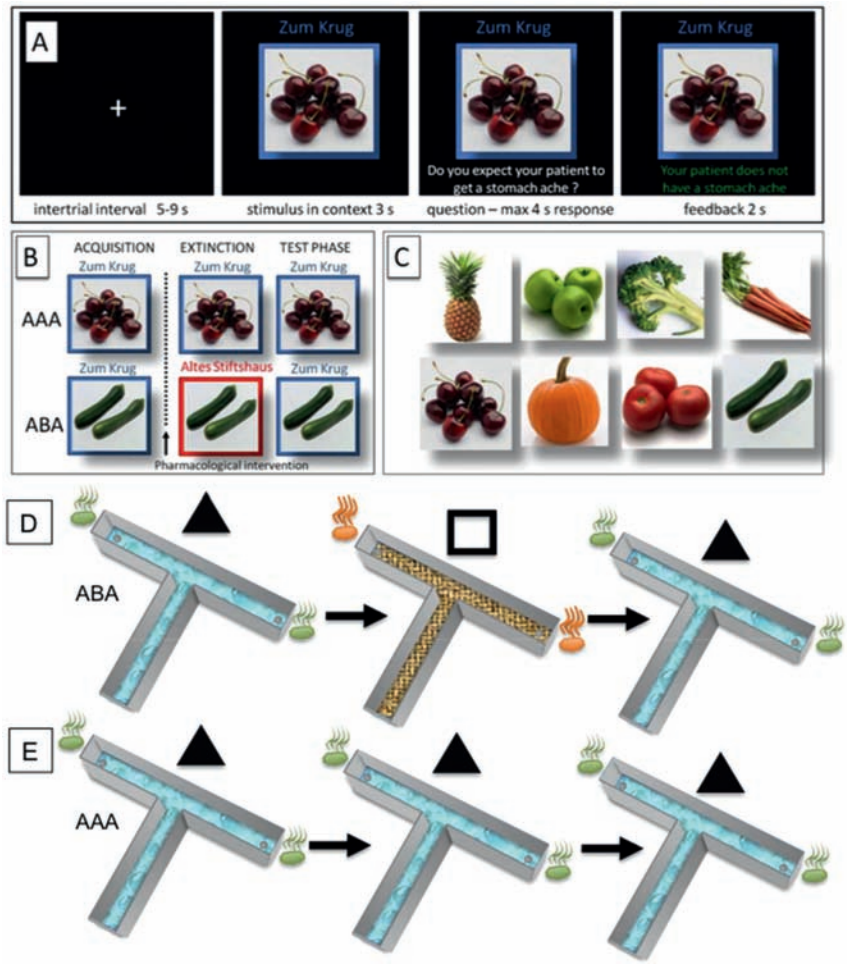

Figure 1: Paradigms for the study of extinction learning in humans or in rodents. A. In this paradigm, human subjects are presented with a sequence of trials each showing a compound of a food item (cue) and the name of a restaurant (context; e.g. "Zum Krug"). Each compound is associated with a specific outcome. Following an intertrial interval of 5–9 s, one cue/context compound is presented for 3 s. Then, a question appears asking the participant to predict whether consumption of the food in the restaurant will cause stomachache in a hypothetical patient, followed by a response period of maximally 4 s. Feedback, providing the correct answer, is then shown for 2 s (Golisch et al., 2017). B. The task comprises three phases: acquisition, extinction, and test. In the AAA condition, all phases occur in the same context, while in the ABA condition, the extinction context differs. During the test in both conditions, cues are presented in the same context as during acquisition (Golisch et al., 2017). C. Examples of food images used in the task (Golisch et al., 2017). D/E. In rodents, nonaversive extinction learning can be studied by examining associative spatial learning and memory. Over a period of days, rodents learn that a food reward can be found (with low probability) at a specific end of a T-Maze arm. The T-Maze has a specific floor pattern, and a mild odor is present at the end of both T-Maze arms and visuospatial cues are placed outside of the T-maze, in visible range. The food reward is hidden in an indentation in the floor near the end of the target arm. One day after the animals have reached at least 80% arm-choice accuracy, extinction learning is examined either in the presence (D) or absence (E) of a context change. Here, the floor pattern, odor cues, and distal visuospatial cues are changed. During extinction learning trials, no food reward is present. Renewal is assessed in the ABA paradigm (D) by returning the animals to the original context. In the AAA paradigm (E), animals are simply reexposed to the same context (André et al., 2015b; Mendez-Couz et al., 2019; Wieschollek et al. 2014).

In line with this, individuals with, and without, a propensity for renewal differ in context-related hippocampal activation not only during extinction but also during initial acquisition, where context is irrelevant (Lissek et al., 2016). All individuals – regardless of their propensity for renewal – showed increased activation of the posterior hippocampus in a novelty response to the presentation of only the context. However, only those participants with a propensity for renewal maintained this hippocampal activation when a cue was added to the context, indicating processing of the context/cue compound.

While the amygdala is consistently active during extinction of fear responses (Hermann et al., 2020; Merz et al., 2013), it is also active in extinction related to nonaversive experience (Lissek et al., 2013). The finding supports a proposed broader role of the amygdala in aversive and appetitive learning (Everitt et al., 2003; Knapska et al., 2006). Other regions previously shown to be involved in fear extinction (Sehlmeyer et al., 2009) that are regularly found to be active during nonaversive extinction learning comprise the anterior cingulate cortex (ACC) and insula, which exhibited higher activity in participants with a propensity for renewal (Lissek et al., 2013). This increased activity indicates that attentional processing mediated by the ACC and processing of salient events by the insula (Menon and Uddin, 2010) are more pronounced in these participants.

Neurotransmitter systems involved in extinction and renewal of nonaversive experience

The creation of associative memories depends on cortical and hippocampal plasticity processes that in turn critically depend on the activation and regulation of neurotransmitter receptor systems including glutamatergic N-methyl-D-aspartate (NMDA) receptors (Hansen et al., 2017), gamma aminobutyric acid (GABA) receptors (Swanson and Maffei, 2019), and catecholaminergic receptors (Hagena et al., 2016; Hansen and Manahan-Vaughan, 2014). Although studies of nonaversive extinction learning are less numerous than the wealth of data available with regard to extinction of aversive learning, it is apparent that neurotransmitter receptors that are essential for cortical and synaptic plasticity serve to modulate the efficacy of extinction of nonaversive learning (Table 1).

Pharmacological manipulation of NMDA receptors modulated extinction related to nonaversive learning in human subjects when conducted within the same context as for initial acquisition: strikingly both the NMDA receptor agonist, D-cycloserine, DCS, (Klass et al., 2017) and the NMDA receptor antagonist, memantine (Golisch et al., 2017), enhanced extinction learning. This latter finding, which was associated with dose-related effects of memantine modulated by body mass index, suggests that fine-tuning of the degree of activation of NMDA receptors is a key facet of effective extinction learning. This may relate to a possible differential regulation, by the ligands used in these studies, of GluN2A- or GluN2B-containing NMDA receptors, which determine, in turn, the amplitude and persistency of synaptic plasticity (Ballesteros et al., 2016).

Research on extinction and renewal related to nonaversive learning in humans demonstrated a specific role for dopamine (DA) receptors for extinction learning in a *novel* context, whereas the DA antagonist, tiapride, when administered as a single dose before the extinction phase, impaired performance (Lissek et al., 2015b), and the DA agonist, bromocriptine, enhanced extinction learning, particularly in those individuals with a propensity for renewal (Lissek et al., 2018). The role of specific DA receptors was scrutinized in rodent experiments: Studies of extinction learning using a spatial appetitive task in rats demonstrated that dopamine acting on the D1/D5 receptor modulates both the acquisition and the consolidation of

Table 1: Overview of the effect of treatment with neurotransmitter receptor ligands on nonaversive extinction learning.

Ligand	Human	Rodent	Reference
NMDAR agonist	enhances	n.t.	Golisch et al., 2017; Klass et al., 2017
NMDAR antagonist	enhances	impairs	Goodmann et al., 2019
DA agonist	enhances	no effect	Andrè and Manahan-Vaughan, 2016; Lissek et al., 2018
DA antagonist	impairs	D1/D5 enhances D2/D3 no effect	Andrè and Manahan-Vaughan, 2016; Lissek et al., 2015b
NA agonist	enhances	enhances	Janak and Corbit, 2011; Lissek et al., 2015a
NA antagonist	n.t.	no effect	André et al., 2015
GABA agonist	impairs	impairs	Corcoran, 2005; Corcoran and Maren, 2001; Lissek et al., 2015a, 2017

Note: DA: dopamine, GABA: gamma amino-butyric acid, NA: noradrenaline, NMDAR: N-methyl-D-aspartate receptor, n.t.: not tested.

extinction learning. D2 receptors modulated context-independent aspects of extinction learning (André and Manahan-Vaughan, 2016).

The noradrenergic system also contributes to extinction learning. Administration of the noradrenaline reuptake inhibitor, atomoxetine, to human subjects (Lissek et al., 2015a) or to rats (Janak and Corbit, 2011) enhanced extinction in nonaversive or appetitive tasks. In rats, extinction learning within a spatial appetitive task was unaffected by antagonism of beta-adrenergic receptors (André et al., 2015), however, suggesting that either this process is supported by alpha-adrenergic receptors or attentional demand is a determinant of the involvement of the noradrenergic system in extinction learning. Consistent with the latter possibility, activation of beta-adrenergic receptors is required for extinction learning in the absence of a context change (André et al., 2015a). This latter process is also supported by metabotropic glutamate receptors (mGluR; André et al., 2015b).

Extinction related to nonaversive learning in human subjects was impaired by pharmacological activation of GABA receptors with the agonist lorazepam, irrespective of the context in which extinction occurred (Lissek et al., 2015a, 2017). These results correspond to animal studies reporting impairments of extinction learning by local hippocampal GABA receptor agonism (Corcoran, 2005; Corcoran and Maren, 2001).

Consistent with the likelihood that extinction learning involves *de novo* encoding of associative experience (Mendez-Couz et al., 2019), enhanced hippocampal activation during extinction learning and renewal testing was observed after stimulation of noradrenergic, dopaminergic, or glutamatergic NMDA receptors in human subjects before extinction training. In contrast, hippocampal activity was reduced by dopaminergic antagonism and GABA agonism (Lissek et al., 2015a, 2015b, 2017). Activation of the vmPFC was enhanced by noradrenergic stimulation during extinction learning and by GABA agonism during renewal testing and reduced by DA antagonism during extinction in the acquisition context, but not in a novel one. NMDA or noradrenergic receptor activation increased activation of the dorsolateral prefrontal cortex and inferior frontal gyrus, whereas the DA receptor antagonism, GABA receptor activation, and NMDA receptor antagonism reduced activation. In addition, both noradrenergic and NMDA receptor stimulation increased ACC and insula activation in extinction and renewal testing, while GABA receptor agonism and the DA receptor antagonism reduced activation in these regions (Lissek et al., 2015a, 2015b; Klass et al., 2017).

Taken together, results obtained in pharmacological studies on humans and rodents indicate that during extinction learning, dopamine, acting in the prefrontal cortex and hippocampus, is involved in readjusting the cue-outcome relationship in the presence of a novel context. Hippocampal dopamine is important for the encoding and provision of context information and is, thus, essentially involved in the renewal effect. In contrast, prefrontal and hippocampal NMDA receptors appear to be specifically involved in the modification of established stimulus-outcome associations in the context of initial acquisition. Moreover, the noradrenergic system is involved in the modification of established associations during extinction learning, regardless of context, underlining the supposed importance of attentional processes in extinction learning.

Catecholaminergic, GABAergic, and glutamatergic regulation of extinction learning is not restricted to nonaversive experience. Noradrenaline acting on beta-adrenergic receptors in the amygdala impairs extinction of fear, whereas noradrenaline acting on alpha-adrenergic receptors in the prefrontal cortex enhances it (Likhtik and Johansen, 2019). Furthermore, the robustness of fear memory and consequently the effectiveness of extinction learning is regulated by dopamine release from the central tegmental area acting on key brain circuitry such as the hippocampus, prefrontal cortex, and amygdala (Likhtik and Johansen, 2019). GABAergic transmission and mGluR and NMDA receptor activity in these structures also modulate fear memory and fear extinction (Courtin et al., 2014; Kaplan and Moore, 2011; Myers et al., 2001; Walker and Davis, 2002).

In conclusion, despite their clear differences in terms of behavior and cognition, extinction learning of aversive and nonaversive experience shares many functional similarities in terms of the brain regions that are engaged by these processes and the neurotransmitter receptors that mediate the behavioral outcome. This suggests that knowledge gained through studies of processes that optimize extinction learning in an experimental setting harbors significant potential in translation into therapeutic strategies for maladaptive behavior.

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References

André, M.E., and Manahan-Vaughan, D. (2016). Involvement of dopamine D1/D5 and D2 receptors in context-dependent extinction learning and memory reinstatement. Front. Behav. Neurosci. *9*, 125.

André, M.E., Wolf, O., and Manahan-Vaughan, D. (2015a). Beta-adrenergic receptors support attention to extinction learning that occurs in the absence, but not the presence, of a context change. Front. Behav. Neurosci. *9*, 125.

André, M.E., Güntürkün, O., and Manahan-Vaughan, D. (2015b). The metabotropic glutamate receptor, mGlu5 is required for extinction learning that occurs in the absence of a context change. Hippocampus, *25*, 149–158.

Ballesteros, J.J., Buschler, A., Köhr, G., and Manahan-Vaughan, D. (2016). Afferent input selects NMDA receptor subtype to determine the persistency of hippocampal LTP in freely behaving mice. Front. Behav. Neurosci. *8*, 33.

Bernal-Gamboa, R., Nieto, J., and Uengoer, M. (2017). Effects of extinction in multiple contexts on renewal of instrumental responses. Behav. Process. *142*, 64–69.

Bouton, M.E. (1993). Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. Psychol. Bull. *114*, 80–99.

Bouton, M.E., and Bolles, R.C. (1979). Contextual control of the extinction of conditioned fear. Learn. Motiv. *10*, 445–466.

Bouton, M.E., and Ricker, S.T. (1994). Renewal of extinguished responding in a second context. Anim. Learn. Behav. *22*, 317–324.

Bouton, M.E., Winterbauer, N.E., and Todd, T.P. (2012). Relapse processes after the extinction of instrumental learning. Renewal, resurgence, and reacquisition. Behav. Process. *90*, 130–141.

Bustamante, J., Uengoer, M., and Lachnit, H. (2016a). Reminder cues modulate the renewal effect in human predictive learning. Front. Psychol. *7*, 80.

Bustamante, J., Uengoer, M., Thorwart, A., and Lachnit, H. (2016b). Extinction in multiple contexts: Effects on the rate of extinction and the strength of response recovery. Learn. Behav. *44*, 283–294.

Corcoran, K.A. (2005). Hippocampal inactivation disrupts the acquisition and contextual encoding of fear extinction. J. Neurosci. *25*, 8978–8987.

Corcoran, K.A., and Maren, S. (2001). Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction. J. Neurosci. *21*, 1720–6.

Courtin, J., Chaudun, F., Rozeske, R.R., Karalis, N., Gonzalez-Campo, C., Wurtz, H., Abdi, A., Baufreton, J., Bienvenu, T.C., and Herry, C. (2014). Prefrontal parvalbumin interneurons shape neuronal activity to drive fear expression. Nature *505*, 92–96.

Craske, M.G., Treanor, M., Conway, C.C., Zbozinek, T., and Vervliet, B. (2014). Maximizing exposure therapy. An inhibitory learning approach. Behav. Res. Ther. *58*, 10–23.

Everitt, B.J., Cardinal, R.N., Parkinson, J.A., and Robbins, T.W. (2003). Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. Ann. N. Y. Acad. Sci. *985*, 233–50.

Goodman, J., Hsu, E., Packard, M.G. (2019). NMDA receptors in the basolateral amygdala mediate acquisition and extinction of an amphetamine conditioned place preference. Neurosci *133*, 428–436.

Golisch, A., Heba, S., Glaubitz, B., Tegenthoff, M., and Lissek, S. (2017). Enhancing effects of NMDA-receptor blockade on extinction learning and related brain activation are modulated by BMI. Front. Behav. Neurosci. *11*. https://doi.org/10.3389/fnbeh.2017.00034.

Hagena, H., Hansen, N., and Manahan-Vaughan, D. (2016). β-adrenergic control of hippocampal function: subserving the choreography of synaptic information storage and memory. Cerebral Cortex. *26*, 1349–1364.

Hansen, N., and Manahan-Vaughan, D. (2014). Dopamine D1/D5 receptors mediate informational saliency that promotes persistent hippocampal long-term plasticity. Cerebral Cortex. *24*, 845–858.

Hansen, K.B., Yi, F., Perszyk, R.E., Menniti, F.S., and Traynelis, S.F. (2017). NMDA receptors in the central nervous system. Methods Mol. Biol. *1677*, 1–80.

Hermann, A., Stark, R., Milad, M.R., and Merz, C.J. (2016). Renewal of conditioned fear in a novel context is associated with hippocampal activation and connectivity. Soc. Cogn. Affect. Neurosci. *11*, 1411–1421.

Hermann, A., Stark, R., Müller, E.A., Kruse, O., Wolf, O.T., and Merz, C.J. (2020). Multiple extinction contexts modulate the neural correlates of context-dependent extinction learning and retrieval. Neurobiol. Learn. Mem. *168*, https://doi.org/10.1016/j.nlm.2019.107150.

Janak, P.H., and Corbit, L.H. (2011). Deepened extinction following compound stimulus presentation: Noradrenergic modulation. Learn. Mem. *18*, 1–10.

Kalisch, R. (2006). Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. J. Neurosci. *26*, 9503–9511.

Kaplan, G.B., and Moore, K.A. (2011). The use of cognitive enhancers in animal models of fear extinction. Pharmacol. Biochem. Behav. *99*, 217–28.

Klass, A., Glaubitz, B., Tegenthoff, M., and Lissek, S. (2017). D-Cycloserine facilitates extinction learning and enhances extinction-related brain activation. Neurobiol. Learn. Mem. *144*, 235–247.

Knapska, E., Walasek, G., Nikolaev, E., Neuhäusser-Wespy, F., Lipp, H.P., Kaczmarek, L., and Werka, T. (2006). Differential involvement of the central amygdala in appetitive versus aversive learning. Learn. Mem. *13*, 192–200.

Laborda, M.A., McConnell, B.L., and Miller, R.R. (2011). Behavioral techniques to reduce relapse after exposure therapy: Applications of studies of experimental extinction.

Associative Learning and Conditioning Theory: Human and Non-Human Applications. T. R. Schachtman and S. Reilly, eds. (Oxford Univ. Press), pp. 79–103.

Lachnit, H., Giurfa, M., and Menzel, R. (2004). Odor processing in honeybees: Is the whole equal to, more than, or different from the sum of its parts?. Adv. Study. Behav. *34*, 241–264.

Lang, S., Kroll, A., Lipinski, S.J., Wessa, M., Ridder, S., Christmann, C., Schad, L.R., and Flor, H. (2009). Context conditioning and extinction in humans: Differential contribution of the hippocampus, amygdala and prefrontal cortex. Eur. J. Neurosci. *29*, 823–832.

Likhtik, E., and Johansen, J.P. (2019). Neuromodulation in circuits of aversive emotional learning. Nat. Neurosci. *22*, 1586–1597.

Lingawi, N.W., Laurent, V., Westbrook, R.F., and Holmes, N.M. (2019). The role of the basolateral amygdala and infralimbic cortex in (re)learning extinction. Psychopharmacology. *236*, 303–312.

Lissek, S., Glaubitz, B., Uengoer, M., and Tegenthoff, M. (2013). Hippocampal activation during extinction learning predicts occurrence of the renewal effect in extinction recall. Neuroimage *81*, https://doi.org/10.1016/j.neuroimage.2013.05.025.

Lissek, S., Glaubitz, B., Güntürkün, O., and Tegenthofl, M. (2015a). Noradrenergic stimulation modulates activation of extinction-related brain regions and enhances contextual extinction learning without affecting renewal. Front. Behav. Neurosci. *9*, https://doi.org/10.3389/fnbeh.2015.00034.

Lissek, S., Glaubitz, B., Wolf, O.T., and Tegenthoff, M. (2015b). The DA antagonist tiapride impairs context-related extinction learning in a novel context without affecting renewal. Front. Behav. Neurosci. *9*, https://doi.org/10.3389/fnbeh.2015.00238.

Lissek, S., Glaubitz, B., Schmidt-Wilcke, T., and Tegenthoff, M. (2016). Hippocampal context processing during acquisition of a predictive learning task is associated with renewal in extinction recall. J. Cogn. Neurosci. *28*, https://doi.org/10.1162/jocn_a_00928.

Lissek, S., Golisch, A., Glaubitz, B., and Tegenthoff, M. (2017). The GABAergic system in prefrontal cortex and hippocampus modulates context-related extinction learning and renewal in humans. Brain Imaging Behav. *11*, 1885–1900.

Lissek, S., Glaubitz, B., Klass, A., and Tegenthoff, M. (2018). The effects of dopaminergic D2-like receptor stimulation upon behavioral and neural correlates of renewal depend on individual context processing propensities. Neuroimage *169*, https://doi.org/10.1016/j.neuroimage.2017.12.022.

Lucke, S., Lachnit, H., Koenig, S., and Uengoer, M. (2013). The informational value of contexts affects context-dependent learning. Learn. Behav. *41*, 285–297.

Lucke, S., Lachnit, H., Stüttgen, M.C., and Uengoer, M. (2014). The impact of context relevance during extinction learning. Learn. Behav. *42*, 256–269.

Marek, R., Sun, Y., and Sah, P. (2019). Neural circuits for a top-down control of fear and extinction. Psychopharmacology *236*, 313–320.

Melchers, K.G., Lachnit, H., Üngör, M., and Shanks, D.R. (2005). Prior experience can influence whether the whole is different from the sum of its parts. Learn. Motiv. *36*, 20–41.

Mendéz-Couz, M., Becker, J.M., and Manahan-Vaughan, D. (2019). Functional compartmentalization of the contribution of hippocampal subfields to context-dependent extinction learning. Front. Beh. Neurosci. *13*, 256.

Menon, V., and Uddin, L.Q. (2010). Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. *214*, 655–667.

Merz, C.J., Hermann, A., Stark, R., and Wolf, O.T. (2013). Cortisol modifies extinction learning of recently acquired fear in men. Soc. Cogn. Affect. Neurosci. *9*, 1426–1434.

Milad, M.R., Wright, C.I., Orr, S.P., Pitman, R.K., Quirk, G.J., and Rauch, S.L. (2007). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol. Psychiatry *62*, 446–454.

Myers, K.M., Carlezon, W.A. Jr, and Davis, M. (2011). Glutamate receptors in extinction and extinction-based therapies for psychiatric illness. Neuropsychopharmacology *36*, 274–293.

Nieto, J., Uengoer, M., and Bernal-Gamboa, R. (2017). A reminder of extinction reduces relapse in an animal model of voluntary behavior. Learn. Mem. *24*, 76–80.

Nieto, J., Mason, T. A., Bernal-Gamboa, R., & Uengoer, M. (2020). The impacts of acquisition and extinction cues on ABC renewal of voluntary behaviors. Learn. Mem. *27*, 114–118.

Pavlov, I. P. (1927). Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex (London: Oxford Univ. Press).

Podlesnik, C.A., Kelley, M.E., Jimenez-Gomez, C., and Bouton, M.E. (2017). Renewed behavior produced by context change and its implications for treatment maintenance. A review. J. Appl. Behav. Anal. *50*, 675–697.

Rosas, J.M., and Callejas-Aguilera, J.E. (2006). Context switch effects on acquisition and extinction in human predictive learning. J. Exp. Psychol. Learn. Mem. Cogn. *32*, 461–474.

Sehlmeyer, C., Schöning, S., Zwitserlood, P., Pfleiderer, B., Kircher, T., Arolt, V., and Konrad, C. (2009). Human fear conditioning and extinction in neuroimaging: a systematic review. PLoS One *4*, e5865.

Skinner, B. F. (1938). The behavior of organisms: an experimental analysis. Appleton-Century.

Swanson, O.K., and Maffei, A. (2019). From hiring to firing: activation of inhibitory neurons and their recruitment in behavior. Front. Mol. Neurosci. *3*, 168.

Uengoer, M., Lucke, S., and Lachnit, H. (2018). Attention toward contexts modulates context-specificity of behavior in human predictive learning. Evidence from the n-back task. Learn. Behav. *46*, 320–326.

Üngör, M., and Lachnit, H. (2006). Contextual control in discrimination reversal learning. J. Exp. Psychol. Anim. Behav. Process *32*, 441–453.

Üngör, M., and Lachnit, H. (2008). Dissociations among ABA, ABC, and AAB recovery effects. Learn. Motiv. *39*, 181–195.

Walker, D.L., and Davis, M. (2002). The role of amygdala glutamate receptors in fear learning, fear-potentiated startle, and extinction. Pharmacol. Biochem. Behav. *71*, 379–392.

Wiescholleck, V., André, M., and Manahan-Vaughan, D. (2014). Early age-dependent impairments of context-dependent extinction learning, object recognition, and object-place learning occur in rats. Hippocampus *24*, 270–279.

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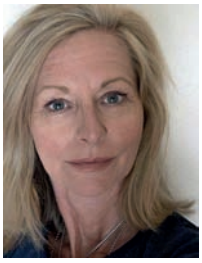

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Review article

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Beyond the classic extinction network: a wider, comparative view

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Abstract: Extinction learning modifies the dynamics of brain circuits such that a previously learned conditioned response is no longer generated. The majority of extinction studies use fear conditioning in rodents and identified the prefrontal cortex, the hippocampus, and the amygdala as core regions of the extinction circuit. We sought to find answers to two questions: First, do we find a similar functional brain circuit in birds, which underwent a 300-million-year separate evolution from mammals? Second, do we have to incorporate the cerebellum as a key component of the central extinction circuit? We indeed show that the avian extinction pathways are not identical but highly similar to those of mammals. In addition, we reveal that the human cerebellum processes prediction errors, a key element driving extinction of learned fear responses, and contributes to context-related effects of extinction.

Keywords: cerebellum; context learning; eyeblink conditioning; pigeons; prediction error.

Zusammenfassung: Extinktionslernen verändert die neurale Dynamik erlernter Assoziationen, sodass zuvor erlernte konditionierte Reaktionen nicht mehr generiert werden. Die meisten Untersuchungen zum Extinktionslernen nutzen die Furchtkonditionierung bei Nagetieren und identifizierten den präfrontalen Kortex, den Hippocampus und die Amygdala als kritische Kernregionen. Wir suchten Antworten auf zwei Fragen: Erstens, finden wir bei Vögeln, die eine 300 Millionen Jahre währende parallele Evolution zu Säugetieren durchlaufen, ein ähnliches neurales System für das Extinktionslernen? Zweitens, müssen wir das Kleinhirn als eine weitere Schlüsselkomponente des zentralen Extinktionskreislaufs einbeziehen? Wir zeigen, dass das Extinktionsnetzwerk bei Vögeln nicht identisch, aber dem der Säugetiere sehr ähnlich sind. Darüber hinaus demonstrieren wir, dass das menschliche Kleinhirn Vorhersagefehler und somit ein Schlüsselelement des Extinktionslernens verarbeitet und zur Kontextkodierung der Extinktion beiträgt.

Schlüsselwörter: Kleinhirn; Kontextlernen; Lidschlagkonditionierung; Tauben; Vorhersagefehler.

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Introduction

Animals rapidly learn to predict which stimuli are followed by reward or punishment, or, in more general terms, by an expected unconditioned stimulus (US). Conversely, this learned association can change when the US is omitted after stimulus presentation. This latter process is known as extinction learning and constitutes one of the most fundamental learning mechanisms (Rescorla and Wagner, 1972). Decades of research show that extinction of a conditioned response due to withholding of the US does

not merely involve forgetting the original association but entails new learning. The principles of extinction learning were demonstrated to be largely similar in animals that reach from humans (Icenhour et al., 2015) to insects (Felsenberg et al., 2018). If a learning "law" occurs in so diverse species with similar or even identical mechanisms, we should expect overlapping neural processes of extinction learning across the animal kingdom. But is this indeed the case? This question is at the core of the first part of this article in which we study extinction circuits in pigeons. Because birds have a more-than-300-million-year-old separate evolutionary history from mammals, we can test, if, at least among amniotes, the neural fundaments of extinction learning are invariant.

We then move on to the extinction-relevant pathways in mammals. Using fear extinction paradigms in rodents, three key neural structures were identified to be at the core of this system: the amygdala, prefrontal cortex, and hippocampus (Orsini and Maren, 2012). In the second part of our article, we aim to add the cerebellum as an overlooked, but, in our opinion, important structure to the established extinction circuitry. As we will show, the cerebellum plays an important role in the processing of prediction errors in sensory and reward-related domains and thus controls core elements of associative learning.

The avian neural circuit for extinction learning

To identify the neural circuit for extinction learning in an appetitive paradigm, we trained pigeons in a within-subject renewal design to peck on two conditioned stimuli (CSs) in two different contexts (sign tracking). Immediately before an extinction session, animals received intracranial injections of saline or drug. In different studies, we used either AP5 to inhibit local N-methyl-D-aspartate (NMDA) receptors or tetrodotoxin (TTX) to block Na+ channels. This intervention was followed by extinction training in the opposite context. Subsequently, pigeons were tested for retrieval of extinction memory in both contexts.

As depicted in Figure 1, visual information about conditional cues ascends via visual pathways to the visual associative nidopallium frontolaterale (NFL). TTX injections into NFL slow down extinction learning and reduce retrieval of context-specific extinction information. Notably, this effect is not due to perceptual impairment during learning (Gao et al., 2019a). Multiple projections fan out of NFL, and one of them leads to the hippocampus. Here, TTX injections caused no deficits in extinction learning but affected the consolidation of extinction memory. Importantly, we obtained no strong evidence for a hippocampus-mediated context dependency of extinction memory (Lengersdorf et al., 2014), in contrast to findings in rodents (Maren and Hobin, 2007) NFL also projects to the nidopallium caudolaterale (NCL) – the avian functional equivalent to the prefrontal cortex. Transiently inactivating the NCL with TTX did not affect extinction learning but impaired consolidation of extinction memory (Lengersdorf et al., 2014). In addition, multiple studies indicate a role of the avian NCL in the integration of context information into extinction memory (Lissek and Güntürkün, 2005; Starosta et al., 2017). NFL also projects to the medial striatum, the NCL, the avian amygdala, and the arcopallium. This last structure is the avian analog to the pre/motor cortex. Inhibiting NMDA receptors in the medial striatum or the amygdala impairs extinction learning, while the same procedure impairs consolidation of extinction memory in the arcopallium (Gao et al., 2018, 2019b; Lengersdorf et al., 2015).

Taken together, the visual-associative NFL, prefrontal-like NCL, amygdala, and medial striatum (StM) are involved in extinction learning. Our pharmacological treatment in these areas possibly impaired the updating of reward prediction errors and thus caused the deficit in extinction learning. A further cluster of structures (hippocampus, NCL, pre/motor arcopallium) is required for consolidation of extinction memory. Finally, NFL and NCL

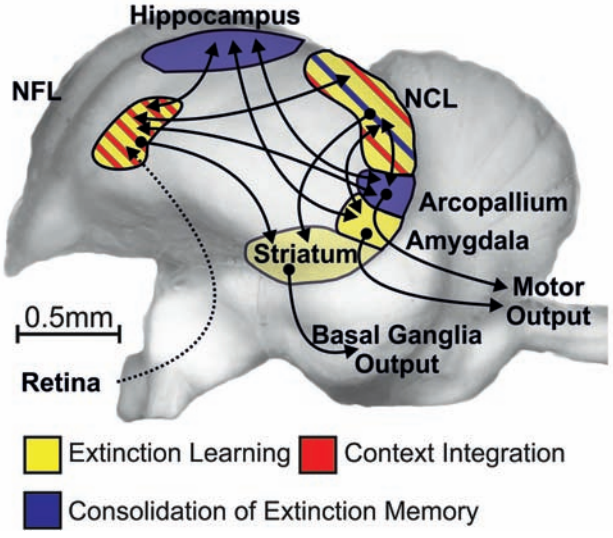

Figure 1: Schematic depiction of the avian extinction network. This circuit encompasses the visual-associative NFL, amygdala, prefrontal-like NCL, hippocampus, medial striatum (StM), and (pre) motor arcopallium. The dashed line indicates an indirect anatomical projection, and the solid lines symbolize direct fiber connections between the corresponding neural structures. NFL, nidopallium frontolaterale; NCL, nidopallium caudolaterale.

play important roles in the context modulation of extinction learning.

By and large, this pattern strongly resembles the systems architecture of extinction learning in mammals (Milad and Quirk, 2012). This would speak in favor of an ancient functional forebrain architecture that goes back more than 300 million years. There is, however, one glaring difference: While a key function of the mammalian hippocampus is the processing of context-dependent extinction information, we found not much evidence for this in pigeons. It is conceivable that the lack of direct connectivity between the avian "prefrontal" NCL and hippocampus is the key difference that drives this functional dissimilarity. This functional characterization of our current understanding of the extinction circuit in pigeons will pave the way for deeper functional analyses of these areas during extinction learning. This is shown for the NCL in the next part.

Single neurons in the avian forebrain dynamically encode acquired and extinguished associations

To elucidate the neuronal underpinnings of extinction learning, we recorded from single neurons in the prefrontal-like NCL during learning. An ideal paradigm to investigate extinction learning allows the observation of single-neuron activity during not only the extinction of conditioned responding but also the preceding acquisition and the subsequent reappearance of responding (spontaneous recovery or reacquisition). To this end, we designed a task that encompasses these three stages of learning in a single behavioral session (Starosta et al., 2014). Single-neuron activity was recorded while animals acquired an instrumental response to a novel visual stimulus for reward, which was subsequently extinguished (reward omission: extinction) and then reestablished (reward for responding was reintroduced: reacquisition). In our task, pigeons were confronted with one of several visual stimuli on one response key and had to learn which of the two adjacent choice keys was associated with that stimulus (Figure 2A). Two stimuli were familiar to the animals from earlier sessions, while two others were new such that the correct response had to be learned. After reaching learning criterion, the response to one of the new stimuli was no longer reinforced (extinction). Once the performance for this stimulus dropped below 65%, the response was reinforced again (reacquisition). Figure 2B shows behavioral results from an example session. Figure 2C–F summarizes the behavioral results of five animals performing this task repeatedly. It illustrates that acquisition, extinction, and reacquisition phases are associated with an increase, decrease, and second increase in performance, respectively. As expected, extinction leads to a decrease of pecks onto the visual stimulus (Figure 2D) and an increase in reaction times which was reversed during reacquisition (Figure 2E). Finally, the number of trials to criterion performance is higher in acquisition than in reacquisition, in line with the hypothesis that extinction is a new learning process and not mere forgetting (Figure 2F).

On a neuronal level, we reasoned that learning affects neuronal responses such that activity should change across the three learning stages (Veit et al., 2015). This was indeed the case: Figure 2G shows neurometric curves from an NCL neuron whose activity profile changed in the course of learning. Specifically, the neuron discriminated the two familiar stimuli (blue curves) almost perfectly across the entire session (area under the receiver operating characteristic curve, AUROC: 1, perfect discriminability; 0.5, no discriminability). In contrast, discriminability for the two novel stimuli changed dramatically over the course of the session: during acquisition, discriminability was relatively constant but moderate; in extinction, discriminability decreased from nearly optimal to chance levels; during reacquisition, neural discriminability again increased.

This pattern was also seen in the population of NCL neurons. Figure 2H depicts in black neural discriminability for the two novel stimuli across the three stages of learning, separately averaged across selective NCL neurons (n = 32 [acquisition phase], 29 [extinction phase], 14 [reacquisition phase]) or not selective (n = 187, 166, 127). Familiar stimuli are shown in gray. Notably, only those neurons that were selective for the familiar stimuli (black curves) showed learning-related modulation. Thus, many NCL neurons reflected the strength of conditioned responding across learning stages. Taken together, our novel paradigm highlights diverse reorganization patterns of neuronal activity in single NCL units during learning. While a subpopulation of neurons faithfully tracks the "ups and downs" of associative strength, others seem to code further aspects of the task that could explain the saving of associative memory across extinction learning. These aspects will be uncovered by a deeper analysis of the activity patterns of these neurons. But only integrating these insights into the framework of the overall functional extinction circuits as outlined in the beginning will allow a deeper understanding of the neuronal dynamics during extinction. This is exemplified in the next part of our article that demonstrates that the cerebellum, a hitherto neglected

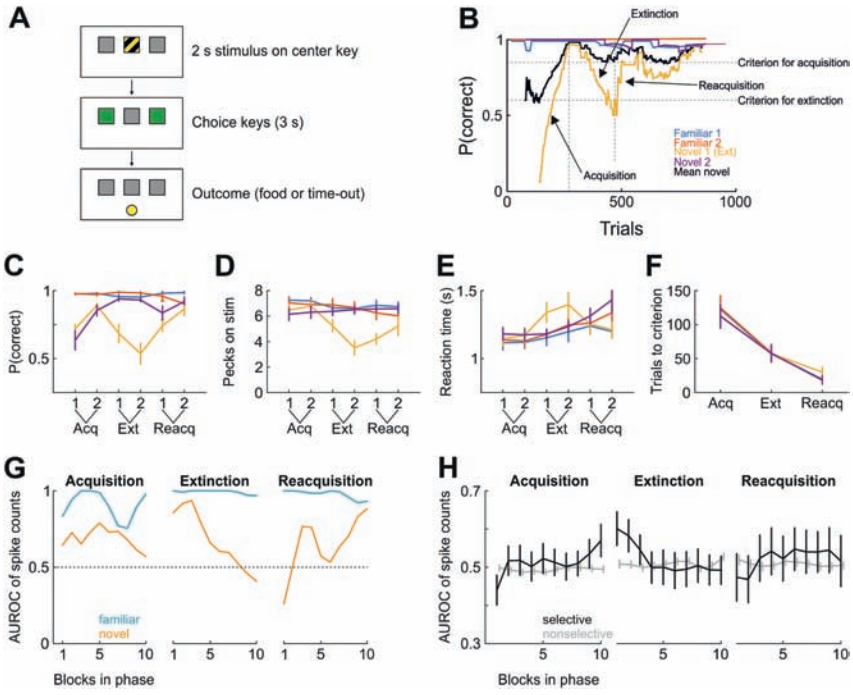

Figure 2: Investigating single-neuron activity during three stages of learning. (A) Schematic of the behavioral paradigm. (B) Performance (moving average of 120 trials) in an example session. Novel stimulus 1 was designated as to-be-extinguished stimulus. Vertical dotted lines signify transitions between learning phases (acquisition, extinction, reacquisition), and horizontal lines denote performance criteria for phase transitions (successful acquisition for the novel stimuli and successful extinction for novel stimulus 2). (C) As in B, but averaged for first and second halves over all sessions from all birds. (D) As in C, but showing the number of pecks emitted onto the visual discriminative stimulus within 2 s. Emitted pecks decreased exclusively for the extinguished stimulus during extinction. (E) As in C, but showing reaction times from stimulus offset to choice. Reaction times increased during extinction only for the extinguished stimulus. (F) The number of trials until the learning phase was considered complete. (G) Neurometric curve for a single NCL neuron during task performance, shown as discriminability (AUROC) of familiar and novel stimuli. During extinction, the neuron becomes less selective for the novel stimuli. During reacquisition, the neuron again starts discriminating. Discrimination for the familiar stimuli is high throughout. (H) As in G, but showing the average AUROC of all recorded neurons for the novel stimulus pair only. All recorded neurons were separated based on the degree to which they discriminated the familiar stimuli (Hedges' g between spike count distributions >/< 0.6 in the first 60 trials of each session). Data points in C through F represent the mean across all birds ($n = 5$). Error bars denote standard error of the mean. AUROC, area under the receiver operating characteristic curve; NCL, nidopallium caudolaterale.

part of the extinction network, is in fact an important component of this system.

The cerebellum as a frequently ignored component of the extinction network

Comparatively little is known about the contribution of the cerebellum to extinction of learned fear responses (Apps and Strata, 2015). Cerebellar contribution to extinction has been studied in most detail in eyeblink conditioning (Hu et al., 2015, for reviews). As yet, most studies focused on the intrinsic cerebellar mechanisms involved in extinction but neglected additional cerebello-cerebral interactions. In the rodent literature, there is some evidence that learning-related changes of Purkinje cell activities in the cerebellar cortex are reversed during extinction. Recording studies show that Purkinje cells learn to reduce their activity ("pause") in response to the CS during acquisition of conditioned eyeblink responses. This pause is reversed during extinction and returns during reacquisition (Jirenhed et al., 2007). The inhibitory feedback connection between the cerebellar nuclei and the inferior olive seems to play a critical role in extinction (Bengtsson et al., 2007; Medina et al., 2002). The results of our functional magnetic resonance imaging (fMRI) studies in humans agree with the hypothesis that at least parts of the initial learning memory in the cerebellar cortex are erased during extinction (Medina et al., 2002).

We established a setup that allows ultra-high-field 7T fMRI of the cerebellum during eyeblink conditioning in humans (Thürling et al., 2015). We found that activations in the cerebellar cortex related to the acquisition of conditioned eyeblink responses were reversed during extinction (Thürling et al., 2015). Findings were largely confirmed in a subsequent 7T fMRI study using the same setup in a different group of participants (Ernst et al., 2017). We were unable to show saving-related cerebellar activation (Ernst et al., 2017). These findings, however, do not exclude the possibility that parts of the initial memory trace remain in the cerebellum during extinction. The cerebellar nuclei, but also extracerebellar regions, may be potential substrates of saving effects (Medina et al., 2001). But also

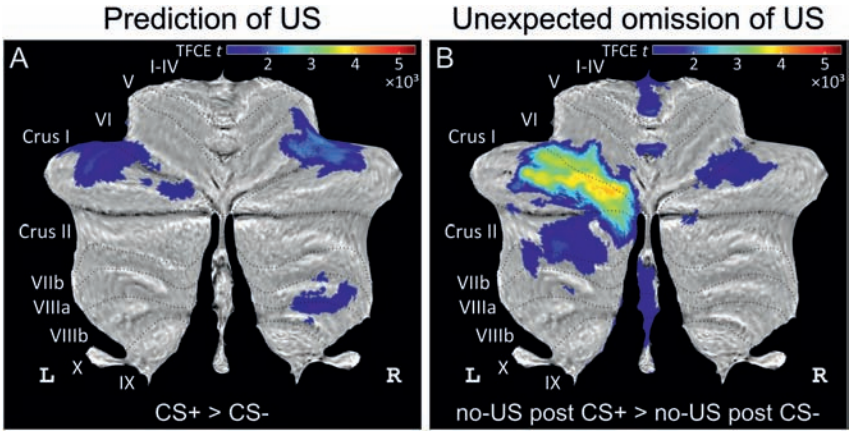

Figure 3: Differential cerebellar activations during fear acquisition. (A) Cerebellar activations related to the prediction of the US (contrast CS+ > CS–) are shown as cerebellar flatmap (Diedrichsen and Zotow, 2015). (B) Cerebellar activations related to the unexpected of the omission of the US (contrast no-US after CS+ > no-US after CS–). Cerebellar activation is abolished during extinction. All contrasts calculated using TFCE and familywise error correction ($p < 0.05$). CS, conditioned stimulus; L, left; R, right; TFCE, threshold-free cluster enhancement; US, unconditioned stimulus. Adapted from Figure 3 in the study by Ernst et al. (2019).

extracerebellar regions may play a role (Kalmbach and Mauk, 2012). These regions may be under the inhibitory control of the known cerebral fear extinction network (Hu et al., 2015, for review), but this has been studied in detail neither in humans nor in animals.

Bidirectional learning within the cerebellar cortex implies that cortical areas involved in acquisition and extinction of learned associations at least partially overlap. Our findings in patients with cerebellar lesions agree with this assumption. We tested acquisition and extinction of conditioned eyeblink responses (Ernst et al., 2016) and acquisition and extinction of cognitive associations (Steiner et al., 2020) in patients with cerebellar disease. Patients who had preserved acquisition – a prerequisite to study extinction effects – showed extinction not different from controls.

Extinction, however, is known to be more context-dependent than acquisition and to involve a more extended cortical network, including the prefrontal cortex and the hippocampus (Milad and Quirk, 2012). Likewise, cerebellar areas involved in extinction may be more extended than cerebellar areas involved in acquisition. Initial findings in cerebellar patients support this assumption (Steiner et al., 2019). We studied patients with focal cerebellar disease and preserved acquisition of conditioned eyeblink responses. Extinction was not different from controls. Renewal effects, however, appeared to be impeded in patients with lesions of the more posterolateral cerebellar hemisphere which has connections with the prefrontal cortex and hippocampus (Bostan et al., 2013; Watson et al., 2019). Furthermore, we found activation of the posterolateral cerebellar hemisphere related to context change during extinction learning of cognitive associations in healthy participants in a 3T fMRI study (Chang et al., 2015). Our findings suggest that the cerebellum contributes to context-related effects of extinction. Our attempts, however, to use cerebellar transcranial direct current stimulation (tDCS) to modulate extinction and context-related extinction effects of conditioned eyeblink responses in healthy participants were largely unsuccessful (Beyer et al., 2017; Lipp et al., 2019). Lack of robustness and reproducibility of cerebellar tDCS effects are increasingly recognized (Mamlins et al., 2019) and call for further methodological refinement before more firm conclusions can be drawn in the application to patient-oriented studies.

Our most recent 7T fMRI studies show that findings related to extinction of conditioned eyeblink responses equally apply to extinction of learned fear. In healthy human participants, cerebellar cortical activations related to the acquisition of learned fear responses were reversed during extinction (Ernst et al., 2019). Furthermore, we observed activation of the posterolateral cerebellar hemisphere related to the renewal of previously extinguished conditioned fear responses in the acquisition context (Timmann, 2019). In fear conditioning paradigms, the CS–US interstimulus intervals (ISIs) typically last several seconds. Therefore, event-related designs allowed us to separate cerebellar fMRI signals related to the visual CS from signals related to the subsequent US (an aversive electric shock). We found that cerebellar activation was most pronounced in unpaired CS+ trials, that is, in trials where the US was expected but did not occur (Figure 3; Ernst et al., 2019). This activation disappeared during extinction when US omission became expected. Findings agree with the assumption that prediction error drives extinction learning (Rescorla and Wagner, 1972). Among others, reward signals may play a role. The unexpected omission of the US is rewarding, and recent studies suggest

that reward signals play a role in extinction (Kalisch et al., 2019). Furthermore, the role of the cerebellum has been shown to go beyond the processing of sensory prediction errors and to include the processing of reward predictions errors (Wagner et al., 2017). The exact nature of the observed error signal in the cerebellum needs to be elucidated in future studies.

In sum, our findings provide evidence that the cerebellum is part of the brain network subserving extinction. The cerebellum likely contributes to different aspects of extinction, and different cerebellar areas appear to be involved.

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References

Apps, R. and Strata, P. (2015). Neuronal circuits for fear and anxiety – The missing link. Nat. Rev. Neurosci. *16*, 642.

Bengtsson, F., Jirenhed, D.A., Svensson, P., and Hesslow, G. (2007). Extinction of conditioned blink responses by cerebello-olivary pathway stimulation. Neuroreport *18*, 1479–1482.

Beyer, L., Batsikadze, G., Timmann, D., and Gerwig, M. (2017). Cerebellar tDCS effects on conditioned eyeblinks using different electrode placements and stimulation protocols. Front Hum. Neurosci. *11*, 23.

Bostan, A.C., Dum, R.P., and Strick, P.L. (2013). Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn. Sci. *17*, 241–254.

Chang, D.I., Lissek, S., Ernst, T.M., Thürling, M., Uengoer, M., Tegenthoff, M., Ladd, M.E., and Timmann, D. (2015). Cerebellar contribution to context processing in extinction learning and recall. Cerebellum *14*, 670–676.

Ernst, T.M., Beyer, L., Mueller, O.M., Göricke, S., Ladd, M.E., Gerwig, M., and Timmann, D. (2016). Pronounced reduction of acquisition of conditioned eyeblink responses in young adults with focal cerebellar lesions impedes conclusions on the role of the cerebellum in extinction and savings. Neuropsychologia *85*, 287–300.

Ernst, T.M., Thürling, M., Müller, S., Kahl, F., Maderwald, S., Schlamann, M., Boele, H.J., Koekkoek, S., Diedrichsen, J., De Zeeuw, C.I., et al. (2017). Modulation of 7 T fMRI signal in the cerebellar cortex and nuclei during acquisition, extinction, and reacquisition of conditioned eyeblink responses. Hum. Brain Mapp. *38*, 3957–3974.

Ernst, T.M., Brol, A.E., Gratz, M., Ritter, C., Bingel, U., Schlamann, M., Maderwald, S., Quick, H.H., Merz, C.J., and Timmann, D. (2019). The cerebellum is involved in processing of predictions and prediction errors in a fear conditioning paradigm. eLife *8*, e46831.

Felsenberg, J., Jacob, P.F., Walker, T., Barnstedt, O., Edmondson-Stait, A.J., Pleijzier, M.W., Otto, N., Schlegel, P., Sharifi, N., Perisse, E., et al. (2018). Integration of parallel opposing memories underlies memory extinction. Cell *175*, 709–722.

Gao, M., Lengersdorf, D., Stüttgen, M.C., and Güntürkün, O. (2018). NMDA receptors in the avian amygdala and the premotor arcopallium mediate distinct aspects of appetitive extinction learning. Behav. Brain Res. *343*, 71–82.

Gao, M., Pusch, R., and Güntürkün, O. (2019a). Blocking NMDA-receptors in the pigeon's medial striatum impairs extinction acquisition and induces a motoric disinhibition in an appetitive classical conditioning paradigm. Front. Behav. Neurosci. *13*, 153.

Gao, M., Lengersdorf, D., Stüttgen, M.C., and Güntürkün, O. (2019b). Transient inactivation of the visual-associative nidopallium frontolaterale (NFL) impairs extinction learning and context encoding in pigeons. Neurobiol. Learn. Mem. *158*, 50–59.

Hu, C., Zhang, L.B., Chen, H., Xiong, Y., and Hu, B. (2015). Neurosubstrates and mechanisms underlying the extinction of associative motor memory. Neurobiol. Learn. Mem. *126*, 78–86.

Icenhour, A., Kattoor, J., Benson, S., Boekstegers, A., Schlamann, M., Merz, C.J., Forsting, M., Forsting, M., and Elsenbruch, S. (2015). Neural circuitry underlying effects of context on human pain-related fear extinction in a renewal paradigm. Hum. Brain Mapp. *36*, 3179–3193.

Jirenhed, D.A., Bengtsson, F., and Hesslow, G. (2007). Acquisition, extinction, and reacquisition of a cerebellar cortical memory trace. J. Neurosci. *27*, 2493–2502.

Lengersdorf, D., Marks, D., Uengoer, M., Stüttgen, M.C., and Güntürkün, O. (2015). Blocking NMDA-receptors in the pigeon's "prefrontal" caudal nidopallium impairs appetitive extinction learning in a sign-tracking paradigm. Front. Behav. Neurosci. *9*, 1–9.

Lengersdorf, D., Stüttgen, M.C., Uengoer, M., and Güntürkün, O. (2014). Transient inactivation of the pigeon hippocampus or the nidopallium caudolaterale during extinction learning impairs extinction retrieval in an appetitive conditioning paradigm. Behav. Brain Res. *265*, 93–100.

Lissek, S. and Güntürkün, O. (2005). Out of context: NMDA receptor antagonism in the avian "prefrontal cortex" impairs context processing in a conditional discrimination task. Behav. Neurosci. *119*, 797–805.

Kalisch, R., Gerlicher, A.M.V., and Duvarci, S. (2019). A dopaminergic basis for fear extinction. Trends Cogn. Sci. *23*, 274–277.

Kalmbach, B.E. and Mauk, M.D. (2012). Multiple sites of extinction for a single learned response. J. Neurophysiol. *107*, 226–238.

Lipp, J., Draganova, R., Batsikadze, G., Ernst, T.M., Uengoer, M., and Timmann, D. (2019). Prefrontal but not cerebellar tDCS attenuates renewal of extinguished conditioned eyeblink responses. Neurobiol. Learn. Mem., 107137. Advance online publication. https://doi.org/10.1016/j.nlm.2019.107137.

Mamlins, A., Hulst, T., Donchin, O., Timmann, D., and Claassen, J. (2019). No effects of cerebellar transcranial direct current

stimulation on force field and visuomotor reach adaptation in young and healthy subjects. J. Neurophysiol. *121*, 2112–2125.
Maren S. and Hobin, J.A. (2007). Hippocampal regulation of context-dependent neuronal activity in the lateral amygdala. Learn. Mem. *14*, 318–324.
Medina, J.F., Garcia, K.S., and Mauk, M.D. (2001). A mechanism for savings in the cerebellum. J. Neurosci. *21*, 4081–4089.
Medina, J.F., Nores, W.L., and Mauk, M.D. (2002). Inhibition of climbing fibres is a signal for the extinction of conditioned eyelid responses. Nature *416*, 330–333.
Milad, M.R. and Quirk, G.J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. Annu. Rev. Psychol. *63*, 129–151.
Orsini C.A., and Maren S. (2012). Neural and cellular mechanisms of fear and extinction memory formation. Neurosci. Biobehav. Rev. *36*, 1773–1802.
Rescorla, R.A. and Wagner, A.R. (1972). A Theory of Pavlovian Conditioning: Variations in the Effectiveness of Reinforcement and Nonreinforcement. A.H. Black and W.F. Prokasy, eds. (Appleton-Century-Crofts), pp. 64–99.
Starosta, S., Bartetzko, I., Stüttgen, M.C., and Güntürkün, O. (2017). Integration of contextual cues into memory depends on "prefrontal" N-methyl-D-aspartate receptors. Neurobiol. Learn. Mem. *144*, 19–26.
Starosta, S., Stüttgen, M.C., and Güntürkün, O. (2014) Recording single neurons' action potentials from freely moving pigeons across three stages of learning, J. Vis. Exp. *88*, 51283.
Steiner, K.M., Gisbertz, Y., Chang, D.I., Koch, B., Uslar, E., Claassen, J., Wondzinski, E., Ernst, T.M., Göricke, S.L., Siebler, M., et al. (2019). Extinction and renewal of conditioned eyeblink responses in focal cerebellar disease. Cerebellum *18*, 166–177.
Steiner, K.M., Jansen, S., Adeishvili, N., Hulst, T., Ernst, T.M., Müller, O., Wondzinski, E., Göricke, S.L., Siebler, M., Uengoer, M., et al. (2020). Extinction of cognitive associations is preserved in patients with cerebellar disease. Neurobiol. Learn. Mem. *169*, 107185. Advance online publication.
Thürling, M., Kahl, F., Maderwald, S., Stefanescu, R.M., Schlamann, M., Boele, H.J., De Zeeuw, C.I., Diedrichsen, J., Ladd, M.E., Koekkoek, S.K., et al. (2015). Cerebellar cortex and cerebellar nuclei are concomitantly activated during eyeblink conditioning: A 7T fMRI study in humans. J. Neurosci. *35*, 1228–1239.
Timmann, D. (2019). The cerebellum and processing of predictions and prediction errors in fear conditioning. Presented at Minisymposium: 714-Adaptive control of movements and emotional states by the cerebellum. SFN 2019.
Veit, L., Pidpruzhnykova, G., and Nieder, A. (2015). Associative learning rapidly establishes neuronal representations of upcoming behavioral choices in crows, PNAS *112*, 15208–15213.
Wagner, M.J., Kim, T.H., Savall, J., Schnitzer, M.J., and Luo, L. (2017). Cerebellar granule cells encode the expectation of reward. Nature *544*, 96–100.
Watson, T.C., Obiang, P., Torres-Herraez, A., Watilliaux, A., Coulon, P., Rochefort, C., and Rondi-Reig, L. (2019). Anatomical and physiological foundations of cerebello-hippocampal interaction. eLife *8*, e41896.
Diedrichsen, J. and Zotow, E. (2015). Surface-based display of volume-averaged cerebellar imaging data. PLoS One *10*, e0133402.

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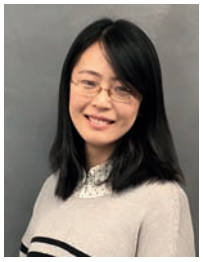

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Review article

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From gut feelings to memories of visceral pain

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Abstract: The role of pain-related fear learning and memory processes, conceptually embedded within the fear-avoidance model of chronic pain, is increasingly recognized. The unique biological salience of interoceptive, visceral pain with its cognitive, emotional, and motivational facets fosters associative learning. Conditioned fear is in principle adaptive but may turn maladaptive and contribute to hypervigilance and hyperalgesia in chronic pain. This review summarizes current knowledge on the formation, extinction, and return of pain-related memories with a focus on visceral pain. It provides a conceptual background, describes experimental approaches, and summarizes findings on behavioral and neural mechanisms in healthy humans and patients with chronic pain. Future directions underscore the potential of refining knowledge on the role of associative learning in the pathophysiology and treatment of chronic visceral pain in disorders of gut–brain interactions such as irritable bowel syndrome.

Keywords: fear-avoidance model; fear conditioning and extinction; irritable bowel syndrome; pain-related fear; visceral pain.

Zusammenfassung: Die Rolle schmerzbezogener Lern- und Gedächtnisprozesse, konzeptionell eingebettet in ein Furcht-Vermeidungsmodell der Schmerzchronifizierung, wird zunehmend gewürdigt. Die biologische Salienz viszeraler Schmerzen mit ihren kognitiven, emotionalen und motivationalen Facetten fördert assoziatives Lernen. Prinzipiell adaptiv kann konditionierte Furcht jedoch zu Hypervigilanz und Hyperalgesie bei chronischem Schmerz beitragen. Dieser Übersichtsartikel fasst Befunde zur Entstehung, Extinktion und dem Wiederauftreten schmerzbezogener Furcht mit Fokus auf viszeralem Schmerz zusammen. Neben einem konzeptionellen Hintergrund werden experimentelle Daten zu behavioralen und neuralen Mechanismen schmerzbezogener Konditionierung bei Gesunden und chronischen SchmerzpatientInnen dargestellt. Ein Ausblick unterstreicht das Potenzial eines tieferen Verständnisses von Lern- und Gedächtnisprozessen für die Pathophysiologie und Therapie chronischer viszeraler Schmerzen bei Störungen der Darm-Gehirn Achse.

Schlüsselwörter: Furchtvermeidungsmodell; Furchtkonditionierung und Extinktion; Reizdarmsyndrom; schmerzassoziierte Furcht; viszeraler Schmerz.

Visceral pain and gut feelings

Pain is a ubiquitous and uniquely aversive experience that is much more than merely an unpleasant sensation. It rather encompasses complex sensory, cognitive, emotional, and motivational components that are ultimately part of an evolutionarily driven adaptive response aimed at self-protection and survival (Lumley et al., 2011). Given its biological significance as a signal indicating bodily harm, it is not surprising that pain is universally feared and may literally be “hard to forget”. Indeed, virtually every one of us can readily recall previous painful episodes, even if they occurred years or decades ago. We are hence “hardwired” to fear and strive to avoid pain, with pain-related fear as the key emotional response essential to triggering adaptive behavior in the face of pain. However, fear can also turn maladaptive and contribute to the pathophysiology of chronic pain. Chronic pain is a major and unresolved healthcare problem with significant individual as well as societal implications

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(Breivik et al., 2006). The burden of pain arising from the internal organs and gastrointestinal tract, referred to as visceral pain, is particularly significant. Visceral pain is highly prevalent, leads to marked reductions in quality of life, and is very difficult to treat, especially in disorders of gut–brain interactions such as the irritable bowel syndrome (IBS). It is particularly sensitive to modulations by psychological factors such as stress, emotions, and cognitions (Elsenbruch and Enck, 2015; Labanski et al., 2020), which are also highly relevant to the pathophysiology of IBS as a biopsychosocial disorder. While psychological factors play a role in all types of pain and across different chronic pain conditions, visceral sensations are demonstrably more unpleasant than exteroceptive, somatic pain and readily evoke negative emotions, especially fear (Benson et al., 2019; Dunckley et al., 2005; Koenen et al., 2017; Strigo et al., 2003). Studying fear learning and memory processes in the context of visceral pain is therefore a clinically relevant and fruitful model to unravel pain-related fear and its mediators and moderators.

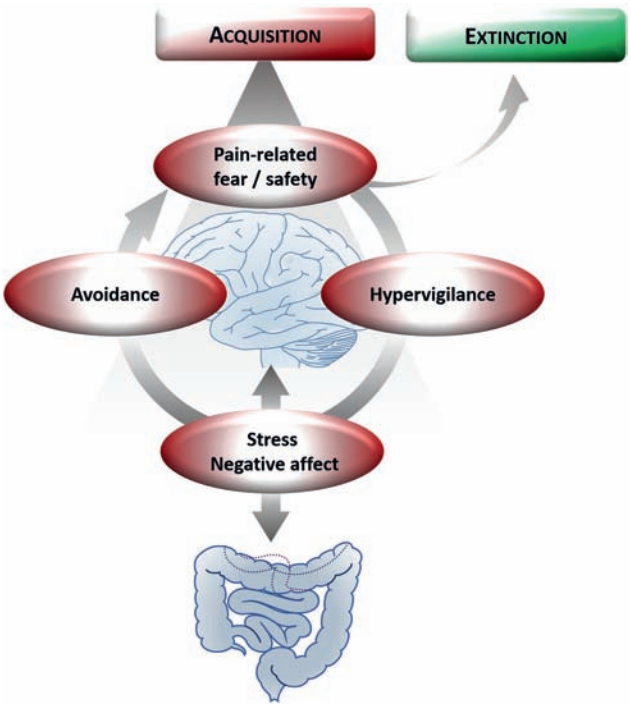

Figure 1: Schematic illustration of visceral pain–related acquisition and extinction embedded within the fear-avoidance model of pain chronification. Associative learning is considered to shape visceral pain–related fear but also safety as key components of a vicious circle in the transition from acute to chronic pain. Accordingly, pain-related emotional responses contribute to visceral hypervigilance, which can increase stress and negative affect. As these factors demonstrably also directly impact gastrointestinal functions along the gut–brain axis, they appear to be of particular relevance in the context of visceral pain. Pain-related fear and safety-seeking are further major triggers of avoidance as a crucial factor in maintaining maladaptive pain-related responses. Importantly, these processes are likely not unidirectional but rather exhibit mutual and dynamic impacts. Within this framework, extinction targeting maladaptive learned responses to predictors of visceral threat appears a promising therapeutic approach to reduce visceral pain–related fear and the complex detrimental emotional, cognitive, and behavioral aspects tightly linked to it.

From fear to avoidance

Dynamic learning and memory processes shape the emergence and persistence of pain-related fear in anticipation of imminent pain. Embedded within the influential fear-avoidance model (Figure 1), classically conditioned pain-related fear is considered to contribute to pain chronification (Vlaeyen, 2015), including chronic visceral pain (Elsenbruch and Labrenz, 2018). Within this framework, several mechanisms, including conditioned changes in perceptual and attentional processes, have been proposed (Vlaeyen, 2015; Zaman et al., 2015) in keeping with the crucial role of hyperalgesia and hypervigilance in the pathophysiology and treatment of chronic pain. Support comes from experimental findings demonstrating altered fear acquisition across different chronic pain conditions (Vlaeyen, 2015), including IBS (Claassen et al., 2017; Icenhour et al., 2015b; Labus et al., 2013). Evidence suggesting deficient safety learning in patients has also emerged (Icenhour et al., 2015b; Meulders et al., 2014), which is interesting as it could reinforce maladaptive safety-seeking as a key component of avoidance behavior (Crombez et al., 2012). Finally, clinical trials testing exposure-based interventions for chronic pain show promising results (e.g., Craske et al., 2011; Linton et al., 2008; Ljótsson et al., 2014), although long-term symptom relief remains difficult to achieve. As in anxiety- and stress-related disorders, overcoming the risk of relapse and treatment failure remains a challenge. Improving knowledge about mediators and moderators of pain-related extinction learning is therefore essential, not only in the context of treatment for chronic pain but also as a fundamental aspect of adaptive human behavior.

Extinction and beyond

Extinction of conditioned fear responses to a former threat-predictive cue is an adaptive process when this threat is no longer present, allowing behavioral flexibility in rapidly changing, complex environments. However, the initially acquired memory trace is not erased during extinction learning but can be reactivated, as evidenced by

spontaneous recovery, savings, renewal, and reinstatement phenomena (Bouton, 2004). Resurging fear poses a major challenge in cognitive-behavioral treatment approaches, especially exposure therapy, which is essentially built on robust extinction of fear. Impaired extinction efficacy hence implies a latent vulnerability for fear memory reactivation and relapse. Indeed, impaired extinction efficacy of maladaptive pain-related fear and safety responses, including reinstatement of pain-related fear, has already been observed in patients with chronic pain (Icenhour et al., 2015b; Labus et al., 2013; Meulders et al., 2017; Schneider et al., 2004), which would fit within but also considerably extend the fear-avoidance model of pain. This is not only conceptually intriguing, yet calls for experimental studies to further elucidate the formation and especially the extinction of pain-related fear and safety learning in a clinically relevant context.

Unraveling the acquisition and extinction of pain-related fear in experimental settings

Pavlovian fear conditioning as a translational model in the neurosciences has proven highly fruitful for investigating associative learning and extinction processes involving aversive stimuli (Milad and Quirk, 2012), including pain (Vlaeyen, 2015). At the interface of the cognitive neurosciences and the visceral pain field, innovative experimental paradigms with visceral stimuli as unconditioned stimuli (US) and/or conditioned stimuli (CS) have been introduced (Ceunen et al., 2016; Gramsch et al., 2014; Icenhour et al., 2015a, 2017; Labrenz et al., 2016; Yágüez et al., 2005; Zaman et al., 2016). Our group established a paradigm with visceral pain induced by rectal distensions as US (reviewed in Elsenbruch and Labrenz, 2018). Contingent CS–US pairings consistently evoked an increase in negative emotional valence of pain-predictive conditioned stimuli (CS^+) when compared with unpaired cues (CS^-) (Gramsch et al., 2014; Icenhour et al., 2015a; Kattoor et al., 2013; Koenen et al., 2018; Labrenz et al., 2016). Within the brain, CS^+ relative to CS^- recruited key regions of the central fear network, including amygdala, as well as the anterior cingulate cortex and insula as core nodes of the salience network with well-established roles in the integration of interoceptive signals with emotional and cognitive input (Menon and Uddin, 2010). At the same time, cues signaling the absence of impending pain (i.e., CS^-) acquired separate emotional value and neural signature, in line with their role as safety signals. While distinct neural processing of CS^- does not appear to be specific to pain-related conditioning (Fullana et al., 2016), it may bear special relevance in chronic pain as a mechanism underlying maladaptive avoidance behavior, particularly regarding interoceptive, visceral pain (Koenen et al., 2018).

During extinction, unpaired CS presentations reproducibly resulted in a return of cue valence to baseline levels, accompanied by accurate contingency ratings, and differential neural responses particularly involving prefrontal regions (Icenhour et al., 2015a; Kattoor et al., 2013). In keeping with the notion that the excitatory memory trace is preserved rather than erased (Bouton, 2004), we were further able to induce a reinstatement effect by unexpected and unsignaled confrontation with visceral pain stimuli (Gramsch et al., 2014; Kattoor et al., 2013, 2014). Interestingly, the involvement of the hippocampus as a central mediator of this effect was more pronounced in patients with IBS (Icenhour et al., 2015b). We finally observed that extinction in the visceral conditioning model is context-dependent (Icenhour et al., 2015a), in line with evidence from the broader field of inhibitory learning (Bouton, 2004). Interestingly, a context change affected particularly differential neural responses to conditioned safety cues, further supporting the distinct relevance of safety learning and memory processes related to visceral pain.

Predictability and contingency awareness

Several cognitive and emotional factors likely shape the successful formation of conditioned pain-related fear and safety not only in healthy individuals but also in patients with chronic pain. These include predictability as well as the conscious awareness of CS–US contingencies – aspects that remain incompletely understood in the context of pain. In light of first data supporting altered contingency learning and extinction in patients with chronic pain (Icenhour et al., 2015b; Meulders et al., 2014), we elucidated the putative role of contingency awareness in shaping the acquisition and extinction of conditioned emotional responses in a large sample of healthy volunteers (Labrenz et al., 2015). Herein, participants with highly accurate contingency awareness revealed greater emotional learning toward both danger as well as safety cues. They further demonstrated full extinction of pain-predictive cue unpleasantness, while exhibiting persistent positive emotional responses to safety signals. Moreover,

contingency accuracy predicted conditioned positive emotional responses to safety cues, while no predictive value was found for danger cues after acquisition. These findings suggest contingency accuracy to distinctly impact learned emotional responses to safety and danger cues.

To address the role of predictability in visceral pain–related fear acquisition and to elucidate its underlying neural mechanisms (Labrenz et al., 2016), we compared healthy individuals undergoing differential fear conditioning involving contingent CS–US pairings (predictable group) with a group experiencing noncontingent presentations of CS and US (unpredictable group). Successful differential learning of pain-related fear and safety was exclusively observed in the classically conditioned predictable group, whereas the unpredictable group perceived both cues experienced during acquisition as danger signals. Intriguingly, predictability as an inherent feature of contingent pairings appears to shape neural responses to the US, which is an entirely novel aspect. Specifically, the unpredictable group revealed enhanced US-related activation in brain regions related to the encoding and modulation of pain, including the prefrontal and somatosensory regions, the insular cortex, and the periaqueductal gray. These observations suggest the experience of unpredictable visceral pain to contribute to a generalized acquisition of putative danger cues.

Together, these findings underscore classically conditioned predictability and awareness of contingencies regarding cues predicting imminent threat but also safety to constitute key moderators of visceral pain–related fear learning and memory processes. Conditioning with interoceptive visceral stimuli appears to not only yield differential anticipatory activation but demonstrably also affects subsequent visceroceptive processing (Icenhour et al., 2017; Labrenz et al., 2016). As a consequence of differential conditioning, neural activation in response to equally intense, nonpainful rectal distensions was observed to evoke greater activation in prefrontal and cingulate regions associated with processes of attention and appraisal when cued by previously conditioned threat–predictive CS compared with conditioned safety predictors (Icenhour et al., 2017). Together with comparable US intensity ratings, these findings lend first support for the notion that visceral pain–related fear induced by prior learning may particularly contribute to visceral hypervigilance (Figure 1). Ultimately, in patients suffering from chronic visceral pain, environmental signals, but also internal and external contexts, including stress, may be readily associated with frequently experienced symptoms in the absence of full awareness, yielding visceral sensations an unpredictable threat and possibly contributing to an overestimation of true contingencies.

From stress to elucidating interindividual differences: the road to personalized interventions?

Stress plays a major role in the etiology and pathophysiology of chronic visceral pain (Labanski et al., 2020) and has well-documented effects on emotional learning and memory processes (Elsenbruch and Wolf, 2015). However, the role of acute or chronic stress and stress mediators in shaping pain-related fear remains unknown. To elucidate the potential impact of the acute stress mediator cortisol on pain-related fear, we recently conducted a randomized, double-blind, placebo-controlled study in healthy volunteers (Benson et al., 2019). We tested the effects of pharmacologically increased cortisol levels on the acquisition and extinction of pain-related fear comparing conditioned responses to cues predicting visceral and somatic pain stimuli applied as US. We could demonstrate that conditioned pain-related fear was significantly reduced after hydrocortisone application for the visceral, but not somatic modality, suggesting that elevated cortisol levels may distinctly interfere with pain-related emotional learning in the context of visceral pain.

In addition to altered stress responsivity to acute challenges in patients with chronic visceral pain involving the release and direct effects of cortisol (Labanski et al., 2020), chronic stress constitutes a major burden in patients and an important risk factor for disease onset and symptom exacerbation. Whether chronic stress impacts pain-related emotional learning and memory remains to be elucidated. First evidence of chronic stress as a possible moderator of memory processes in the context of visceroception, however, was recently established in a study elucidating the putative link between perceived chronic stress burden and various facets of visceroception in a large sample of healthy men and women (Icenhour et al., 2020). Results supported that chronic stress not only increased the feeling of defecatory urgency induced by rectal distensions as a particularly troublesome visceral symptom with a profound emotional dimension but was also associated with a memory bias for visceral sensations. Specifically, highly stressed individuals recalled more intense feelings of urgency than participants reporting low levels of stress, as well as relative to their initial

perception (Icenhour et al., 2020). Together, these findings lend further support to the notion that persisting interoceptive hypervigilance may be distinctly shaped not only by the salience of visceral pain (Koenen et al., 2018) but also by acute and chronic stress.

Stress is an important yet not the only putative source of interindividual variability in the acquisition, extinction, and return of learned emotional responses (Lonsdorf and Merz, 2017), including pain-related fear. As a crucial psychological modulator, anxiety likely also plays a pivotal role. Anxiety not only demonstrably affects pain-related memory formation and reinstatement in patients with IBS (Icenhour et al., 2015b) but was also recently linked to aberrant neurotransmitter levels and altered functional connectivity in patients with chronic visceral pain, particularly involving the medial prefrontal cortex as a key hub of the extinction network (Icenhour et al., 2019). Together, a complex interplay between psychological traits, including anxiety, cognitive biases, stress, and stress reactivity, and biological factors such as age, sex, stress hormones, and brain morphology may increase the vulnerability for altered pain-related learning and memory processes, which likely contribute to the transition from acute to chronic pain. Ultimately, identifying moderators and mediators of pain-related fear learning and extinction and elucidating mechanisms underlying extinction efficacy using reinstatement or renewal paradigms may help to unravel variability in extinction learning and long-term efficacy relevant to the pathophysiology and treatment of numerous conditions associated with recurring visceral symptoms, particularly disturbances of gut–brain interaction.

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References

Benson, S., Siebert, C., Koenen, L.R., Engler, H., Kleine-Borgmann, J., Bingel, U., Icenhour, A., and Elsenbruch, S. (2019). Cortisol affects pain sensitivity and pain-related emotional learning in experimental visceral but not somatic pain: A randomized controlled study in healthy men and women. Pain *160*, 1719–1728.

Bouton, M.E. (2004). Context and behavioral processes in extinction. Learn. Mem. *11*, 485–494.

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., and Gallacher, D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur. J. Pain *10*, 287–333.

Ceunen, E., Zaman, J., Weltens, N., Sarafanova, E., Arijs, V., Vlaeyen, J.W.S., Van Oudenhove, L., and Van Diest, I. (2016). Learned fear of gastrointestinal sensations in healthy adults. Clin. Gastroenterol. Hepatol. *14*, 1552–1558.e2.

Claassen, J., Labrenz, F., Ernst, T.M., Icenhour, A., Langhorst, J., Forsting, M., Timmann, D., and Elsenbruch, S. (2017). Altered cerebellar activity in visceral pain-related fear conditioning in irritable bowel syndrome. Cerebellum *16*, 508–517.

Craske, M.G., Wolitzky-Taylor, K.B., Labus, J., Wu, S., Frese, M., Mayer, E.A., and Naliboff, B.D. (2011). A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. Behav. Res. Ther. *49*, 413–421.

Crombez, G., Eccleston, C., Van Damme, S., Vlaeyen, J.W.S., and Karoly, P. (2012). Fear-avoidance model of chronic pain: The next generation. Clin. J. Pain *28*, 475–483.

Dunckley, P., Wise, R.G., Aziz, Q., Painter, D., Brooks, J., Tracey, I., and Chang, L. (2005). Cortical processing of visceral and somatic stimulation: Differentiating pain intensity from unpleasantness. Neuroscience *133*, 533–542.

Elsenbruch, S. and Enck, P. (2015). Placebo effects and their determinants in gastrointestinal disorders. Nat. Rev. Gastroenterol. Hepatol. *12*, 472–485.

Elsenbruch, S. and Labrenz, F. (2018). Nocebo effects and experimental models in visceral pain. Int. Rev. Neurobiol. *138*, 285–306.

Elsenbruch, S. and Wolf, O.T. (2015). Could stress contribute to pain-related fear in chronic pain? Front. Behav. Neurosci. *9*, 340.

Fullana, M.A., Harrison, B.J., Soriano-Mas, C., Vervliet, B., Cardoner, N., Àvila-Parcet, A., and Radua, J. (2016). Neural signatures of human fear conditioning: An updated and extended meta-analysis of fMRI studies. Mol. Psychiatry *21*, 500–508.

Gramsch, C., Kattoor, J., Icenhour, A., Forsting, M., Schedlowski, M., Gizewski, E.R., and Elsenbruch, S. (2014). Learning pain-related fear: Neural mechanisms mediating rapid differential conditioning, extinction and reinstatement processes in human visceral pain. Neurobiol. Learn. Mem. *116*, 36–45.

Icenhour, A., Kattoor, J., Benson, S., Boekstegers, A., Schlamann, M., Merz, C.J., Forsting, M., and Elsenbruch, S. (2015a). Neural circuitry underlying effects of context on human pain-related fear extinction in a renewal paradigm. Hum. Brain Mapp. *36*, 3179–3193.

Icenhour, A., Labrenz, F., Ritter, C., Theysohn, N., Forsting, M., Bingel, U., and Elsenbruch, S. (2017). Learning by experience? Visceral pain-related neural and behavioral responses in a classical conditioning paradigm. Neurogastroenterol. Motil. *29*, e13026–n/a.

Icenhour, A., Labrenz, F., Roderigo, T., Benson, S., and Elsenbruch, S. (2020). The role of chronic stress in normal visceroception: Insights from an experimental visceral pain study in healthy volunteers. Front. Psychiatry *11*, 107.

Icenhour, A., Langhorst, J., Benson, S., Schlamann, M., Hampel, S., Engler, H., Forsting, M., and Elsenbruch, S. (2015b). Neural circuitry of abdominal pain-related fear learning and reinstatement in irritable bowel syndrome. Neurogastroenterol. Motil. *27*, 114–127.

Icenhour, A., Tapper, S., Bednarska, O., Witt, S.T., Tisell, A., Lundberg, P., Elsenbruch, S., and Walter, S. (2019). Elucidating the putative

link between prefrontal neurotransmission, functional connectivity, and affective symptoms in irritable bowel syndrome. Sci. Rep. *9*, 1–11.
Kattoor, J., Gizewski, E.R., Kotsis, V., Benson, S., Gramsch, C., Theysohn, N., Maderwald, S., Forsting, M., Schedlowski, M., and Elsenbruch, S. (2013). Fear conditioning in an abdominal pain model: Neural responses during associative learning and extinction in healthy subjects. PLoS One *8*. https://doi.org/10.1371/journal.pone.0051149.
Kattoor, J., Thürling, M., Gizewski, E.R., Forsting, M., Timmann, D., and Elsenbruch, S. (2014). Cerebellar contributions to different phases of visceral aversive extinction learning. Cerebellum *13*, 1–8.
Koenen, L.R., Icenhour, A., Forkmann, K., Theysohn, N., Forsting, M., Bingel, U., and Elsenbruch, S. (2018). From anticipation to the experience of pain: The importance of visceral versus somatic pain modality in neural and behavioral responses to pain-predictive cues. Psychosom. Med. *80*, 826–835.
Koenen, L.R., Icenhour, A., Forkmann, K., Pasler, A., Theysohn, N., Forsting, M., Bingel, U., and Elsenbruch, S. (2017). Greater fear of visceral pain contributes to differences between visceral and somatic pain in healthy women. Pain *158*, 1599–1608.
Labanski, A., Langhorst, J., Engler, H., and Elsenbruch, S. (2020). Stress and the brain-gut axis in functional and chronic-inflammatory gastrointestinal diseases: A transdisciplinary challenge. Psychoneuroendocrinology *111*, 104501.
Labrenz, F., Icenhour, A., Benson, S., and Elsenbruch, S. (2015). Contingency awareness shapes acquisition and extinction of emotional responses in a conditioning model of pain-related fear. Front. Behav. Neurosci. *9*, 318.
Labrenz, F., Icenhour, A., Schlamann, M., Forsting, M., Bingel, U., and Elsenbruch, S. (2016). From Pavlov to pain: How predictability affects the anticipation and processing of visceral pain in a fear conditioning paradigm. Neuroimage *130*, 104–114.
Labus, J.S., Hubbard, C.S., Bueller, J., Ebrat, B., Tillisch, K., Chen, M., Stains, J., Dukes, G.E., Kelleher, D.L., Naliboff, B.D., et al. (2013). Impaired emotional learning and involvement of the corticotropin-releasing factor signaling system in patients with irritable bowel syndrome. Gastroenterology *145*, 1253–1261. e1–3.
Linton, S.J., Boersma, K., Jansson, M., Overmeer, T., Lindblom, K., and Vlaeyen, J.W.S. (2008). A randomized controlled trial of exposure in vivo for patients with spinal pain reporting fear of work-related activities. Eur. J. Pain *12*, 722–730.
Ljótsson, B., Hesser, H., Andersson, E., Lackner, J.M., El Alaoui, S., Falk, L., Aspvall, K., Fransson, J., Hammarlund, K., Löfström, A., et al. (2014). Provoking symptoms to relieve symptoms: A randomized controlled dismantling study of exposure therapy in irritable bowel syndrome. Behav. Res. Ther. *55*, 27–39.
Lonsdorf, T.B. and Merz, C.J. (2017). More than just noise: Inter-individual differences in fear acquisition, extinction and return of fear in humans – biological, experiential, temperamental factors, and methodological pitfalls. Neurosci. Beiobehav. Rev. *80*, 703–728.
Lumley, M.A., Cohen, J.L., Borszcz, G.S., Cano, A., Radcliffe, A.M., Porter, L.S., Schubiner, H., and Keefe, F.J. (2011). Pain and emotion: A biopsychosocial review of recent research. J. Clin. Psychol. *67*, 942–968.
Menon, V. and Uddin, L.Q. (2010). Saliency, switching, attention and control: A network model of insula function. Brain Struct. Funct. *214*, 655–667.
Meulders, A., Harvie, D.S., Bowering, J.K., Caragianis, S., Vlaeyen, J.W.S., and Moseley, G.L. (2014). Contingency learning deficits and generalization in chronic unilateral hand pain patients. J. Pain *15*, 1046–1056.
Meulders, A., Meulders, M., Stouten, I., De Bie, J., and Vlaeyen, J.W.S. (2017). Extinction of fear generalization: A comparison between fibromyalgia patients and healthy control participants. J. Pain *18*, 79–95.
Milad, M.R. and Quirk, G.J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. Annu. Rev. Psychol. *63*, 129–151.
Schneider, C., Palomba, D., and Flor, H. (2004). Pavlovian conditioning of muscular responses in chronic pain patients: Central and peripheral correlates. Pain *112*, 239–247.
Strigo, I.A., Duncan, G.H., Boivin, M., and Bushnell, M.C. (2003). Differentiation of visceral and cutaneous pain in the human brain. J. Neurophysiol. *89*, 3294–3303.
Vlaeyen, J.W.S. (2015). Learning to predict and control harmful events: Chronic pain and conditioning. Pain *156* Suppl 1, S86–S93.
Yágüez, L., Coen, S., Gregory, L.J., Amaro, E., Altman, C., Brammer, M.J., Bullmore, E.T., Williams, S.C.R., and Aziz, Q., (2005). Brain response to visceral aversive conditioning: A functional magnetic resonance imaging study. Gastroenterology *128*, 1819–1829.
Zaman, J., Vlaeyen, J.W.S., Van Oudenhove, L., Wiech, K., and Van Diest, I. (2015). Associative fear learning and perceptual discrimination: A perceptual pathway in the development of chronic pain. Neurosci. Biobehav. Rev. *51*, 118–125.
Zaman, J., Weltens, N., Ly, H.G., Struyf, D., Vlaeyen, J.W.S., Van den Bergh, O., Wiech, K., Van Oudenhove, L., and Van Diest, I. (2016). Influence of interoceptive fear learning on visceral perception. Psychosom. Med. *78*, 248–258.

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Review article

Martin Hadamitzky*, Laura Lückemann, Manfred Schedlowski and Harald Engler

How learning shapes immunity

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Abstract: Experimental studies in rodents and humans have convincingly demonstrated that immune functions can be modulated by associative learning processes. We have established a conditioned taste avoidance (CTA) paradigm in rats by pairing a novel taste (conditioned stimulus, CS) with an injection of the immunosuppressive drug cyclosporine A (CsA; unconditioned stimulus, US). Re-exposure to the CS results in a pronounced CTA and, more importantly, in a selective suppression of specific T-cell functions, mimicking the drugs' effects. To provide a basis for using learned immunosuppressive strategies in clinical situations, we are currently investigating the neurobiological mechanisms underlying the extinction of conditioned immunosuppressive responses and the generalizability of our findings to other immunomodulatory drugs.

Keywords: classical conditioning; extinction; immunosuppression; reconsolidation; taste-associative learning.

Zusammenfassung: Experimentelle Studien bei Mensch und Tier zeigen eindrucksvoll, dass Immunfunktionen durch assoziative Lernprozesse beeinflusst werden können. In einem von unserer Arbeitsgruppe etablierten Konditionierungsparadigma bei Ratten wird die Darbietung eines neuartigen Geschmacks als konditionierter Stimulus (CS) unmittelbar mit der Injektion des immunmodulierenden Medikaments Cyclosporin A (CsA; unkonditionierter Stimulus, US) gekoppelt. Bei erneuter Präsentation des CS zu einem späteren Zeitpunkt vermeiden konditionierte Tiere, die Saccharinlösung zu trinken (konditionierte Geschmacksaversion, CTA). Zudem lassen sich Veränderungen im Immunsystem beobachten, die den pharmakologischen Effekten des als US eingesetzten Medikaments entsprechen. Um einen möglichen Einsatz von Lernprotokollen im Rahmen pharmakologischer Interventionen in der Klinik zu ermöglichen, untersuchen wir gegenwärtig die neurobiologischen Mechanismen, welche der Extinktion konditionierter immunsuppressiver Antworten zugrunde liegen. Darüber hinaus überprüfen wir die Generalisierbarkeit unserer Ergebnisse im Hinblick auf andere immunmodulierende Medikamente.

Schlüsselwörter: Klassische Konditionierung; Extinktion; Immunsuppression; Rekonsolidierung; Geschmacksassoziatives Lernen.

Background

The central nervous system (CNS) and the immune system have been classically considered as independent and autonomously acting systems (Tracey, 2009). During the last three decades, clinical observations and experimental findings in animals and humans have provided compelling evidence that the brain and the immune system are intimately linked, sharing a common chemical language and continuously exchanging information (Dantzer et al., 2008; Tracey, 2010). In this context, the immune system acts as a sensory organ with immune cells as mobile sentinels that inform the brain about the immune status in the periphery (Blalock and Smith, 2007). Interestingly, immunological responses can be learned and memorized by associative learning or Pavlovian conditioning. From an evolutionary perspective, the ability to associate a certain immune response or threat (e.g., allergen, toxin, antigen) with environmental cues (e.g., context or flavor) has evolved as an adaptive mechanism to protect the organism from potentially harmful consequences by avoiding ingestion or contact with contagious or poisonous agents (Ader, 2003; Hadamitzky et al., 2020). However, this phenomenon can be also used therapeutically by combining

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the administration of an immunomodulatory drug with a gustatory or olfactory stimulus.

By applying a conditioned taste avoidance (CTA) paradigm in rats with a saccharin drinking solution as conditioned stimulus (CS) and the injection of the immunosuppressive calcineurin inhibitor cyclosporine A (CsA) as unconditioned stimulus (US), we established a clinically relevant model of behaviorally conditioned immunosuppression (Figure 1). In this model, re-exposure to the CS (i.e., sweet taste) results in conditioned suppression of interleukin (IL)-2 and interferon (IFN)-γ cytokine production as well as reduced splenic T-cell proliferation (Pacheco-Lopez et al., 2009). These conditioned effects on T-cell functions are mediated centrally via the insular cortex (IC) and the amygdala. On the efferent arm, the conditioned response is mediated via sympathetic noradrenergic nerve fibers and adrenoceptor-dependent inhibition of calcineurin activity in splenic T lymphocytes (Pacheco-Lopez et al., 2005). Importantly, the clinical relevance of conditioned immunosuppression has been proven by markedly prolong heart allograft survival (Exton et al., 1998; Hadamitzky et al., 2016a). Moreover, experimental studies in rodents and humans have convincingly demonstrated that suppression of immune functions can be elicited by behavioral conditioning paradigms aiming at a controlled dose reduction of drugs while maintaining efficacy of treatment (Albring et al., 2014; Enck et al., 2013; Hadamitzky et al., 2020; Wirth et al., 2011). However, the mechanisms of this learned immunosuppression are still incompletely understood.

Abrogating extinction of learned immune responses

To provide a basis for using learned immunosuppressive strategies in clinical situations as supportive therapy together with a standard pharmacological regimen, it is important to elucidate neural processes mediating extinction of the conditioned response at the behavioral level (CTA) and, in particular, at the level of the immune system. We performed a series of experiments to elucidate the mechanism underlying the extinction of conditioned immunosuppression. First, we could show that animals that

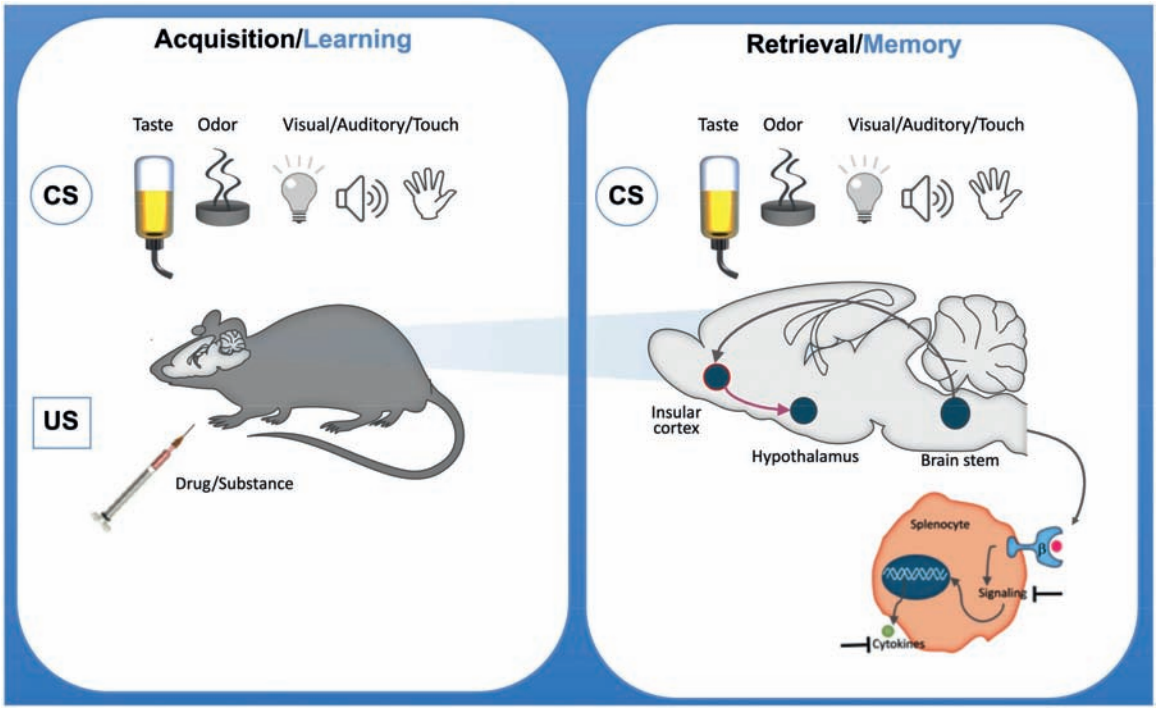

Figure 1: Principles of taste-immune conditioning. In rodents the presentation of a conditioned stimulus (**CS**; olfactory, gustatory, visual, auditory, touch, respectively) is paired with the administration of a drug or substance with immunological properties (unconditioned stimulus/**US**). During central perception of the **CS** via neural afferences, the neuro-molecular and/or immunological alterations induced by the **US** are detected by the CNS via neural or humoral afferent pathways (*Acquisition* – Learning). By re-exposing the organism to the **CS** only, the initially conditioned information is processed via the insular cortex, hypothalamus, and sympathetically transferred to secondary lymphatic organs such as the spleen. Subsequently, the changes in immune responses (diminished cytokine production/ T cell proliferation) originally induced by the drug or substance administered as the **US** become apparent (*Retrieval* – Memory).

displayed a strong CS-US association during acquisition phase also showed a strong CTA during unreinforced CS re-exposures (i.e., extinction learning). Moreover, extinction of the conditioned response was accompanied by increased neuronal activity in the IC, measured as enhanced mRNA expression of the unspecific neuronal activity marker c-fos (Hadamitzky et al., 2015). In another study, extinction of the CTA was efficiently prevented by administering the protein synthesis inhibitor anisomycin into the IC immediately after retrieval of the conditioned response (presentation of the CS in the absence of the US), indicating that *de novo* protein synthesis is required for extinction of the CsA-induced CTA (Hadamitzky et al., 2016b). Importantly, taste-avoidance studies with other drugs used as US (e.g., lithium chloride) indicate that extinction learning is affected by context change (Bouton et al., 2006). However, divergent from these findings, extinction of a learned CS-US association with CsA was not sensitive to contextual changes but rather seems to depend on the physiological and neuropharmacological effects of the US (Tuerkmen et al., 2016).

Conditioned responses gradually weaken over time and eventually disappear when animals are repeatedly exposed to the CS in the absence of the US (Berman and Dudai, 2001; Pavlov, 1927). However, experimental data suggest that extinction involves the consolidation of a new trace but may also comprise destabilization of the initially acquired memory. By applying a sub effective dose of the US (LiCl), which was ineffective in inducing CTA in naive rats during extinction, conditioned animals regained a CTA score as if they had never been subjected to the extinction procedure before (Berman et al., 2003). These findings indicate that memories enter a transient labile phase in which they can be impaired or enhanced by a new stabilization process termed reconsolidation (Myers and Carlezon, 2010). This process of reconsolidation seems to be dependent on a narrow time frame, the so-called reconsolidation window (Nader et al., 2000) (Figure 2). However, even though the empirical picture is not clear, data suggest that during retrieval of a memory trace, this reconsolidation window opens up, where the memory trace can be erased when certain proteins cannot be synthesized, or when extinction training is performed (de Carvalho Myskiw et al., 2014; Tronson and Taylor, 2007). Using our standard taste-immune conditioning protocol with CsA as US, we could demonstrate that extinction of CTA and, more importantly, extinction of learned immunosuppressive effects (reduced IL-2 and IFN-γ cytokine production) can be abrogated by subtherapeutic doses of the US, given as reminder cue together with the CS during retrieval. In contrast, such subtherapeutic CsA injections were completely ineffective when administered 8 h after CS re-exposure. These findings suggest that the timing of the reminder cue during the labile phase of the memory trace after retrieval (i.e., inside vs. outside the reconsolidation window) is crucial for initiating a reconsolidation-like process, involving *de novo* protein synthesis. Importantly, this updated learned immunosuppressive response and its maintenance is of clinical relevance because it significantly prolonged the survival time of heterotopically transplanted hearts (Hadamitzky et al., 2016a).

Generalization and clinical relevance of learned immune responses

The majority of studies on learned immunopharmacological responses in animals and humans were so far focusing on calcineurin inhibitors such as CsA. However, for a more general application of taste-immune associative learning protocols, it is important to investigate whether this phenomenon also applies to other clinically relevant drugs with different immunomodulatory properties. Against this background, we recently started using rapamycin (sirolimus), a small-molecule drug used as antitumor medication and to prevent graft rejection, in behavioral immunoconditioning. For this purpose, presentation of a novel taste (saccharin, CS) was paired with injections of rapamycin (US). Subsequent re-exposure to the CS alone revealed that taste-immune learning with rapamycin induced a moderate CTA but pronounced conditioned immunopharmacological effects, reflected by reduced levels of IL-10 cytokine production and diminished proliferation of splenic T cells (Lückemann et al., 2019). These results provide further evidence that the phenomenon of learned immune responses also applies to other small-molecule drugs with different immunosuppressive properties, thereby providing the basis for using immunepharmacological learning paradigms in clinical contexts, e.g., as supportive therapy (Hadamitzky et al., 2020).

In a model of murine allergic contact dermatitis (contact hypersensitivity), it has been shown that T cell–dependent immune responses can be suppressed by behavioral conditioning, reflected by a conditioned reduction in swelling and leukocyte infiltration into the inflamed tissue (Exton et al., 2000). To extend these observations and to analyze the potential clinical relevance of a reconsolidation-like process, we applied this taste-immune associative learning protocol in rats with collagen type II–induced arthritis (CIA) as a model for T cell–dependent chronic inflammatory autoimmune disease. We could show that this learning protocol together

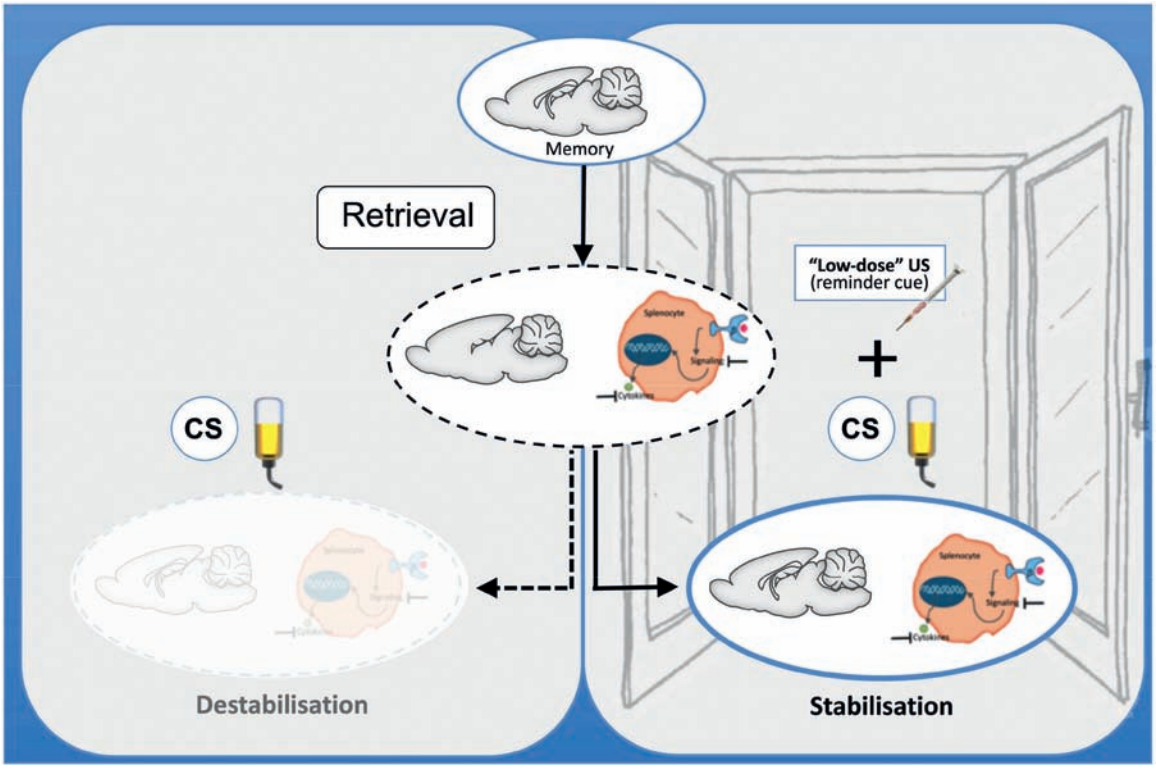

Figure 2: Abrogating extinction in conditioned immunosuppression. During recall or retrieval, the taste-immune memory enters a transient labile phase in which it can be modulated. This transient labile phase, which lasts for approx. 4 h (reconsolidation window) is characterized by protein synthesis in the insular cortex and amygdala. Following withdrawal of reinforcement (only the conditioned stimulus is presented), the memory destabilizes and the learned immunosuppressive response ultimately extinguishes (left hand panel). Stabilization or reconsolidation of memory is achieved by simultaneous presentation of sub-therapeutic drug doses of the unconditioned stimulus (CsA) as a reminder cue together with the CS (saccharin) (within the reconsolidation window), thereby abrogating extinction of the conditioned response (right hand panel). When receiving the reminder cues 8 h following CS re-exposure (outside the reconsolidation window) reconsolidation-like processing fails to appear and the conditioned response extinguishes.

with the application of only 25% amount of the drug used as CS lead to an almost identical clinical outcome as seen after full dose (100%) CsA treatment. Conditioned animals showed less signs of inflammation, such as swollen joints and paws, as well as less bone destruction and infiltration in surrounding tissue. In addition, performance in a functional grip strength test was improved. Furthermore, we observed that attenuating effects on inflammatory progression in CIA triggered by conditioning were blocked by continuous application of the β-adrenoceptor antagonist nadolol (Luckemann et al., 2019). Together, these findings suggest that learned immunosuppression, mediated via β-adrenoceptors, might be beneficial as a supportive tool in the treatment of chronic inflammatory autoimmune diseases by diminishing disease exacerbation. Importantly, in a distinct approach, a taste-immune associative learning paradigm was recently added to the standard immunosuppressive therapy with CsA or tacrolimus in patients who underwent renal transplantation. At retrieval, when patients were re-exposed to the CS (a novel taste), capacity of T-cell proliferation was significantly reduced compared with baseline kinetics of T-cell functions during pharmacotherapy (Kirchhof et al., 2018). This proof-of-concept study provides evidence for the possible effectiveness of learned immune-pharmacological strategies in clinical situations as supportive therapy together with the standard pharmacological regimen in conditions where continuous immunosuppressive drug treatment is required.

Future perspectives

Together, experimental data in rodents and first observations in healthy humans and patients demonstrate that taste-immune associative learning and reconsolidation-like processes can interfere with extinction of learned immunosuppression (Hadamitzky et al., 2020). However, a major challenge is to gain deeper insights into the neurobiological underpinnings of learned immunosuppressive responses. Using chemogenetic techniques such as

designer receptors exclusively activated by designer drugs (DREADDs) for interfering with neuronal activity during conditioning, we aim to identify relevant brain structures and to characterize neural mechanisms mediating learning conditioned immunopharmacological effects. Moreover, to exploit these mechanisms for clinical practice, it is necessary to analyze the effectiveness and clinical relevance of reconsolidation-like processes of behaviorally conditioned immunomodulation in different translational disease models, as well as the generalization across distinct immunopharmacological mechanisms. Thorough knowledge of the basic mechanisms of extinction learning is essential to achieve the long-term goal of the learned immune response: to use these learning paradigms in clinical situations as supportive therapy together with the standard immunopharmacological regimen with the aim to maximize the therapeutic outcome for the patient's benefit (Enck et al., 2013; Schedlowski et al., 2015).

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References

Ader, R. (2003). Conditioned immunomodulation: Research needs and directions. Brain Behav. Immun. *17*, 51–57.

Albring, A., Wendt, L., Benson, S., Nissen, S., Yavuz, Z., Engler, H., Witzke, O., and Schedlowski, M. (2014). Preserving learned immunosuppressive placebo response: Perspectives for clinical application. Clin. Pharmacol. Ther. *96*, 247–255.

Berman, D.E., and Dudai, Y. (2001). Memory extinction, learning anew, and learning the new: Dissociations in the molecular machinery of learning in cortex. Science *291*, 2417–2419.

Berman, D.E., Hazvi, S., Stehberg, J., Bahar, A., and Dudai, Y. (2003). Conflicting processes in the extinction of conditioned taste aversion: Behavioral and molecular aspects of latency, apparent stagnation, and spontaneous recovery. Learn Mem. *10*, 16–25.

Blalock, J.E., Smith, E.M. (2007). Conceptual development of the immune system as a sixth sense. Brain Behav. Immun. *21*, 23–33.

Bouton, M.E., Westbrook, R.F., Corcoran, K.A., and Maren, S. (2006). Contextual and temporal modulation of extinction: Behavioral and biological mechanisms. Biol. Psychiatry *60*, 352–360.

Dantzer, R., O'Connor, J. C., Freund, G. G., and Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. Nat. Rev. Neurosci. *9*, 46–56.

de Carvalho Myskiw, J., Furini, C.R.G., Benetti, F., and Izquierdo, I. (2014). Hippocampal molecular mechanisms involved in the enhancement of fear extinction caused by exposure to novelty. Proc. Natl. Acad. Sci. U. S. A. *111*, 4572–4577.

Enck, P., Bingel, U., Schedlowski, M., and Rief, W. (2013). The placebo response in medicine: Minimize, maximize or personalize?. Nat. Rev. Drug Discov. *12*, 191–204.

Exton, M.S., Elfers, A., Jeong, W.Y., Bull, D.F., Westermann, J., and Schedlowski, M. (2000). Conditioned suppression of contact sensitivity is independent of sympathetic splenic innervation. American Journal of Physiology, Endocrinol. Metabol. *279*, R1310–R1315.

Exton, M.S., Schult, M., Donath, S., Strubel, T., and Nagel, E. (1998). Behavioral conditioning prolongs heart allograft survival in rats. Transplant Proc. *30*, 2033.

Hadamitzky, M., Bösche, K., Engler, A., Schedlowski, M., and Engler, H. (2015). Extinction of conditioned taste aversion is related to the aversion strength and associated with c-fos expression in the insular cortex. Neuroscience *303*, 34–41.

Hadamitzky, M., Bösche, K., Wirth, T., Buck, B., Beetz, O., and Christians, U. (2016a). Memory-updating abrogates extinction of learned immunosuppression. Brain Behav. Immun. *52*, 40–8.

Hadamitzky, M., Lückemann, L., Pacheco-López, G., and Schedlowski, M. (2020). Pavlovian conditioning of immunological and neuroendocrine functions. Physiol. Rev. *100*, 357–405.

Hadamitzky, M., Orlowski, K., Schwitalla, J. C., Bosche, K., Unteroberdorster, M., Bendix, I., et al. (2016b). Transient inhibition of protein synthesis in the rat insular cortex delays extinction of conditioned taste aversion with cyclosporine A. Neurobiol. Learn. Mem. *133*, 129–135.

Kirchhof, J., Petrakova, L., Brinkhoff, A., Benson, S., Schmidt, J., Unteroberdörster, M., Wilde, B., Kaptchuk, T.J., Witzke, O., and Schedlowski, M. (2018). Learned immunosuppressive placebo responses in renal transplant patients. Proc. Natl. Acad. Sci. U. S. A. *115*, 4223–4227.

Luckemann, L., et al. (2020). Learned immunosuppressive placebo response attenuates disease progression in a rodent model of rheumatoid arthritis. Arthritis Rheumatol. *72*, 588–597.

Lückemann, L., Unteroberdorster, M., Martinez Gomez, E., Schedlowski, M., and Hadamitzky, M. (2019). Behavioral conditioning of anti-proliferative and immunosuppressive properties of the mTOR inhibitor rapamycin. Brain Behav. Immun. *79*, 326–331.

Myers, K. M., Carlezon, W. A. Jr. (2010). Extinction of drug- and withdrawal-paired cues in animal models: Relevance to the treatment of addiction. Neurosci. Biobehav. Rev. *35*, 285–302.

Nader, K., Schafe, G. E., and Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature *406*, 722–726.

Pacheco-Lopez, G., Niemi, M. B., Kou, W., Harting, M., Fandrey, J., and Schedlowski, M. (2005). Neural substrates for behaviorally conditioned immunosuppression in the rat. J Neurosci. *25*, 2330–2337.

Pacheco-Lopez, G., Riether, C., Doenlen, R., Engler, H., Niemi, M. B., and Engler, A. (2009). Calcineurin inhibition in splenocytes induced by pavlovian conditioning. FASEB J. *23*, 1161–1167.

Pavlov, I.P. (1927). Conditioned Reflexes Dover Publications, Inc. (New York: Mineola).

Schedlowski, M., Enck, P., Rief, W., and Bingel, U. (2015). Neuro-bio-behavioral mechanisms of placebo and nocebo responses:

Implications for clinical trials and clinical practice. Pharmacol. Rev. *67*, 697–730.
Tracey, K.J. (2009). Reflex control of immunity. Nat. Rev. Immunol. *9*, 418–428.
Tracey, K.J. (2010). Understanding immunity requires more than immunology. Nat. Immunol. *11*, 561–564.
Tronson, N.C., Taylor, J.R. (2007). Molecular mechanisms of memory reconsolidation. Nat. Rev. Neurosci. *8*, 262–275.
Tuerkmen, A., Bosche, K., Luckemann, L., Engler, H., Schedlowski, M., and Hadamitzky, M. (2016). Rats taste-aversive learning with cyclosporine a is not affected by contextual changes. Behav. Brain Res. *312*, 169–173.
Wirth, T., Ober, K., Prager, G., Vogelsang, M., Benson, S., and Witzke, O. (2011). Repeated recall of learned immunosuppression: Evidence from rats and men. Brain. Behav. Immun. *25*, 1444–1451.

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Presentation of scientific institutions

Kristina Endres* and Simone Eggert*

Forschungskolleg "NeurodegX"

https://doi.org/10.1515/nf-2020-0019

„Isolation and characterization of neuroprotective substances from fungi and cyanobacteria as potential substances for treatment of neurodegenerative diseases"

In 2018, a new concept for a research college (Forschungskolleg) has been established: the "Forschungskolleg Rheinland-Pfalz". This funding was especially conceptualized by the Ministry of Science to support cooperation between Universities of Applied Sciences and academic universities, which will promote students from the Universities of Applied Sciences to receive a doctoral degree. Four research colleges of this type are currently funded and in 2020, two more are going to be included. In 2019, a joint project proposal „Neuroprotective substances – NeurodegX" from the Technical University (TU) Kaiserslautern and the Johannes Gutenberg University (JGU) Mainz as well as the University of Applied Sciences Kaiserslautern (HS Kaiserslautern) was positively evaluated. As PIs Simone Eggert, Gerhard Erkel, Stefan Kins, and Michael Schroda (Technical University Kaiserslautern), Tanja Brigadski, Bernd Bufe, Peter Groß, Michael Lakatos, Holger Rabe, and Karl-Herbert Schäfer (University of Applied Sciences Kaiserslautern) as well as Kristina Endres and Till Opatz (Johannes Gutenberg-University Mainz) are participating (https://www.hs-kl.de/verbundvorhaben/neurodegx). A total of eight doctoral students, performing their thesis in eight different labs (see Figure 1), benefits directly from this support.

The scientific focus of this cooperation is to identify natural compounds from fungi and cyanobacteria and to test them for their potential therapeutic effect on neurodegenerative diseases such as Alzheimer's dementia. While over 30 million patients are currently suffering from Alzheimer's disease worldwide, only drugs for the treatment of symptoms are clinically available and there is an urgent need for innovative new drugs. According to the Aβ hypothesis, the loss of nerve cells in Alzheimer's disease patients is caused by accumulation and aggregation of the Aβ peptide, which is derived by enzymatic cleavages of the amyloid precursor protein (APP).

Accordingly, within the framework of this consortium, active substances from differentially cultivated microorganisms will be identified. We aim to find antioxidative, anti-inflammatory and in the end neurosupportive drugs against neurotoxicity of the Aβ peptide (Figure 1).

After initial mid-throughput screening using crude extracts and selected secondary cell lines, fractionation will identify potential candidate substances. These will – together with already known candidates from former pilot projects – be subjected to in-depth functional testing including electrophysiology and synaptogenesis in primary cell cultures of cortical but also enteric neurons. Finally, single candidates with the best outcome will be tested *in vivo* in transgenic mouse models of Alzheimer`s disease. The consortium provides a fungal and cyanobacterial biobank with various organisms that have even not been cultivatable before and has many years of expertise in identification of those organisms, their propagation and the isolation of substances. The broad chemical, biotechnical, cellular, and biomedical expertise of the aforementioned groups will promote interdisciplinary working and professional development of the PhD students integrated in the consortium.

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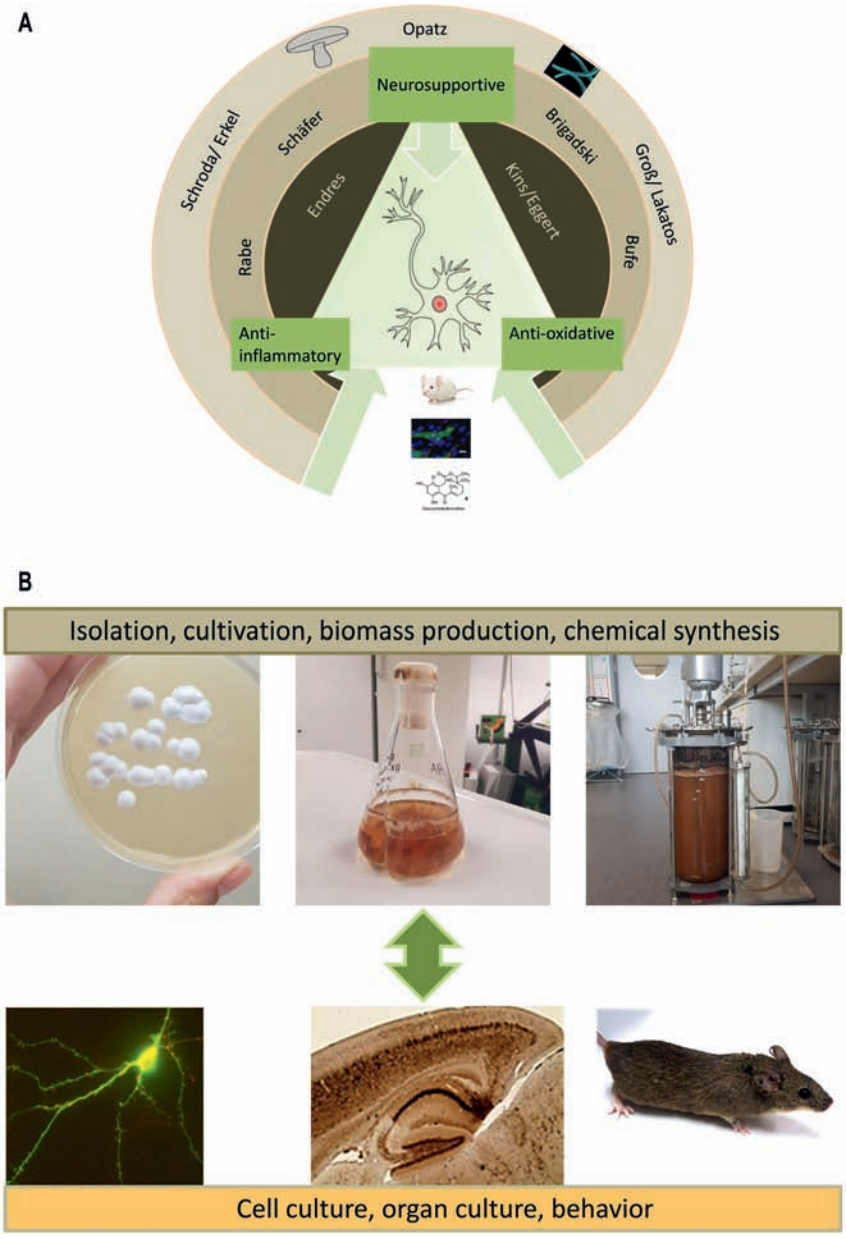

Figure 1: Structure and work schedule of NeurodegX. (A) Central goal of the consortium is the identification and characterization of new drugs from fungi or cyanobacteria for treatment of neurodegenerative diseases. Therefore, scientists from three institutions teamed up: the Technical University Kaiserslautern, the University of Applied Sciences Kaiserslautern and the Johannes Gutenberg-University Mainz. (B) With this, a combination of chemical, biotechnical, cellular, and biomedical expertise was gained, which provides a highly interdisciplinary working environment.

Nachrichten aus der Gesellschaft

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Göttingen Meeting of the German Neuroscience Society (24. – 27. März 2021)

Die folgenden 34 Symposien wurden vom Programmkomitee für die Göttinger Tagung der NWG ausgewählt. Die Liste der Sprecher wird in jedem Symposium noch um maximal zwei Kurzvorträge von studentischen Teilnehmenden ergänzt werden. Um diese Vorträge kann man sich während der Registrierung bei der Einreichung der Posterabstracts bewerben. Aus diesen Bewerbungen werden die Kurzvorträge von den Symposiumsorganisatoren ausgewählt. Zusätzlich wird es noch zwei Breaking News Symposien geben, für die sich studentische Teilnehmende ebenfalls bewerben können.

Advanced optics for neuroscience
Organized by: Lauterbach, Marcel (Homburg)
Speakers: Emiliani, Valentina (Paris, France); Hell, Stefan (Göttingen); Lauterbach, Marcel (Homburg); Nägerl, Valentin (Bordeaux, France)

Challenges in autism: beyond species and brain regions – common mechanisms for neuronal dysfunction?
Organized by: Böckers, Tobias M. (Ulm); Le, Kim Chi (Aachen)
Speakers: Parma, Valentina (Philadelphia, USA); Schmid, Susanne (London, Canada); Soba, Peter (Hamburg); Yizhar, Ofer (Rehovot, Israel)

Emerging views on microglia and oligodendrocytes in Alzheimer's disease
Organized by: Nave, Klaus-Armin (Göttingen)
Speakers: Haass, Christian (München); Depp, Constanze (Göttingen); Karadottir, Ragnhildur (Cambridge, UK); Heneka, Michael (Bonn)

FAIR data management and data sharing in neuroscience
Organized by: Kühn, Esther (Magdeburg); Scherberger, Hansjörg (Göttingen)
Speakers: Grün, Sonja (Jülich); Hanke, Michael (Düsseldorf); Kremkow, Jens (Berlin); Martone, Maryann (La Jolla, USA)

From sensation to action: shaping neuronal representations during learning
Organized by: Pakan, Janelle (Magdeburg)
Speakers: Ammer, Julian (Edinburgh, UK); Dityatev, Alexander (Magdeburg); Mikulovic, Sanja (Bonn); Pakan, Janelle (Magdeburg)

Functions of motor cortex circuits for movement control
Organized by: Leukel, Christian (Freiburg)
Speakers: Baker, Stuart (Newcastle, UK); Diester, Ilka (Freiburg); Leukel, Christian (Freiburg); Poulet, James (Berlin)

Gene and cell based therapies to counteract neuroretinal degeneration (SPP2127)
Organized by: Hauck, Stefanie (Neuherberg); Stieger, Knut (Giessen)
Speakers: Ader, Marius (Dresden); Harmening, Wolf (Bonn); Hauck, Stefanie (Neuherberg); Michalakis, Stylianos (München)

Genetic and environmental aspects in chronic pain (SFB1158)
Organized by: Mauceri, Daniela (Heidelberg); Tost, Heike (Mannheim)
Speakers: Eippert, Falk (Leipzig); Mauceri, Daniela (Heidelberg); Tost, Heike (Mannheim); Üçeyler, Nurcan (Würzburg)

Genetic and environmental factors shaping neuronal network defects and cognitive impairment
Organized by: Häussler, Ute (Freiburg); Sauer, Jonas-Frederic (Freiburg)
Speakers: Fisher, Elizabeth (London, UK); Hanganu-Opatz, Ileana (Hamburg); Schulz, Jan (Basel, Switzerland); Sigurdsson, Torfi (Frankfurt/M.)

How microglia fulfill distinctive functions throughout development, during adulthood and under disease conditions (DGNN Symposium)
Organized by: Blank, Thomas (Freiburg); Stadelmann-Nessler, Christine (Göttingen)
Speakers: Blank, Thomas (Freiburg); Eggen, Bart (Groningen, Netherlands); Simons, Mikael (München); Stadelmann-Nessler, Christine (Göttingen)

Hypothalamic neuron-glial network in obesity and type 2 diabetes
Organized by: García-Cáceres, Cristina (Neuherberg); Yi, Chun-Xia (Amsterdam, Netherlands)
Speakers: Cota, Daniela (Bordeaux, France); Steculorum, Sophie (Köln); Verkhratsky, Alexei (Manchester, UK); Yi, Chun-Xia (Amsterdam, Netherlands)

Modulation and plasticity of inhibition in neocortical circuits
Organized by: Busse, Laura (Planegg-Martinsried); Letzkus, Johannes (Frankfurt/M.)
Speakers: Barkat, Tania (Basel, Switzerland); Letzkus, Johannes (Frankfurt/M.); Staiger, Jochen (Göttingen); Veit, Julia (Freiburg)

MultiSenses – MultiScales: deciphering neural processing in multisensory integration
Organized by: Kampa, Bjoern (Aachen); Spehr, Marc (Aachen)
Speakers: Bremmer, Frank (Marburg); López-Bendito, Guillermina (San Juan de Alicante, Spain); Prieto-Godino, Lucia (London, UK); Silberberg, Gilad (Stockholm, Sweden)

Neuronal autophagy – implications for disease and therapy
Organized by: Behl, Christian (Mainz); Sendtner, Michael (Würzburg)
Speakers: Clement, Albrecht (Mainz); Holzbaur, Erika (Philadelphia, USA); Lüningschrör, Patrick (Würzburg); Nixon, Ralph (New York, USA)

Neuronal circuit mechanisms of socio-sexual behavior
Organized by: Lenschow, Constanze (Lisbon, Portugal); Simonnet, Jean (Berlin)
Speakers: Kohl, Johannes (London, UK); Lima, Susana (Lisbon, Portugal); Lenschow, Constanze (Lisbon, Portugal); Simonnet, Jean (Berlin)

Odor spaces: from odor molecules to behavior
Organized by: Schmuker, Michael (Hatfield, Hertfordshire, UK); Silke, Sachse (Jena)
Speakers: Couzin-Fuchs, Einat (Konstanz); Hansson, Bill S. (Jena); Schmuker, Michael (Hatfield, Hertfordshire, UK); Sharpee, Tatyana (La Jolla, USA)

Odors and metabolism – neuromodulation in sensory processing
Organized by: Grunwald Kadow, Ilona (Freising); Rothermel, Markus (Aachen)
Speakers: Egger, Veronica (Regensburg); Riera, Celine (Los Angeles, USA); Vogt, Katrin (Cambridge, USA); Wright, Geraldine (Oxford, UK)

Optical imaging to assess the plasticity function of sleep
Organized by: Born, Jan (Tübingen); Niethard, Niels (Tübingen)
Speakers: Adamantidis, Antoine (Bern, Switzerland); Gan, Wen-Biao (New York, USA); Niethard, Niels (Tübingen); Seibt, Julie (Surrey, UK)

Post-translational modifications of proteome in neuronal development
Organized by: Ambrozkiewicz, Mateusz (Berlin); Tarabykin, Victor (Berlin)
Speakers: Ambrozkiewicz, Mateusz (Berlin); Brockmann, Marisa (Berlin); Gupton, Stephanie (Chapel Hill, USA); Vogl, Annette (South San Francisco, USA)

Principles of decision-making across species
Organized by: Jovanic, Tihana (Gif-sur-Yvette, France); Schleyer, Michael (Magdeburg)
Speakers: Fernandes, Miguel (Martinsried); Marquez Vega, Cristina (San Juan de Alicante, Spain); Ribeiro, Carlos (Lisbon, Portugal); Thura, David (Bron, France)

Regulation of synaptic vesicle recycling: from physiology to disease
Organized by: Fejtova, Anna (Erlangen)
Speakers: Fassio, Anna (Genova, Italy); Fejtova, Anna (Erlangen); Rizzoli, Silvio (Göttingen); Roy, Subhojit (La Jolla, USA)

Revealing the evolutionary trajectory of the first nervous systems: genomics, structure and dynamics
Organized by: Burkhardt, Pawel (Bergen, Norway); Wolf, Fred (Göttingen)

Speakers: Dupre, Christophe (Cambridge, USA); Hernandez Nicaise, Mari-Luz (Nice, France); Memmesheimer, Raoul-Martin (Bonn); Varoqueaux, Frederique (Lausanne, Switzerland)

Same, same but different – Emergence of individuality in the nervous system (jNWG Symposium)
Organized by: Maraslioglu, Ayse (Kaiserslautern); Ritzau-Jost, Andreas (Leipzig)
Speakers: Bierbach, David (Berlin); Bogado Lopes, Jadna (Dresden); Fayad, Sophie (Paris, France); Linneweber, Gerit (Paris, France)

Sino-German joint symposium on cutting-edge neurotechnology in behavioral and systems neuroscience
Organized by: Fries, Pascal (Frankfurt/M.); Wang, Liping (Shenzhen, China)
Speakers: Chen, Xiaowei (Chongqing, China); Fries, Pascal (Frankfurt/M.); Hegemann, Peter (Berlin); Li, Yulong (Beijing, China)

Sound processing, adaptation, and perception in the auditory system – from midbrain to cortical networks
Organized by: Hirtz, Jan (Kaiserslautern); Rosskothen-Kuhl, Nicole (Freiburg)
Speakers: King, Andrew (Oxford, UK); Malmierca, Manuel Sánchez (Salamanca, Spain); Pecka, Michael (Planegg-Martinsried); Rosskothen-Kuhl, Nicole (Freiburg)

Store-operated calcium entry in neurons and glia
Organized by: Niemeyer, Barbara (Homburg); Kirchhoff, Frank (Homburg)
Speakers: Garaschuk, Olga (Tübingen); Niemeyer, Barbara (Homburg); Prakriya, Murali (Chicago, USA); Schwarz, Yvonne (Homburg)

Structure and dynamics of inhibitory synapses in health and disease
Organized by: Barberis, Andrea (Genova, Italy); Werner, Christian (Würzburg)
Speakers: Petrini, Enrica (Genova, Italy); Specht, Christian (Paris, France); Villmann, Carmen (Würzburg); Werner, Christian (Würzburg)

Tanycytes – walk between worlds
Organized by: Prevot, Vincent (Lille, France); Schwaninger, Markus (Lübeck)
Speakers: Brüning, Jens (Köln); Duquenne, Manon (Lille, France); Langlet, Fanny (Lausanne, Switzerland); Nogueiras, Ruben (Santiago de Compostela, Spain)

The choice is yours: multicircuit regulation of motivated behaviors
Organized by: Gogolla, Nadine (München); Korotkova, Tatiana (Köln)
Speakers: Gogolla, Nadine (München); Korotkova, Tatiana (Köln); Lammel, Stephan (Berkeley, USA); Mameli, Manuel (Lausanne, Switzerland)

The entorhinal micronetwork – how connectivity determines function
Organized by: Draguhn, Andreas (Heidelberg); Egorov, Alexei V. (Heidelberg)
Speakers: Cappaert, Natalie L.M. (Amsterdam, Netherlands); Egorov, Alexei V. (Heidelberg); Sürmeli, Gülsen (Edinburgh, UK); Witter, Menno P. (Øya, Norway)

The impact of the immune system on psychiatric disorders (DGPPN Symposium)
Organized by: Heinz, Andreas (Berlin), Ludolph, Albert (Ulm)
Speakers: Regen-Hellmann, Julian (Berlin); Wolf, Susanne (Berlin); Gold, Stefan (Berlin); Köhler, Stephan (Berlin)

The undiscovered country – plasticity in the enteric nervous system
Organized by: Mozzuoli-Weber, Gemma (Hannover); Neckel, Peter (Tübingen)
Speakers: Boesmans, Werend (Maastricht, Netherlands); Bondurand, Nadege (Creteil Cedex, France); Mozzuoli-Weber, Gemma (Hannover); Neckel, Peter (Tübingen)

Tools for the future of synaptic neuroscience: super-resolution imaging meets artificial intelligence (SFB1286)
Organized by: Moser, Tobias (Göttingen); Rizzoli, Silvio (Göttingen); Steinem, Claudia (Göttingen)
Speakers: Choquet, Daniel (Bordeaux, France); Cox, Susan (London, UK); Lavoie-Cardinal, Flavie (Quebec, Canada); Sauer, Markus (Würzburg)

Translational aspects in neurological diseases: from pathophysiology to new therapeutic approaches (DGN Symposium)
Organized by: Linke, Ralf (Regensburg); Bähr, Mathias (Göttingen)
Speakers: Geis, Christian (Jena); Ellrichmann, Gisa (Bochum); Höglinger, Günter (Hannover); Wilke, Melanie (Göttingen)

Für die Teilnahme junger Studierender an der Tagung vergibt die NWG Reisestipendien in Höhe von 300 Euro. Die Bewerbung dafür erfolgt über die Website der Tagung.

NEU auf dasGehirn.info

Mit dem Themenschwerpunkt **Struktur und Funktion neuronaler Netzwerke** wurde im Mai das Portfolio des Internetportals um ein wichtiges Thema ergänzt. Dabei handelt es sich um eine Partnerschaft mit dem SFB 870.

Hierfür wurden die folgenden Beiträge erstellt:

Das Nervensystem reparieren: Beim Menschen verursachen Verletzungen des Nervensystems und neurodegenerative Krankheiten meist dauerhafte Schäden. Womöglich schlummert in uns aber ein Selbstheilungspotential, das sich für künftige Therapien nutzen lässt.

Das Nervensystem – ein Wandlungskünstler: Ob einzelne Nervenzellen oder ganze Netzwerke: Das Gehirn ist äußerst wandlungsfähig und ermöglicht uns damit, zu lernen und uns an neue Umweltbedingungen anzupassen.

Die Wunder des Lebens: Einst war das Leben ein Wunder. Seitdem wurde es Organ für Organ, Zelle für Zelle, Molekül für Molekül erklärbar. Und siehe: Ein Zahnrad greift ins andere. Das nimmt dem Leben das Wunderbare? Ganz im Gegenteil!

Vom Schicksal der Zelle: Aus einer einzigen befruchteten Eizelle wächst eine der komplexesten Strukturen überhaupt – das menschliche Gehirn. Dafür braucht es viel Faltkunst und etliche Schicksalsschritte.

Gut vernetzt: Das Gehirn besteht aus einem komplexen Netzwerk von Nervenzellen, die miteinander kommunizieren. Die neuronale Verdrahtung ist enorm effizient und passt sich fortwährend an die Herausforderungen des Lebens an.

Neben den Texten gibt es die Animation **Regeneration in Zukunft**: Das Gehirn ist großartig, aber anfällig – Neurodegeneration und Schlaganfall können gravierende Schäden anrichten. Umso wichtiger sind effektive Therapien. Tatsächlich gibt es Hoffnung: Bei Mäusen funktioniert eine Stammzelltherapie, die neuen Zellen vernetzen sich tatsächlich. Auch über weite Strecken.

In der Rubrik **Neues aus der Wissenschaft** macht dasGehirn.info auf die folgenden **Pressemeldungen** aus den Instituten aufmerksam:

Wie sich Nervenzellen zum Abruf einer Erinnerung gezielt reaktivieren lassen | Ruprecht-Karls-Universität Heidelberg (03.06.2020), *Schutz der neuronalen Architektur* | Ruprecht-Karls-Universität Heidelberg (05.06.2020), *Alzheimerforschung: Störfeuer von Nervenzellen legen Erinnerung lahm* | Deutsches Zentrum für Neurodegenerative Erkrankungen e. V. (DZNE) (09.06.2020), *Rauschen stört den Kompass des Gehirns* | Deutsches Zentrum für Neurodegenerative Erkrankungen e. V. (DZNE) (10.06.2020)

Möchten Sie eine Pressemeldung an “dasGehirn.info” weitergeben, wenden Sie sich bitte an Arvid Leyh (e-mail: a.leyh@dasgehirn.info).

Neueintritte

Folgende Kolleginnen und Kollegen dürfen wir als Mitglieder der Neurowissenschaftlichen Gesellschaft begrüßen:

Ali Cillov (Göttingen)
Christine Grienberger, Dr. (Houston, USA)
Aleksandar Janjic (Martinsried)
Norisa Meli (Bonn)
Dragomir Milovanovic, Dr. (Berlin)
Alex Palumbo (Lübeck)
Stefanie Perl (Leipzig)
Bernd Polder (Tamm)
Saeed Salehinajafabadi (Berlin)
Julia Veit (Freiburg)
Marietta Zille, Dr. (Lübeck)

Der Mitgliedsstand zum 22. Juni 2020 beträgt 2.197 Mitglieder.

Ausblick

Marlene Bartos, Jonas Sauer
The role of the dentate gyrus in mnemonic functions

Dorothea Schulte et al.
Synapses, Networks, Brain Development – Funding Basic Neuroscience Research in Germany by the Schram Foundation

Carmen Ruiz de Almodovar et al.
Direct contribution of angiogenic factors to neurodevelopment: a focus on angiopoietins

Volker Haucke, Natalia Kononenko
Neuronal functions of clathrin-associated endocytic sorting adaptors – from molecules to disease

Alexander Gottschalk
Optogenetic analyses of neuronal networks that generate behavior in Caenorhabditis elegans

Schuljahr
2020
2021

NEURO WISSEN SCHAFTEN

in der gymnasialen Oberstufe

NWG
NeuroWissenschaftliche Gesellschaft
German Neuroscience Society

› PROGRAMMÜBERSICHT https://nwg-info.de/

Die Neurowissenschaftliche Gesellschaft e.V. (NWG) bietet bundesweit kostenlose Fortbildungsveranstaltungen für (Oberstufen-)LehrerInnen an. Interessierte LehrerInnen sind herzlich zur Teilnahme eingeladen.
Für die Anmeldung zur jeweiligen Veranstaltung wenden Sie sich bitte an den lokalen Kontakt.

Das Internetportal
dasGehirn.info
informiert umfassend, verständlich und wissenschaftlich geprüft über alle Bereiche der Neurowissenschaften und bietet ein Lernportal für Schüler.

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1. OKTOBER 2020 | FREIBURG
SENSORISCHE WAHRNEHMUNG UND GEDÄCHTNIS
Kontakt: Fiona Siegfried
Telefon: 0761 203-9549
E-Mail: siegfried@bcf.uni-freiburg.de

27. OKTOBER 2020 | SPEYER
ÜBER DAS VERGESSEN LERNEN – ALZHEIMER IM BIOLOGIE-UNTERRICHT
Kontakt: Prof. Dr. Stefan Kins
Telefon: 0631 205 2106/2107
E-Mail: l.hanke@biologie.uni-kl.de

5. NOVEMBER 2020 | GÖTTINGEN
NEUROWISSENSCHAFTEN (als Zoom-Webinar)
Kontakt: Dr. Anika Appelles
Telefon: 0551 3851424
E-Mail: aappelles@dpz.eu

17. NOVEMBER 2020 | BERLIN
NEUES AUS DER HIRNFORSCHUNG
Kontakt: Prof. Dr. Helmut Kettenmann/ Helga Fenz
Telefon: 030 94892931
E-Mail: h.fenz@campusberlinbuch.de

5. FEBRUAR 2021 | HEIDELBERG
SUCHT – ERSCHEINUNGSFORMEN, NEURONALE MECHANISMEN, PRÄVENTION UND THERAPIE
Kontakt: Prof. Dr. Andreas Draguhn/ Susanne Bechtel
Telefon: 06221 544056
E-Mail: susanne.bechtel@physiologie.uni-heidelberg.de

25. FEBRUAR 2021 | TÜBINGEN
NEUROWISSENSCHAFTEN UND IMMUNOLOGIE
Kontakt: Prof. Dr. Uwe Ilg
Telefon: 07071 2980464 (Hertie-Institut)
07071 2982377 (Schülerlabor)
E-Mail: uwe.ilg@uni-tuebingen.de

17. MÄRZ 2021 | LEIPZIG
NEUE ENTWICKLUNGEN IN DER MIKROSKOPIE
Kontakt: Prof. Dr. Steffen Rossner/Dr. Max Holzer
Telefon: 0341 9725758 / 0341 9725759
E-Mail: rossn@medizin.uni-leipzig.de oder holm@medizin.uni-leipzig.de

FRÜHLING 2021 | SAARLAND
ÜBER DAS VERGESSEN LERNEN – ALZHEIMER IM BIOLOGIE-UNTERRICHT
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SOMMER 2021 | BADEN-WÜRTTEMBERG
ÜBER DAS VERGESSEN LERNEN – ALZHEIMER IM BIOLOGIE-UNTERRICHT
Kontakt: Prof. Dr. Stefan Kins
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Informationsmaterial für Lehrer finden Sie auf der Homepage der NWG.

NEUROWISSENSCHAFTLICHE GESELLSCHAFT
GERMAN NEUROSCIENCE SOCIETY

Neurowissenschaftliche Gesellschaft e.V. (NWG)

- Beitrittserklärung -

Hiermit erkläre ich meinen Beitritt zur Neurowissenschaftlichen Gesellschaft e.V. (NWG).

Eintrag in das Mitgliederverzeichnis:

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Titel

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Datum/Unterschrift des Mitglieds Datum/Unterschrift des Mitglieds

Bitte senden Sie Ihren Antrag an die Geschäftsstelle der NWG:

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Ich optiere für folgende 2 Sektionen:

- ☐ Computational Neuroscience
- ☐ Entwicklungsneurobiologie/Neurogenetik
- ☐ junge NWG (jNWG)
- ☐ Klinische Neurowisschenschaften
- ☐ Kognitive Neurowissenschaften
- ☐ Molekulare Neurobiologie
- ☐ Neuropharmakologie und -toxikologie
- ☐ Systemneurobiologie
- ☐ Verhaltensneurowissenschaften
- ☐ Zelluläre Neurobiologie

Ich bin Student ☐ ja ☐ nein
(Bescheinigung anbei)
Ich bin ☐ weiblich ☐ männlich ☐ divers

☐ **Ich erkläre mich einverstanden**, dass meine Daten zum Zwecke wissenschaftlicher Informationsvermittlung (z.B. **FENS-Mitgliedschaft**) weitergegeben werden.
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