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# Editorial

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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.