IV. Abstract

Strong memories following an emotionally aversive experience are common and are of highly adaptive value as they allow a better retention of potentially harmful stimuli and contexts. In the majority of cases, the aversive memories tend to subside and weaken over time. In anxiety disorders (e.g. phobias) and post-traumatic stress disorder, in contrast, the strong memories persist, leading to clinical symptoms such as fear and re-experiencing. Various cognitive-behavioral therapies (e.g. exposure therapy) for these disorders are based on extinction learning, in which repeated unreinforced presentations of the stimulus lead to a decrease in the fear response. Extinction is thought to be a new learning, creating a new safe memory that competes with, but does not erase, the original fear memory. A change of context (renewal), re-exposure to the unconditioned stimulus (reinstatement) or mere passage of time (spontaneous recovery) may increase the dominance of the original fear memory over the safe memory and lead to relapse, commonly termed ‘return of fear’. Indeed, relapse following the conclusion of therapy is a major challenge in the treatment of these disorders. Targeting the original fear memory can theoretically offer a more long-lasting effect and prevent the return of fear. As opposed to the traditional view on memory, according to which consolidation is a one-time event that occurs shortly after acquisition, reconsolidation studies suggest that (re)consolidation is needed again upon retrieval. This time-limited lability period that follows the retrieval (or ‘reactivation’) of memory offers an additional opportunity for therapeutic intervention. Indeed, several pharmacological and behavioral manipulations have been shown to successfully effect (impair, enhance or update) reactivated memories for the long term.

The present thesis aimed to investigate the effects of cortisol and stress on the reconsolidation of reactivated fear memories in healthy human males and females. Cortisol, a glucocorticoid hormone secreted in a circadian rhythm and following exposure to stress, is a potent modulator of learning and memory, and its effects on memory consolidation and retrieval are well studied. Its possible influences on fear memory reconsolidation in humans remain unclear as animal and human studies report conflicting results. To this adds a gap of knowledge on sex differences. Despite growing evidence on the effects of sex and alternating sex hormones on emotional learning, potential effects on the reconsolidation of emotional memories have not been investigated as of today.
Three studies were conducted to investigate the effects of cortisol (Study 1 and 2; males and females, respectively) and stress (Study 3; males only) on fear memory reconsolidation in humans. All studies were identical in design apart from the post-reactivation manipulation and sex of the participants. Employing a three-day reconsolidation design, fear memories were created using the fear conditioning paradigm (day 1), retrieved following a pharmacological or behavioral manipulation (day 2), extinguished and tested for reinstatement (day 3). Geometrical shapes served as conditioned stimuli; electrical shock served as unconditioned stimulus. To test for the specificity of the reconsolidation effect, three different stimuli were used (two reinforced, one unreinforced) for conditioning on day 1, while only one of the previously reinforced stimuli was presented during the reactivation session on the second day. Skin conductance response was used as a measure of conditioned fear during acquisition, extinction and reinstatement test. Cortisol samples were collected to confirm the success of the pharmacological/behavioral manipulation.

Study 1, conducted in males, demonstrated an enhancing effect of high cortisol concentrations specifically on the reactivated fear. Study 2, conducted in females, showed no effect of cortisol on reactivated fear memories. Study 3, conducted in males using stress as a post-retrieval manipulation, demonstrated a general impairing effect on reactivated fear memories following stress induction. The results of the male studies suggest a dose-dependent effect of cortisol on reactivated fear memories. Additional factors (SNS activity, affective and cognitive factors) may also account for the results of the stress manipulation in males. The lack of effect in the female study could be attributed to the mixed hormonal status of the female participants and to the relatively small sample size, which did not allow the investigation of possible influence of alternating sex hormones concentrations. Further investigations are highly important in order to understand the role of sex hormones in mental health and disease in women. The presented findings contribute to the understanding of similarity and difference between reconsolidation and initial consolidation, and may explain the persistence and strength of aversive memories. The results have additional implications with regard to preferable treatments for anxiety disorders and post-traumatic stress disorder.