Neural mechanisms of adolescent fear extinction and fear extinction during reconsolidation: a literature review

Dorien Huijser
Student number: 4174259

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Master Neuroscience and Cognition, Graduate School of Life Sciences
Utrecht University, the Netherlands

Supervisors

Supervisor host institute: dr. Marieke Bos
Department of Developmental and Educational Psychology, Institute of Psychology,
Leiden University, the Netherlands

Utrecht examiner: prof. dr. Joke Baas
Department of Experimental Psychology, Utrecht University, the Netherlands

Contact: d.c.huijser@students.uu.nl

Laymen's summary

Anxiety disorders and phobias are a growing problem in today's society, and their emergence peaks in adolescence. Currently, anxiety is often treated using exposure-based cognitive-behavioral therapy (CBT). This therapy relies on the principles of a phenomenon called fear extinction. During such therapies, patients are exposed to the feared stimulus without the presence of the feared outcome, in that way enabling them to re-interpret the feared stimulus as safe. However, many patients show relapses after fear extinction training, in that their fear suddenly comes back in some form or under certain circumstances. Such relapse may occur, because extinction training is thought to create a new memory in which the feared stimulus is not coupled to the feared outcome, whereas the fear memory itself stays in existence and therefore needs to be suppressed. Importantly, especially adolescents seem prone to anxiety and seem to be impaired in extinguishing their fear. Therefore, researchers have started searching for new methods for reducing anxiety in adolescents. One such method relies on memory reconsolidation. When we retrieve a memory, that memory can come into a labile state in which it can be updated with new knowledge. Putting the memory in a stable state after this updating process is called reconsolidation. Performing fear extinction training during this window in which the fear memory is labile has been used to adjust the emotional value of the fear memory itself. Modifying the fear memory this way has been shown successful in both adults and adolescents. However, the different brain mechanisms involved in extinction and memory reconsolidation in adolescents are still unclear. In this review, we find that fear extinction may be impaired in adolescence, because the mechanisms that are needed to suppress the fear memory in favor of the extinction memory are still developing during adolescence. These mechanisms reside in prefrontal regions that show a delayed development compared to the emotional system that involves fear learning. In contrast, memory reconsolidation in adults likely involves directly adjusting the fear memory in the amygdala, a brain region that is part of this relatively early matured emotional system. Moreover, memory reconsolidation does not seem to require prefrontal activity involved in suppression as much, because the fear memory is itself modified and therefore does not need to be suppressed. However, it has not been investigated whether these mechanisms may be different in adolescents. The findings presented in this review suggest that extinction training performed during the memory reconsolidation window may be a promising new method to reduce anxiety in adolescents compared to extinction training on its own. Research on the brain mechanisms of memory reconsolidation in adolescence, however, is needed. Moreover, the memory reconsolidation paradigm seems to work only under certain conditions that need further investigation in adolescence. For example, a memory needs to be sufficiently destabilized before it can be modified. However, the circumstances under which memories of adolescents become destabilized are as of yet unknown.

Abstract

Anxiety disorders and phobias are a growing problem in today's society. Currently, anxiety is often treated using therapies that rely on the principles of fear extinction, in which patients are exposed to the feared stimulus without the feared outcome, enabling them to re-interpret the feared stimulus as safe. However, relapse for fear extinction is high. Moreover, anxiety peaks during adolescence, a period in which extinction retention has been shown to be especially impaired. Recently, a new paradigm has been brought forward that relies on bringing the fear memory into a labile state and then modifying it using extinction training. This paradigm has shown positive results compared to extinction alone in both adults and adolescents. However, the development of the neural mechanisms of extinction alone and during memory reconsolidation is as of yet unclear, and is reviewed here. The literature suggests that extinction retention may be impaired in adolescents, because of the relatively delayed development of the ventromedial prefrontal cortex during adolescence, a region involved in the inhibition of the fear memory in favor of the extinction memory, as compared to subcortical regions such as the amygdala. In contrast, extinction during memory reconsolidation may involve directly modifying the fear memory in the lateral amygdala, requiring significantly less to no inhibition from prefrontal regions. The results suggest that the memory reconsolidation paradigm may be beneficial for use in both adults and adolescents. However, more research investigating the neural mechanisms of memory reconsolidation is needed. Moreover, the boundary conditions of the memory reconsolidation paradigm need further investigation in adolescence. For example, the circumstances under which memories of adolescents are destabilized are as of yet unknown.

Keywords: fear extinction, reconsolidation update, adolescence, neural mechanisms, anxiety

Introduction

Fear is an evolutionary ancient function that serves to keep species from danger. Generally, fear responses are naturally extinguished when the feared stimulus is not accompanied anymore by an aversive event. However, when this is not the case, fear can become pathological and as such result in anxiety disorders or phobias (Casey, Glatt, & Lee, 2015). Anxiety can take on many forms and impacts a large part of the population (Drysdale et al., 2014). In fact, anxiety disorders emerge surprisingly often during adolescence (Casey et al., 2015; Drysdale et al., 2014; Crone & Dahl, 2012), a period in which fear memories seem to be significantly less extinguishable as well (Patwell et al., 2012; Kim, Li, & Richardson, 2011; McCallum, Kim, & Richardson, 2010; Zbukvic, Park, Ganella, Lawrence, & Kim, 2017).

An important question is why adolescents seem so vulnerable to anxiety. Adolescence is the developmental period between the start of puberty and the onset of adulthood (Crone & Dahl, 2012; Casey, Jones, & Somerville, 2011; Shulman et al., 2016; Pattwell, Lee, & Casey, 2013). During adolescence, the brain undergoes major changes. The largest neural changes occur in regions subserving higher-order functions, such as emotion regulation and cognitive control (Tamnes, Østby,

Fjell, Westlye, Due-Tønnessen, & Walhovd, 2009; Tamnes et al., 2017; Casey et al., 2011). In contrast, subcortical regions involved in emotion expression, such as the amygdala, develop steadily and mature earlier than cortical regions (Wierenga et al., 2018; Wierenga, Langen, Ambrosino, van Dijk, Oranje, & Durston, 2014). This relative delay in cortical development has previously been used to explain the increased risk-taking behaviors as seen in adolescence (Shulman et al., 2016; Casey et al., 2011). An important hypothesis is that this mismatch between cortical and subcortical brain development may also explain the increased emergence of anxiety in adolescence and the decreased ability of adolescents to extinguish their fear. In this review, we will look into this hypothesis further.

More knowledge about the development of the underlying neural mechanism of fear extinction is indeed highly relevant when looking at its clinical value. Most existing treatments for anxiety consist of exposure-based cognitive-behavioral therapy (CBT), which relies on the principles of fear extinction (Drysdale et al., 2014; Quirk & Mueller, 2008). During fear extinction training, patients are exposed to the feared stimulus in the absence of the feared outcome. In turn, the feared stimulus is reinterpreted as safe, which leads to a decreased fear response. However, exposure-based CBT has been shown to have a high relapse rate in the form of spontaneous recovery, renewal, or reinstatement of fear (20 to 60%; Vervliet, Craske, & Hermans, 2013; Drysdale et al., 2014). This apparent ineffectiveness of extinction has led researchers to believe that during extinction training, a new memory is created in which the feared stimulus is uncoupled from the feared outcome, whereas the fear memory itself stays in existence and therefore needs to be inhibited (Bouton, 2002; Vervliet et al., 2013; Monfils et al., 2009; Kindt, 2018; Pattwell et al., 2013). Importantly, the relapse rate for exposure-based CBT is also high in adolescents (about 40%; James, Soler, & Weatherall, 2005; James, James, Cowdrey, Soler, & Choke, 2015). Moreover, laboratory experiments studying fear extinction in healthy samples have shown that adolescents show significant impairments in the retention of fear extinction, compared to adults (Pattwell et al., 2012; Drysdale et al., 2014; Kim et al., 2011; McCallum et al., 2010). This suggests that, especially for adolescents, fear extinction training may not be an optimal therapy for treating anxiety.

Recently, researchers have started looking for alternative paradigms to reduce anxiety, one of which relies on the principles of memory reconsolidation. Memory reconsolidation is thought to be a mechanism that serves to update already existing memories (Schiller, Monfils, Raio, LeDoux, & Phelps, 2010; Monfils et al., 2009). When a memory is retrieved, it is believed to come into a labile state, in which new, relevant information can be incorporated into the memory, before restabilizing (Nader, Schafe, & LeDoux, 2000; Monfils, Cowansage, Klann, & LeDoux, 2009). Studies seeking to diminish anxiety have used this principle to modify the fear memory directly, by performing extinction training during this reconsolidation window. Many studies targeting reconsolidation of the fear memory this way have shown promising results, both in adults and in adolescents (e.g., Steinfurth, Kanen, Raio, Clem, Huganir, & Phelps, 2014; Monfils et al., 2009; Oyarzún et al., 2012; Soeter & Kindt, 2015; Lee, Haberman, Roquet, & Monfils, 2016; Agren et al., 2012; Schiller, Kanen, LeDoux,

Monfils, & Phelps, 2013). Currently, however, it is unclear how the underlying neural mechanisms of fear extinction alone and during memory reconsolidation develop during adolescence. The current review therefore investigates the development of the neural mechanisms underlying these methods during adolescence. We will first briefly go into the mechanisms of fear acquisition and then follow with sections about fear extinction and memory reconsolidation in adults and adolescents. In the discussion, we will summarize our findings and go into their implications for future research and clinical practice.

Cued and contextual fear conditioning

Fear is a broad phenomenon that can be studied on many levels. In this review, we focus on classical fear conditioning. During classical conditioning, a neutral stimulus (the conditioned stimulus, CS) is repeatedly paired with one that elicits a fear response (unconditioned stimulus, US), such as freezing in rodents, increased skin conductance, or a startle response in humans (LeDoux, 2000; Casey et al., 2015). One example of classical fear conditioning is when a sound, the CS, is repeatedly coupled with a shock to the wrist, the US. A conditioned fear memory has been acquired when the sound also elicits a fear response in the absence of the shock (LeDoux, 2000, then called the CS+). Similarly, the context in which conditioning took place can also become associated with a feared outcome, so that a return to the conditioning context can elicit a contextual fear response (LeDoux, 2000). Importantly, adolescents have been shown to exhibit normal cued fear acquisition, but impaired contextual fear acquisition (Pattwell et al., 2013; Casey et al., 2015; Pattwell et al., 2016).

Animal and human studies have indicated that the amygdala, the medial prefrontal cortex (mPFC) and the hippocampus, are the key regions involved in fear acquisition, see Figure 1A (LeDoux, 2000). Many of the insights presented here and in the rest of this review come from rodent studies. However, since human and rodent fear circuitry seem to be highly conserved across species (Quirk & Mueller, 2008), studying the rodent brain can provide useful and more detailed insights into the neural mechanisms of fear in humans. During fear conditioning, thalamic inputs from both the US and the CS project to the lateral amygdala (LA), the first site of plasticity involved in fear conditioning (LeDoux, 2000; Quirk & Mueller, 2008). The LA projects to the central amygdala (CE), which in turn projects to the hypothalamic and brainstem nuclei that trigger an autonomic fear response, such as freezing or increased heart rate (LeDoux, 2000; Quirk & Mueller, 2008). The hippocampus is involved in detecting environmentally relevant cues and provides contextual information through projections to the basal amygdala (BA; LeDoux, 2000; Pattwell et al., 2013). Activity in the BA, in turn, influences downstream CE activity, and thus, the fear response. Finally, the dorsal anterior cingulate cortex (dACC; prelimbic region in rodents; Quirk & Mueller, 2008), also plays a role in fear expression by increasing amygdala output (LeDoux, 2000).

Extinction

Fear extinction is a phenomenon that is often used to reduce anxiety. During extinction acquisition, the first phase of extinction, a memory of the CS that is not coupled to the US is acquired, leading to a decrease in the conditioned fear response (CR; Quirk & Mueller, 2008). In the extinction consolidation phase, the extinction memory is consolidated into long-term memory, lasting a couple of hours for the physiological and molecular processes to stabilize (Quirk & Mueller, 2008). Finally, successful extinction retrieval occurs when a presentation of the CS does not elicit a CR anymore (Quirk & Mueller, 2008). In standard human fear-extinction experiments, participants first acquire a fear memory through classical conditioning, such as picture-shock pairings. In the second phase, participants undergo extinction training in which the CS (e.g., the picture) is presented without the US (e.g., the shock; e.g., Vervliet et al., 2013; Monfils et al., 2009). Finally, during the third phase, participants often undergo a fear recovery test followed by reacquisition or re-extinction. In all cases, a CS which is never coupled to the US serves as control stimulus. Figure 2A visualizes this paradigm.

Fear is said to be recovered when the CR during test is higher than the CR at the end of the extinction training (Vervliet et al., 2013). Spontaneous recovery occurs when the CR in response to the extinguished CS recovers after a delay. Reinstatement is tested by presenting a number of unsignaled USs. Finally, renewal occurs when the CR reappears when extinction occurred in a different context than conditioning, and the individual is placed back into the conditioning context (Vervliet et al., 2013). As said, adolescents have been shown to exhibit greater spontaneous recovery, reinstatement, and renewal of fear compared to adults (Pattwell et al., 2012; Casey et al., 2015). Below, we review the neural mechanisms of fear extinction in adults and adolescents, investigating adolescents' impairment in retaining extinction memories.

Neural mechanisms of fear extinction in adults

Rodent studies on cued fear extinction are widespread and give great insight into the neural mechanisms that may underlie fear extinction in humans. These studies have indicated that acquisition of the extinction memory occurs in the basolateral amygdala (BLA; Quirk & Mueller, 2008; Baker, Bisby, & Richardson, 2016). Stabilizing the extinction memory through consolidation relies on activation and morphological changes in the BLA as well (Quirk & Mueller, 2008; Baker et al., 2016; Schiller & Delgado, 2010). On the other hand, the hippocampus and the infralimbic (IL) region in the mPFC, which corresponds to the human ventromedial prefrontal cortex (vmPFC), are also important regions involved in extinction (Quirk & Mueller, 2008; Baker & Richardson, 2015), see Figure 1B.

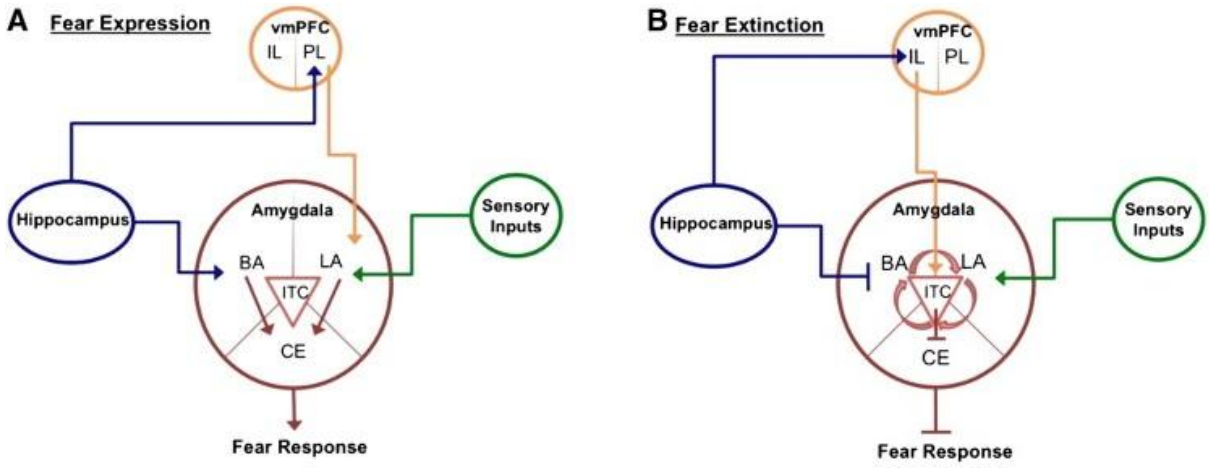

Figure 1. Neural mechanisms of fear acquisition (A) and fear extinction (B), figure taken from Pattwell et al. (2013). During fear acquisition (A), sensory inputs from the US and CS, and, after fear acquisition, projections from the PL, excite the LA, leading to CE activation and expression of fear once acquired. The hippocampus, providing contextual information, modulates CE activity via the PL and BA. During fear extinction (B), the hippocampus excites the IL, which in turn projects to the amygdala's ITC cells that inhibit CE output. The hippocampus can also inhibit CE output by inhibiting the BA. Arrows indicate excitatory projections, straight ends indicate inhibitory projections. BA: basal amygdala; LA: lateral amygdala; CE: central amygdala; vmPFC: ventromedial prefrontal cortex; PL: prelimbic region; IL: infralimbic region; ITC: intercalated cells.

The IL region in particular plays a large role in extinction consolidation and retrieval. Potentiation of this region after extinction training has been associated with suppression of the fear response (Quirk & Mueller, 2008; Pattwell et al., 2012; Baker et al., 2016; Pattwell et al., 2013; Baker & Richardson, 2015). The IL region has projections to the amygdala and to the amygdala's targets in the brainstem and hypothalamus (Quirk & Mueller, 2008). It can inhibit the fear response through its projections to intercalated cells (ITC) in the amygdala. These cells lie in between the BLA and the CE and can inhibit CE output, and therefore the fear response, by integrating BLA and IL output (Quirk & Mueller, 2008; Pattwell et al., 2013; Schiller & Delgado, 2010).

Two other regions also play an important role in fear extinction. Firstly, the hippocampus provides contextual information that can influence extinction consolidation and retrieval, modulating the inhibitory process of the IL region (Quirk & Mueller, 2008; Pattwell et al., 2013; Schiller & Delgado, 2010). Moreover, crosstalk between the CA1 and CA3 hippocampal regions is necessary for the retrieval of cued fear extinction (Pattwell et al., 2013). Secondly, the prelimbic (PL) region in the mPFC, corresponding to the human dorsal anterior cingulate cortex (dACC), is involved in the production and expression of conditioned fear (Quirk & Mueller, 2008; Baker et al., 2016; Pattwell et al., 2013). After fear extinction, synaptic glutamate transmission in this region is depotentiated, consistent with a decrease in fear expression after fear extinction (Pattwell et al., 2012). In sum, the amygdala, the IL and PL, and the hippocampus are key regions involved in rodent fear extinction.

Especially IL suppression of amygdala activation seems critical for extinction retention, see Figure 1B.

Studies in adult humans also suggest a critical role for the vmPFC, the human analog of the rodent IL, in fear extinction (Phelps, Delgado, Nearing, & LeDoux, 2004; Milad, Wright, Orr, Pitman, Quirk, & Rauch, 2007; Milad et al., 2009; Schiller & Delgado, 2010; Schiller et al., 2013). In one of the first functional MRI studies in humans, subjects between 18 and 25 years old were fear conditioned with colored windows (yellow or blue) as CSs, one of which was reinforced with a mild shock to the wrist, while measuring skin conductance responses (SCR) as a measure of the CR. Immediately following fear acquisition, an extinction training followed on day 1, as well as on day 2. The authors found that amygdala activation was associated with the CR in both fear acquisition and early extinction. The further the extinction training progressed, the less activation there was in the amygdala, and the smaller the CR. Moreover, the authors found that activation in the vmPFC was associated with the success of the extinction training, suggesting that the more the vmPFC was involved during extinction, the better participants' extinction retention was (Phelps et al., 2004).

Later studies in humans have confirmed rodent studies indicating that the hippocampus plays an important role in extinction retrieval. For example, Milad et al. (2007) found that the vmPFC and the hippocampus were activated in concert in response to an extinguished CS. Moreover, their activation was positively associated with retrieval success. A later study (Milad et al., 2009) showed that subjects with post-traumatic stress disorder (PTSD) showed impaired extinction retrieval that was associated with greater amygdala and dACC activation and less hippocampus and vmPFC activation. Moreover, the amount of activation in both the vmPFC and the hippocampus was also associated with the fear response (Milad et al., 2009). These studies suggest that, besides the vmPFC, the hippocampus is indeed also required for the retrieval of extinction memories.

In all, studies on adult fear extinction suggest that the vmPFC and the hippocampus are required for extinction retrieval. The vmPFC in particular plays an important role in inhibiting the fear memory in favor of the extinction memory. In this line of thought, the process of extinction may be seen as a form of emotion regulation (Schiller & Delgado, 2010), in that the vmPFC can regulate the fear response through inhibiting amygdala output (Schiller & Delgado, 2010). Schiller and Delgado (2010) hypothesized that the vmPFC may encode a safety signal when the CS is presented in the absence of the US and in that way inhibit a CR. This inhibitory control by the vmPFC may be lost when spontaneous recovery, reinstatement or renewal occur (e.g., see Ganella, Drummond, Ganella, Whittle, & Kim, 2018).

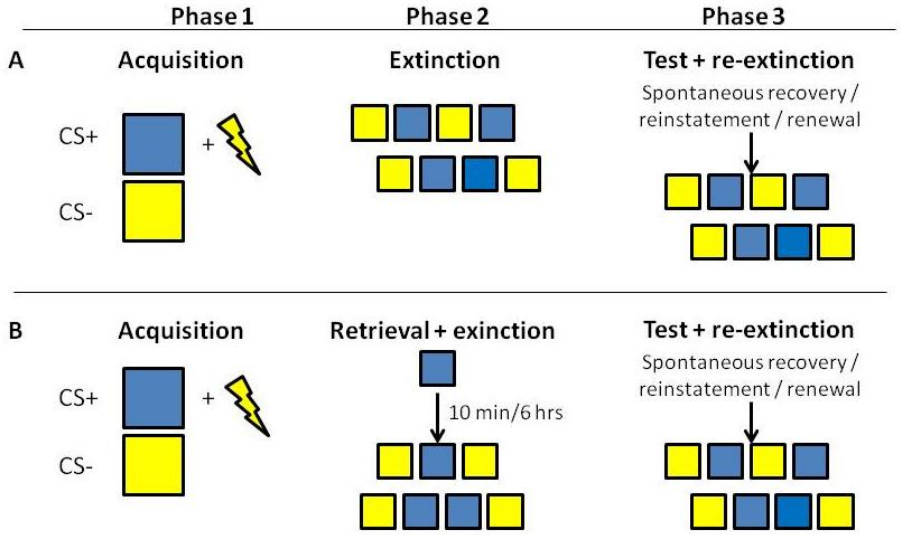

Figure 2. Examples of human fear extinction (A) and fear extinction during memory reconsolidation (B) paradigms. In both paradigms, participants acquire fear in the first phase, for example by coupling a colored square with a shock to the wrist. In the memory reconsolidation paradigm, a second reinforced CS can also be used that will not be reminded in Phase 2 (e.g., see Schiller et al., 2013). During the second phase, participants in both paradigms undergo extinction training, in which none of the CSs are accompanied by the US. Importantly, in the extinction during memory reconsolidation paradigm (B), participants are first reminded of (one of) the CS(s)+, with a waiting period between the reminder trial and the extinction training. In the third phase, fear recovery is tested, testing either spontaneous recovery, reinstatement, or renewal of fear. Afterwards, participants undergo either re-extinction (in the figure) or reacquisition. In human studies, the behavioral fear response is calculated as the difference in response (SCR or startle response) between the CS+ and the CS-.

Neural mechanisms of fear extinction in adolescents

In both rodent (postnatal (P) day 29-50) and human adolescents, cued fear extinction retention, but not cued fear acquisition and within-session extinction, has been shown to be impaired compared to that of both adults and juveniles (McCallum et al., 2010; Kim et al., 2011; Pattwell et al., 2012; Zbukvic et al., 2017). Baker and Richardson (2015) found that cued extinction retention was only impaired when cued fear was both acquired and extinguished during adolescence, and not when cued fear was acquired prior to adolescence or extinguished during adulthood. These results suggest that cued fear encoding and extinction mechanisms may differ in adolescents compared to adults.

Consolidation and retrieval of adolescent cued extinction memories have been shown to rely on the *N*-methyl-D-aspartate (NMDA) system, a glutamatergic signaling system in the brain. Administration of an NMDA receptor agonist in adolescent rats improved cued extinction retention to levels comparable to those of adult rats (McCallum et al., 2010; Baker & Richardson, 2015). Also, cued extinction in juvenile and adult rats led to increased NMDA-mediated synaptic plasticity in the IL, PL, and BLA, as indicated by increased phosphorylation of mitogen-activated protein kinase

(MAPK), a downstream signaling cascade of the NMDA receptor (Baker & Richardson, 2015). In contrast, this increase in synaptic plasticity after cued extinction seemed to be absent in adolescent rodents (Kim et al., 2011; Baker & Richardson, 2015). Increasing the amount of extinction training in the adolescents, however, resulted in better extinction retention and significantly increased synaptic plasticity in the IL of the adolescent rodents (Kim et al., 2011; McCallum et al., 2010). Thus, adolescent rodents show delayed synaptic plasticity in the IL required for the consolidation and retrieval of the cued extinction memory (Kim et al., 2011; Baker & Richardson, 2015). This suggests that adolescents may require more extinction training to reach adult levels of extinction retention.

In agreement with above mentioned studies, Pattwell et al. (2012) found decreased cued extinction retention as indicated by the freezing response, in adolescent (P29) mice, compared to juvenile (P23) and adult (P70) mice. Parallel to these behavioral findings, they found that after extinction, neural activation, as indicated by c-Fos protein levels, was increased in the IL region and downregulated in the PL region, but only in the P23 and P70 mice. Also, during extinction, there was enhanced glutamatergic transmission in the IL region in P23 and P70 mice, but not in the P29 mice. Altogether, these results suggested that the adolescent mice exhibited altered synaptic plasticity in the IL and PL regions during cued extinction (Pattwell et al., 2012). Altogether, studies suggest that adolescent rodents may use the IL region less efficiently compared to adults, leading to increased difficulties in inhibiting the fear memory in favor of the extinction memory.

Hyperactivity of the fear expression pathway may also contribute to the adolescent impairment in extinction retention (Pattwell et al., 2012; Baker et al., 2016). For example, Pattwell et al. (2016) showed that postsynaptic spine formation and density in the PL region peak in adolescence. Moreover, the amount of cells in the BLA projecting to the PL region also peak (Pattwell et al., 2016). The authors suggested that increased activation in the amygdala during adolescence may activate a positive feedback loop with the PL region that maintains fear expression and leads to impaired cued extinction retention (Pattwell et al., 2016). In contrast, the IL region undergoes changes in synaptic transmission and strength of projections to the amygdala (Baker et al., 2016; Pattwell et al., 2013), leading to immature inhibition of amygdala activity (Pattwell et al., 2013; Casey et al., 2015).

The studies discussed so far suggest that the impaired cued extinction retention in adolescent rodents is due to quantitative differences in extinction mechanisms. However, some studies have suggested that additionally, different signaling mechanisms may underlie cued fear extinction in adolescence. For example, reducing levels in the IL of a tyrosine kinase, an enzyme involved in signal transduction, improved fear extinction acquisition in adolescents, but not in adults (Cruz, Soler-Cedeño, Negrón, Criado-Marrero, Chompré, & Porter, 2015). Zbukvic et al. (2017) found differences in dopamine signaling in the PFC after fear extinction in adolescents compared to adults. Whereas adolescent rats exhibited a decreased ratio of different dopamine receptors after extinction, that of adult rats increased. Moreover, enhancing signaling of the dopamine 2 receptor improved long-term extinction in adolescents, but delayed extinction acquisition in adults (Zbukvic et al., 2017). These

results suggest that besides a disturbed excitation/inhibition balance between IL, PL, and amygdala, additional signaling cascades may also underlie altered fear extinction during adolescence.

Interestingly, contextual fear extinction does not seem to be impaired in adolescents (Kim et al., 2011; Pattwell et al., 2013). Thus, different mechanisms may underlie contextual compared to cued fear extinction. Pattwell et al. (2016) found that there is a peak in connectivity between the hippocampal CA1 region and the PL region during adolescence, and this increased hippocampal inhibition of the PL may contribute to the lack of contextual fear expression in adolescence. The reorganization of hippocampal connections with the PL and IL may interfere with the ability to retrieve contextual fear memories and cued extinction memories by interfering with synaptic plasticity in the BLA (Pattwell et al., 2013; Pattwell et al., 2016).

Studies on the neural mechanisms of fear extinction in human adolescents are more scarce, especially studies looking at the developmental perspective instead of simply comparing adolescents with adults. However, the literature reviewed here is generally in line with rodent research. As said, fear extinction can be seen as a form of emotion regulation, in that the vmPFC regulates amygdala activation during fear extinction retrieval (Schiller & Delgado, 2010). Studies investigating emotion regulation have indeed offered insights into the development of the circuitry underlying fear extinction. For example, one study in children, adolescents, and adults found that adolescents exhibited impaired emotion regulation compared to adults, which was accompanied by larger amygdala responses (Hare, Tottenham, Galvan, Voss, Glover, & Casey, 2008). Reversely, greater ventral PFC activation was associated with better emotion regulation, and was generally lower in adolescents than in adults. Finally, poorer emotion regulation in adolescents was associated with worse functional connectivity between the ventral PFC and the amygdala (Hare et al., 2008). This functional connectivity between the ventral PFC and the amygdala may influence emotion regulation capacities, or may be a consequence of decreased ventral PFC or increased amygdala activation.

PFC-amygdala connectivity is indeed still developing during adolescence, as shown by Swartz, Carrasco, Wiggins, Thomason, and Monk (2014), and may that way influence fear extinction retention capabilities. Swartz et al. (2014) found an increase in structural connectivity (as indicated by fractional anisotropy) from adolescence to adulthood in the uncinate fasciculus, a major white matter tract connecting the PFC and the amygdala. Moreover, they found decreased amygdala activation for emotional faces with age, and that less amygdala activation in response to sad and happy faces was related to increased connectivity in the uncinate fasciculus. This increase in structural connectivity may thus contribute to increased emotion regulation abilities and to the decrease in amygdala activation to emotional faces with age (Swartz et al., 2014). This would imply that extinction retention is impaired in adolescence because the heightened amygdala activation characteristic of adolescent emotion processing is not sufficiently suppressed by the vmPFC. This in turn may be the result of an immature structural connectivity between the vmPFC and the amygdala.

Studies investigating fear extinction in adolescents directly are in accordance with this idea. Preliminary results from Morriss, Christakou, and van Reekum (2018), testing a sample of adolescents and adults between 12 and 28 years old, indeed showed that during extinction, younger participants exhibited increased and prolonged amygdala activation and delayed mPFC engagement in response to the CS+. Moreover, they found that with age, structural connectivity between the PFC and the amygdala increased, which in turn led to increased mPFC engagement during extinction (Morriss et al., 2018). Ganella et al. (2018) also found that during retrieval, adolescents between 14 and 16 years old exhibited an increased SCR and reduced vmPFC activation compared to adults between 25 and 35. Adolescents also exhibited increased vmPFC activation during early extinction compared to early conditioning, suggesting that more vmPFC activation was required to suppress the fear memory in adolescents than in adults (Ganella et al., 2018). Despite the fact that only a small sample of mid-adolescents was tested, and all experimental phases were conducted within one day, this study offers a good starting point for future research into the development of the neural mechanisms of fear extinction in adolescents.

Summary neural mechanisms of fear extinction in adolescents

The above described results are largely consistent with the dual systems model of adolescent brain development. This model posits that adolescents exhibit impaired cognitive control and emotion regulation, because subcortical responses to emotional stimuli are heightened and prefrontal control areas are still developing during adolescence (Shulman et al., 2016; Casey et al., 2011). In light of this model and the literature reviewed here, impaired cued extinction retention during adolescence may be attributed to heightened amygdala activation, less efficient fear inhibition, or still developing connectivity between fear regulating and expressing brain regions during adolescence. Heightened amygdala activation in response to emotional stimuli may lead to an increased and less easily inhibited fear response. Also, the vmPFC, which is involved in inhibiting the fear memory during extinction retrieval, exhibits a delayed and less efficient engagement during extinction retrieval (Ganella et al., 2018; Morriss et al., 2018). This may be attributed to the protracted development of cortical compared to subcortical regions during adolescence (Shulman et al., 2016; Casey et al., 2011). Finally, immature vmPFC-amygdala connectivity may lead to impaired vmPFC inhibition of amygdala activation and may therefore also contribute to impaired adolescent extinction retention (Morriss et al., 2018; Swartz et al., 2014). A combination of all three of these possibilities likely explains the impaired adolescent fear extinction retention. Future studies should investigate the temporal and causal dynamics of these developments simultaneously, as these are not yet fully known.

Using memory reconsolidation to reduce anxiety

Recently, memory reconsolidation has been introduced as a new construct that can be used to reduce anxiety. Memory reconsolidation is the process of restabilizing a memory trace (Nader et al., 2000;

Beckers & Kindt, 2017). It is generally agreed upon that when a memory is retrieved, it is brought into a labile state lasting for about six hours, in which the memory can be subjected to interference, and which is dependent upon protein synthesis in order to restabilize (Nader et al., 2000; Lee, Nader, & Schiller, 2017; Beckers & Kindt, 2017). In the context of fear, this phenomenon of memories being temporarily subject to change has been used to either alter an existing fear memory during the reconsolidation window or to erase it by blocking protein synthesis required for reconsolidation (Monfils et al., 2009; Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2015).

The method of fear memory modification through performing extinction training during the reconsolidation window (see Figure 2B) was first proposed and shown successful in rats by Monfils et al. (2009). They presented extinction training to fear-conditioned rats either ten minutes, one hour, six hours, or 24 hours after the presentation of a CS (without US presentation). They found that a retrieval trial followed either ten minutes or one hour by extinction training resulted in a lack of spontaneous recovery, renewal, and reinstatement of the fear memory, and that rats in these groups were less susceptible to reacquisition of the fear memory (Monfils et al., 2009). In humans, a comparable paradigm with extinction training performed either ten minutes or six hours after retrieval, showed that only the ten-minute group did not exhibit spontaneous recovery after one day, nor did they show reinstatement one year later (Schiller et al., 2010). After these initial studies, many others followed showing the effectiveness of the paradigm (Baker, McNally, & Richardson, 2013; Steinfurth et al., 2014; Golkar, Tjaden, & Kindt, 2017; Oyarzún et al., 2012; Brunet et al., 2011), although replication failures also exist (e.g., Wood et al., 2015; Bos, Beckers, & Kindt, 2014; Kredlow, Orr, & Otto, 2018; Klucken et al., 2016, see Beckers & Kindt, 2017). Nonetheless, in order to investigate the neural mechanisms of this paradigm in adolescents, we will turn to studies in which it was shown successful.

Neural mechanisms of fear extinction during memory reconsolidation in adults

Rodent studies have provided detailed insights into the neural mechanisms of fear extinction during memory reconsolidation. In rats, fear extinction after memory retrieval has been shown to elicit changes in glutamate receptor function in the lateral amygdala, whereas those changes did not occur during fear extinction alone (LA; Monfils et al., 2009; Lee et al., 2017). Directly comparing fear extinction-only with fear extinction during memory reconsolidation in rats, Lee et al. (2016) found that, in the extinction-only group, engagement of the PL and IL regions intensified as extinction training progressed. In contrast, in the reconsolidation-extinction group that underwent a retrieval trial 15 minutes before extinction training, engagement of these regions *de*creased as extinction training progressed (Lee et al., 2016). Moreover, during extinction training, the LA was initially involved to the same extent in both groups. However, as extinction training progressed, the LA became less engaged in the reconsolidation-extinction group compared to the extinction group (Lee et al., 2016). These results suggest that the IL and PL regions may play a small role at the start of fear extinction during memory reconsolidation, but that as fear extinction training progresses, the LA is crucial for

memory reconsolidation (Lee et al., 2016; Monfils et al., 2009; Merlo, Milton, Goozée, Theobald, & Everitt, 2014). Thus, fear extinction during memory reconsolidation may occur by actively reversing plasticity in the LA, with a decreased engagement of the IL and PL regions compared to extinction only (Lee et al., 2016). Neural plasticity in the LA may thus underlie the weakening or lack of return of the fear memory as seen in extinction during memory reconsolidation (Baker et al., 2016; Monfils et al., 2009; Lee et al., 2016).

The results found in humans are largely in line with those found in rodents. Agren et al. (2012) were among the first to investigate the neural mechanisms of fear extinction during memory reconsolidation in humans. Behaviorally, they showed that the group undergoing extinction ten minutes, but not six hours, after a retrieval trial, showed a lack of return of the CR. Moreover, in accordance with rodent studies, the CR was positively associated with activation in the BLA during a renewal session on day 3 (Agren et al., 2012). Interestingly, during a follow-up study 18 months later, the six hour-group reacquired the original fear memory and showed a return of fear, whereas the ten minute-group did not. Also, amygdala activation from both the original as well as the follow-up study predicted the fear response only in the six hour-group, and not in the ten minute-group (Björkstrand et al., 2015). The authors suggested that the fear memory in participants in the ten minute-group did not engage the amygdala anymore, indicating that the memory reconsolidation process may be mediated by the amygdala as the primary site of plasticity (Agren et al., 2012).

A second study (Schiller et al., 2013) used a within-participant design, in which one CS+ was reminded, and another CS+ and a CS- were not reminded prior to extinction training. Schiller et al. (2013) found that, for both CSs+, a decrease in CR was accompanied by a decrease of amygdala activation as extinction training progressed. However, return of fear only occurred for the CS+ that was not reminded prior to extinction as opposed to the one that was. Moreover, only the non-reminded CS+ engaged the vmPFC during extinction training, increasing with time, whereas the vmPFC was not differentially engaged for the reminded CS+ and the CS-. Also, extinction of the non-reminded CS+ was associated with increased functional connectivity between the vmPFC and the amygdala, whereas that of the reminded CS+ was not (Schiller et al., 2013). These results suggested that the non-reminded CS+ underwent regular fear extinction, in that the original fear memory was maintained and needed to be inhibited, whereas the reminded CS+ may have been updated and therefore modified, removing the need for inhibition (Schiller et al., 2013).

In a subclinical sample of individuals with spider phobia, fear extinction ten minutes but not six hours after a reminder trial facilitated approach behavior towards a spider (Björkstrand et al., 2016). Although both the ten minute-group as well as the six hour-group exhibited decreased amygdala activation as a function of extinction training, amygdala activation towards the reminded spider was significantly lower in the ten minute-group and significantly higher in the six hour-group during re-exposure on day 2, compared to day 1. Moreover, BLA activation towards pictures of spiders that were not reminded or not extinguished increased from day 1 to day 2 in the six hour-

group, but not in the ten minute-group, suggesting that the reconsolidation manipulation had affected the broader concept of spiders instead of the picture of the one spider (Björkstrand et al., 2016). Interestingly, in a follow-up six months later, amygdala activation in both groups, but more so in the ten minute-group, was further reduced, and the behavioral effect as found in the original study also persisted (Björkstrand et al., 2017). In accordance with rodent studies, suggesting that fear extinction during the reconsolidation window reverses synaptic plasticity in the LA, the results of this study indeed suggest that cued fear extinction during memory reconsolidation can alter the fear memory in the BLA, consequently reducing BLA activation in response to the previously feared stimulus.

Summary neural mechanisms of fear extinction during memory reconsolidation in adults

Together, studies indicate that fear extinction performed during the memory reconsolidation window has long-lasting effects that exceed that of extinction alone (Beckers & Kindt, 2017). Moreover, it seems that during fear extinction during memory reconsolidation, activation in both the amygdala and the vmPFC decrease, as the memory may be re-encoded or modified in the amygdala instead of creating a new extinction memory that needs inhibiting. However, another possibility is that the memory becomes state-dependent or in another way unassociated with the feared outcome, for example when the physiological state of the treatment becomes crucial for the retrieval of the extinction memory (Beckers & Kindt, 2017; Lee et al., 2017). Moreover, a retrieval trial previous to extinction training may also increase discrimination between the training and the extinction memories or enhance subsequent extinction training (Baker et al., 2013; Lee et al., 2017). Future studies will need to disentangle these possibilities.

Neural mechanisms of fear extinction during memory reconsolidation in adolescents

As of yet, not much is known about the development of the neural mechanisms of fear extinction during memory reconsolidation during adolescence (Baker et al., 2016). Baker et al. (2013) found that a retrieval trial shown before extinction training also improved extinction retention and reduced renewal of fear in adolescent rats, indicating that this method may be just as effective in adolescents as in adults. On a neural level, they hypothesized that, as has been shown in adult rodents, fear extinction during memory reconsolidation in adolescents may also involve reversal of the fear memory in the amygdala (Baker et al., 2013; Flint, Noble, & Ulmen, 2013). That would suggest that the memory reconsolidation process may already be mature in adolescence. In contrast, however, Tallot et al. (2017) found that inhibiting the mammalian target of rapamycin (mTOR), a protein complex regulating many cellular processes, after reactivation did not affect the CR in adolescents, whereas it decreased the CR in adult rats, suggesting in contrast that the mechanisms of reconsolidation in adolescents and adults may rely on different signaling mechanisms.

Recently, the first human study on memory reconsolidation mechanisms in adolescents was conducted (Johnson & Casey, 2015). Johnson and Casey (2015) directly compared both fear extinction

and fear extinction during memory reconsolidation in adolescents and adults. This study used a standard, three-day design, in which participants acquired fear on the first day, had either extinction training or extinction during memory reconsolidation on day 2, and a fear recovery test followed by re-extinction on day 3 (see Figure 2B). The authors replicated the finding that adolescents exhibited impaired fear extinction learning and retention. Moreover, both adolescents and adults undergoing regular extinction training exhibited clear fear recovery on day 3. In contrast, both adolescents and adults receiving a reminder cue ten minutes before the extinction training showed a significantly decreased CR and no reinstatement of fear. These results suggest that equally effective, and possibly similar, memory reconsolidation mechanisms may be at play in adolescents and adults. Unfortunately, as of yet, no other publications exist that replicate these results.

In sum, not much is known about the development of the neural mechanisms of fear extinction during memory reconsolidation during adolescence. Behaviorally, studies show that the memory reconsolidation paradigm may be equally effective in adolescents and adults. On a neural level, it may be the case that the mechanisms underlying memory reconsolidation in adolescents are comparable with those in adults, in contrast to those underlying fear extinction alone. This would imply that the adolescent amygdala also undergoes a reversal of synaptic plasticity during fear extinction during memory reconsolidation, modifying the fear memory directly. Indeed, compared to cortical regions, the amygdala does not undergo major changes during adolescence (Wierenga et al., 2018), supporting the hypothesis that the process of memory reconsolidation may already be developed sufficiently in adolescence. However, research investigating this hypothesis directly is warranted.

Discussion

Summary

The current review investigated the neural mechanisms of fear extinction, a mechanism underlying current therapies used to treat anxiety, and fear extinction during memory reconsolidation, a relatively new paradigm aiming to reduce anxiety, during adolescence. Adolescence is a developmental period characterized by great changes in neural structure and function, as well as in behavior (Crone & Dahl, 2012). Specifically, adolescents have been found to be more responsive to emotional stimuli and more prone to developing anxiety than other age groups (Casey et al., 2015; Crone & Dahl, 2012). Moreover, emotion regulation is impaired in adolescence (Pattwell et al., 2012; Johnson & Casey, 2015; Hare et al., 2008). Research suggests that this may be because of a protracted development of prefrontal cognitive control regions and still maturing cortical-subcortical connections (Schiller & Delgado, 2010; Casey et al., 2011; Shulman et al., 2016).

A great amount of research has been done on the neural mechanisms of fear extinction. Fear extinction in adults involves the amygdala for forming a new extinction memory, the hippocampus in providing contextual information, and the vmPFC in inhibiting the existing fear memory in favor of the extinction memory (Pattwell et al., 2013; Quirk & Mueller, 2008; Phelps et al., 2004; Milad et al.,

2007). Research conducted in adolescents indicates that adolescents exhibit impaired extinction retention. The studies reviewed here suggest that this impairment may be explained by a delayed engagement of the vmPFC during fear extinction retrieval, whereas amygdala activation is increased, as compared to adults. This is in line with the dual systems account of adolescent brain development (Shulman et al., 2016; Casey et al., 2011), in that cortical, emotion regulation and cognitive control-related regions, show a delayed development compared to the development of the socio-emotional, subcortical system.

The mechanisms of fear extinction during memory reconsolidation in adolescence, in contrast, have not been elucidated yet. The research done on extinction during memory reconsolidation in adults suggests that both amygdala and vmPFC activation decrease as extinction training progresses (Lee et al., 2016; Schiller et al., 2013; Agren et al., 2012). This suggests that the vmPFC is much less involved in fear extinction during memory reconsolidation than in fear extinction alone. It may be the case that in extinction during memory reconsolidation, one isolated retrieval trial indeed causes the fear memory to get into a labile state, enabling modification of the memory itself in the lateral amygdala (Monfils et al., 2009; Lee et al., 2017; Lee et al., 2016). Thus, because the memory itself is modified and no extinction memory is newly created, much less or no vmPFC activation is required to inhibit the pre-existing fear memory. Despite the fact that this paradigm has shown positive results in adolescents as well (Johnson & Casey, 2015; Baker et al., 2013), the neural mechanisms of extinction during memory reconsolidation in adolescents are yet to be elucidated. One hypothesis that needs to be investigated is that adolescents recruit comparable neural resources during memory reconsolidation as compared to adults. The positive behavioral results reported for adolescents (Johnson & Casey, 2015) may then be explained by the observation that vmPFC inhibition is much less required during this paradigm than during extinction alone. This would in turn suggest that fear extinction during memory reconsolidation may be a suitable method of reducing anxiety in adolescents.

Methodological remarks

Some methodological remarks must be kept in mind when interpreting the studies reviewed here. Firstly, the developmental studies reviewed here differ greatly in their definition of adolescence. Many studies investigating adolescents use a limited age range, instead of the entire period of adolescence (Crone & Dahl, 2012). This limits the validity of the results, since differences between adolescents and adults do not necessarily indicate how the mechanisms under investigation develop. Additionally, different definitions of adolescence may yield different results when comparing them to adults. Moreover, when testing a larger age range, linear trends are almost exclusively tested, whereas some cognitive functions, such as emotion regulation, may not develop linearly (Crone & Dahl, 2012). Investigating different trajectories, such as quadratic or even cubic trends, may more accurately inform researchers about the development of the underlying neural mechanisms. In addition, most studies reviewed here focus on the development of the standard neural fear circuitry (amygdala, vmPFC, and

hippocampus), whereas other regions may also play a role in adolescent fear extinction (during memory reconsolidation). In order to get a more complete picture of the neural mechanisms of the paradigm under study, future studies should conduct whole-brain analyses, instead of region-of-interest (ROI) analyses only. Finally, puberty effects have been overlooked in most studies reviewed here (Crone & Dahl, 2012). This is important since hormonal development has been shown to have a great influence on neural development, with puberty stage in many regions explaining neural development better than age alone (Wierenga et al., 2018). In this respect, future studies should look into puberty effects on the development of fear extinction retention and memory reconsolidation.

For the memory reconsolidation paradigm, contradicting results have been reported (e.g., Steinfurth et al., 2014; Wood et al., 2015; Kredlow et al., 2018; Klucken et al., 2016). These differences may be largely attributed to methodological differences in all three phases of the paradigm (see Figure 2). For example, differences in fear acquisition may influence the strength of the fear memory, such as differences in reinforcement rates, or in the kind of CSs (e.g., colored squares versus fear-relevant stimuli) or USs (e.g., wrist shock or aversive sounds and pictures) used. Importantly, some USs may elicit differential fear responses in adolescents and adults, because experience with the US used may differ between those age groups (Pattwell et al., 2013; Chan et al., 2011). For example, an adolescent may interpret a picture of a snake or a frightened face differently than an adult, possibly having less knowledge of or experience with it signaling danger. The strength of the fear memory may in turn influence the success of the subsequent extinction training or memory destabilization (Lee et al., 2017). Also, many more factors may play a role in determining the strength of the fear memory or the ability to destabilize or modify it, such as the amount of CS exposure during extinction, the context of fear acquisition and extinction, or the instructions given during the experiment.

A final point concerns that of the measurement of the human fear response. Most studies reviewed here used the skin conductance response (SCR) as a measure of fear, whereas the fear potentiated startle response (FPS) is also often used. Whereas both are considered acceptable measures of fear, different mechanisms are thought to underlie them. The SCR reflects arousal as a consequence of contingency learning, irrespective of the valence of the stimulus, and is mediated by hypothalamus and brainstem structures (Hamm & Weike, 2005; Schiller & Delgado, 2010). The SCR is closely related to contingency awareness and may therefore reflect a more declarative, cognitive level of fear (Hamm & Weike, 2005; Kindt et al., 2009; Sevenster, Beckers, & Kindt, 2012). On the other hand, the FPS may be considered a more direct measure of fear, because it does not require cortical processing or awareness of the CS-US contingency, and seems to more directly rely on the amygdala (Hamm & Weike, 2005). Differences in the reported success of extinction or extinction during memory reconsolidation could therefore be explained by differences in contingency awareness, as opposed to amygdala-mediated fear responses. Additionally, it is uncertain whether these two measures of fear are equally valid in adolescents as in adults. This possibility should be investigated in future research.

Implications

Adolescence is thought to be a time of leaving the safe environment of the family and of becoming independent and sexually mature (Pattwell et al., 2013; Crone & Dahl, 2012; Casey et al., 2015). It has been suggested that the impaired fear extinction seen in adolescence stems from the need to identify threatening stimuli in new environments, whereas impaired contextual fear acquisition and increased exploratory behaviors are needed to explore and adapt to those new environments (Pattwell et al., 2013; Casey et al., 2015; Crone & Dahl, 2012). However, navigating changing environments, in which stimuli may signal danger only under certain circumstances, may also require regular updating of existing fear memories.

An important question, then, is whether fear extinction during memory reconsolidation can be effective in reducing clinical anxiety in adolescents as an alternative to extinction training. As mentioned before, studies in adults on this paradigm show mixed results (Steinfurth et al., 2014; Oyarzún et al., 2012; Brunet et al., 2011; Wood et al., 2015; Kredlow et al., 2018; Klucken et al., 2016). Literature in adults has indicated that specific boundary conditions for memory destabilization and modification need to be identified, before being able to implement the method in clinical practice (see Beckers & Kindt, 2017 for a discussion on this topic). That is, a memory must be sufficiently destabilized before new information can be incorporated into it, and the reconsolidation process must be interfered with effectively (Lee et al., 2017). For example, upon retrieval, something in the environment should signal a prediction error, i.e., a mismatch between the expected and the actual experience (Sevenster et al., 2012; Bos et al., 2014; Lee et al., 2017), such that the memory is only destabilized when new information needs to be incorporated into the memory.

It is important to identify these boundary conditions in adolescents as well, before the memory reconsolidation paradigm can be implemented in the clinic. As said, adolescents may to a different extent rely on memory updating mechanisms. For example, prediction errors may be a specifically well-suited source of fear-learning for adolescents, who find themselves in a changing environment, in which stimuli may signal danger only under certain circumstances, whereas under others, they may be safe (see Crone & Dahl, 2012). This idea of the memory system being flexible to allow adolescents to adapt to their environment may be key to facing the challenges that come with being an adolescent, such as making new friends, having a successful romantic relationship, resisting peer pressures, or becoming independent from the family (see Crone & Dahl, 2012). Also, adolescent fear memories may differ in how easily they are destabilized or modified. For example, adolescent fear memories may either be stronger (since they are less extinguishable), or weaker (since adult memories may be older) than those of adults. Alternatively, some adolescent fear memories may be formed under more stressful circumstances, leading them to be less easily destabilized or modified (e.g., Beckers & Kindt, 2017; Kindt, 2018; Casey et al., 2015).

Future directions

Memory reconsolidation may be an effective target mechanism to reduce anxiety in adolescents. However, in order for this paradigm to be implemented in clinical practice, the positive effects of the technique should be replicated and its longitudinal effects should be investigated in adolescents and clinical groups. Determining the boundary conditions of memory destabilization for adolescents, for example which kind of stimuli are most effective for them, is paramount. For example, since social context plays a large role in adolescence (Shulman et al., 2016; Crone & Dahl, 2012), social stimuli or memory reconsolidation in a social context may be more effective for reducing anxiety in adolescents than in adults or children. Alternatively, since contextual fear extinction seems normal in adolescence, finding a way to extinguish fears using contextual markers may also offer a solution.

Developmental studies on the neural mechanisms of fear extinction during memory reconsolidation are lacking. Therefore, we recommend investigating these mechanisms across adolescence and adulthood, and looking at whole-brain results instead of regions-of-interest only. This will provide crucial and more complete insights into the development of memory reconsolidation mechanisms, and may put forward neural markers of memory destabilization (Lee et al., 2017). Moreover, since anxiety often arises in adolescence (Casey et al., 2015; Drysdale et al., 2014), clinical adolescent groups will also benefit from such research as it will put forward more suitable treatments for adolescent anxiety. In all, the memory reconsolidation paradigm seems a promising alternative for reducing adolescent anxiety compared to fear extinction training, but there is still a long way to go before it may be implemented in clinical practice.

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