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Invited Review

Oxytocin for learning calm and safety

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ABSTRACT

The appropriate discrimination between safe and dangerous situations and the subsequent decrease of fear expression in the presence of safety signals are crucial for survival and mental health.

Learning of safety associations is often studied in terms of fear extinction, that is re-learning of a previously conditioned stimulus which is now no longer positively associated with danger. Numerous studies investigated neurobiological processes of fear extinction and provide a valid picture of the underlying neural structures and endocrine processes involved.

However, a formerly *neutral* conditioned stimulus (CS) can also predict the *non-occurrence* of an aversive, potentially dangerous, unconditioned stimulus (US) from the very beginning and thus can serve as a safety stimulus. This process has been termed safety learning. Although safety learning has been known for almost a century, there has been little research on its underlying neurobiological mechanisms, in contrast to the more prominent Pavlovian fear conditioning and fear extinction.

In this review, we propose that the well-known action of the hypothalamic neuropeptide oxytocin (OXT) in the regulation of fear and stress responses is complementary to safety learning. We summarize the literature focused on OXT signaling and safety learning in animals and humans, from the first studies of fear extinction and conditioned inhibition of fear to the most recent findings in molecular and behavioral research on initial social safety stimuli. At the end, we discuss the application of OXT as a therapeutic agent to psychopathologies related to deficits in safety learning.

1. Introduction

Detecting and reacting to external events is possible even for the simplest single cell organisms and is very evolved in humans. The underlying processes in learning the combination of neutral and aversive events and resulting fear responses have been studied intensively in invertebrates and vertebrates over the last centuries (see reviews by LeDoux, 2000; Thompson, 1986). By contrast, much less is known about the inhibition of fear with learned signals of safety, a process that can also be observed in invertebrates and vertebrates, suggesting an evolutionary conserved nature of the underlying molecular mechanisms (for overview, see Giurfa and Sandoz, 2012; Krasne and Glanzman, 1995).

From the very early stages of primate evolution, humans and their ancestors have lived in social groups. Social interaction and the processing of communicative information have had clear advantages for survival (see review by Ohman and Mineka, 2001). Current concepts of fear assume that it constitutes an evolutionarily shaped reaction enabling humans to respond to and avoid danger in both social and non-social contexts. Humans, however, communicate not only about fear-provoking signals or learn to react with adequate fear in response to danger, but also about signals indicating safety from harm (as discussed by Christianson et al., 2012).

2. Fear learning and fear extinction

It is plausible that an emotion essential for survival has evolutionary and ontogenetic determinants: animal species early in the evolutionary

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process, as well as humans very early from infancy on, react to potential or actual threat with fear. In this context, it is important to differentiate mechanisms that detect and respond to threats from those that give rise to conscious fear (as discussed by LeDoux, 2014). The neural fear system is of high importance and detecting signals of fear in others is neuroanatomically allocated in a network encompassing the amygdala, anterior cingulate, insular and prefrontal cortices. Top-down regulatory processes, such as active cognitive strategies and re-learning of associations are known to control negative emotions such as fear (e.g. by extinction learning in human subjects, Eckstein et al., 2014a), therefore building an important flexible and plastic system (see review by Ohman and Mineka, 2001). In some human individuals (Bishop, 2009), this top-down control seems to be impaired; this is thought to underlie the development of anxiety disorders and might explain their high prevalence rates.

There are only very few examples where a stimulus or a signal eliciting an emotion is inherent. For most signals, the association with an emotion is learned over repeated exposures (as shown in studies by Dunsmoor et al., 2015). The process of fear conditioning is known to result from the combined presentation of one previously neutral conditioned stimulus (CS) and one aversive unconditioned stimulus (US).

One important form of fear inhibition is fear extinction (Furini et al., 2014): Fear extinction is an is an explicitly distinctive process that can be dissociated from safety learning. Fear extinction is defined as the decrement in conditioned fear responses after repeated presentations of a former conditioned fear stimulus that is no longer reinforced (see for excellent reviews on the animal literature, Milad and Quirk, 2012; Orsini and Maren, 2012). In this context, the phenomenon of so-called "renewal" describes how the fear response can reoccur in new contexts even after extinction (Maren et al., 2013).

Another form of fear inhibition is called safety learning (see below), which defines the process of learning that a stimulus predicts safety (i.e. the absence of aversive events) from the very first place (see Fig. 1 for a schema of learning processes).

Investigating these processes of emotional learning can either focus on the learning phase itself, during which an individual learns to form associations between former neutral stimuli and the emotional content (e.g. fear or safety), or focus on the result of the learning process, the so-called recall (studied by Acheson et al., 2013; Milad et al., 2009), that indicates the strength of the memory. Both mechanisms are highly relevant for survival.

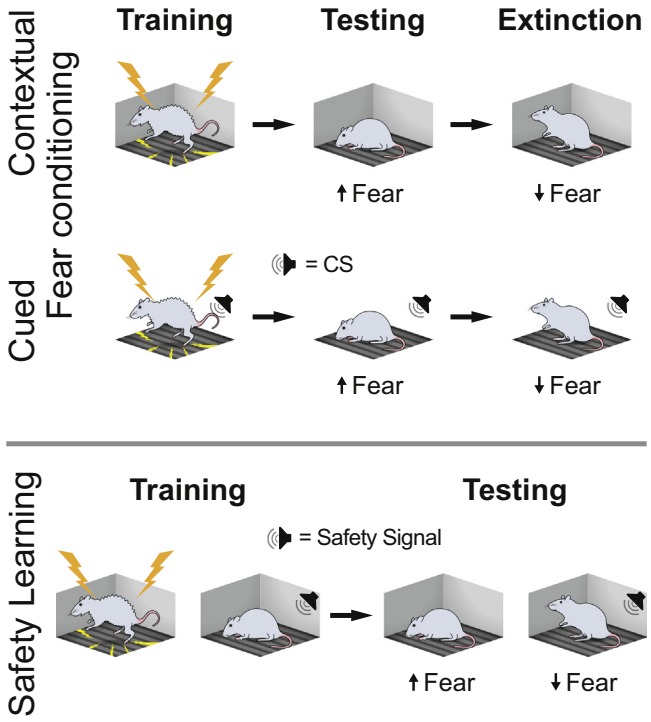

Fig. 1. Comparison between safety learning and fear extinction processes. In the contextual fear conditioning paradigm, fear is elicited by the context where the conditioning took place, whereas in cued fear conditioning, fear is triggered by the conditioned stimulus (CS) represented by the auditory cue. In the testing phase of both contextual and cued fear conditioning, subjects show high levels of fear expression, whereas in extinction, after repeated exposure to the same stimuli but without unconditioned stimulus (US), or foot shock, this outcome is reduced. In safety learning, the inhibition of fear begins in the phase of training, in which the safety signal never co-occurs with the danger signal. In the current schema, the safety signal is represented by the auditory cue and the danger signal is the conditioning context. In the testing phase, when the danger signal is presented alone, subjects show high levels of fear expression, but when it occurs simultaneously with the safety signal, fear expression is decreased. In the study with humans, more complex paradigms can be used with the inclusion of another cue as danger signal, along with the context.

3. Safety learning

The concept of safety learning is related to "conditioned inhibition", which was first described by Ivan Pavlov (1927) as one form of internal inhibition of conditioned reflexes, apart from *extinction* and *delay* (the latter means that the conditioned stimulus and reinforcement are presented with a longer interval). Pavlov described "conditioned inhibition" as a combination of the previously established positive conditioned stimulus (CS with positive reinforcement) and an additional, neutral stimulus, presented simultaneously without reinforcement. The additional stimulus, therefore, acquired the properties of an inhibitory stimulus. Pavlov stated that the establishment of conditioned inhibition depended on the "time relations between the applications of the two stimuli".

In 1969, Robert Rescorla described two techniques for identifying a stimulus as a Pavlovian conditioned inhibitor. The first one, *summation*, requires that a stimulus, when presented in combination with a positive conditioned stimulus, produces a reduced response compared with the response to the positive stimulus alone. The second procedure, *retardation-of-acquisition*, consists of the impedance of the acquisition of excitatory properties by the inhibitory stimulus.

In the context of aversive stimuli, conditioned inhibition was named "safety learning" and the inhibitory stimulus was termed "safety stimulus" (Walasek et al., 1995). Safety learning is also based upon associative learning processes, however in contrast to fear conditioning and extinction, it consists in the *negative* correlation between these two stimuli *from the offset*: the CS predicts the *non-occurrence* of the aversive US and for this reason, it is called a "safety stimulus".

Although fear extinction is the most studied form of fear inhibition, the safety stimulus has particular properties that the extinction context does not, for instance by reducing immobility and anhedonia in mice, which has been interpreted as antidepressant effects by the authors of the study (Pollak et al., 2008) (see also section on Depression below). Safety learning and extinction are therefore clearly distinct processes. In the following sections, we will focus on safety learning, as the concept which has received only limited scientific attention.

Similar to the transfer of conditioned fear, safety stimuli can inhibit fear in a novel context, where the safety conditioning itself did not occur (Denniston et al., 1998). For instance, as an auditory cue, the safety stimuli increased exploratory behavior of mice in the open field and led to subjects' preference for a neutral room (different from the safety-conditioning chamber) where the safety stimulus was heard, compared to a neutral room where no such cue occurred (Rogan et al., 2005).

A safety stimulus, therefore, represents more than just the absence of danger, or "meaninglessness", as it was suggested in initial studies (Best, 1975), but it is rather associated with the presence of *protection* from danger, comparable to the shelter or home cage (Rogan et al.,

2005) in mice. Its presence leads to an increase of exploration and appetitive behaviors, such as pressing a bar for food (Rogan et al., 2005; Walasek et al., 1995).

The experimental coupling of former neutral cues with a safety association has successfully been done in rodents subjected to light signals (Christianson et al., 2012), suggesting that such basic associations could be investigated in humans as well. On a neural level, the available data (Likhtik et al., 2014) suggest that rather than being involved exclusively with fear, amygdala-driven processes might also be integral in the processing of safety stimuli. However, exactly in which way social cues can act as safety stimulus in healthy humans and the dynamics of the relevant neuroendocrine systems underlying this process are yet to be determined.

Emerging studies (Jovanovic et al., 2012; Jovanovic et al., 2014) by clinical groups have indicated that safety learning, at least towards non-social signals, is deficient in traumatized patients and hence impaired safety learning might be a risk factor for anxiety-related disorders.

3.1. Social fear and safety learning

A very important aspect of emotional learning is learning associations with social stimuli. Studies have shown that using social stimuli (e.g. faces) in contrast to non-social stimuli (e.g. houses) elicited both specific fear and safety responses in human subjects (Hornstein et al., 2016; Olsson et al., 2005). Above this, social stimuli seem to be learned more easily than non-social stimuli (reviewed by Adolphs, 2008), which can be interpreted in terms of preparedness.

4. Parallels between safety learning, fear learning, and preparedness

Interestingly, in emotional learning, there are certain associations which are more easily learned than others. For example, fear of stimuli related to survival (such as snakes, spiders, and heights) is much more common and much easier to induce in the laboratory than other kinds of fears (such as fear of cars) although they constitute a much greater danger in modern lives. Taste aversions in general are learned very quickly and efficiently, as compared with other kinds of conditioning senses. The concept of the so-called “preparedness” postulates that fear learning is preferentially performed in aversive contexts by stimuli that are fear relevant from an evolutionary perspective (Ohman and Mineka, 2001).

Research on the basic mechanisms of fear learning has shown that fear stimuli with a social content can lead to specific findings as compared to non-social stimuli (Olsson et al., 2005; Olsson and Phelps, 2007). One interesting finding is that learned fear is more persistent if the feared stimulus is a member of another racial group and therefore less familiar (Olsson et al., 2005). However, this race-bias in fear is attenuated if a person has an individual history of romantic dating with a person from this group. It can, thus, be followed that the repeated positive contact might have been learned as a safety association with a person from this group.

In parallel with the preparedness to fear, some stimuli may act in a sense of preparedness for safety. For example, in the presence of physical pain, viewing the romantic partner results in an activation of the medial prefrontal cortex along with a decreased subjective sensation of pain (Eisenberger and Cole, 2012; Eisenberger et al., 2011). The authors interpreted these activation patterns and behavioral responses as learned safety associations. However, although it makes sense that an attachment figure provides a feeling of safety, how exactly this social safety association is formed on a neurobiological and self-referential level is not well understood. In a very recent phenomenological studies, it was suggested that social support figures are less likely to function as learned fear stimuli (i.e. opposite to preparedness for fear) and more likely to act as inhibitors of fear (Hornstein and Eisenberger, 2017; i.e. serve as learned safety stimuli; see Hornstein et al., 2016).

4.1. Social learning by observation

Another central concept within the area of social learning is learning by observation of another person's actions and experience (see the pioneering work of Bandura, 1962, 1978). Learning associations of stimuli with emotional content (Golkar et al., 2016; Olsson and Phelps, 2007), pain (Jeon et al., 2010) and also actions (Fuhrmann et al., 2014; Monfardini et al., 2013) by observation of a conspecific primate or rodent, activate very similar neural networks as the direct individual learning and result in similar behavior. One possible mechanism to mediate such learning by observation might be the activation in the mirror neuron system (as studied by Fuhrmann et al., 2014; Perry et al., 2010), but effects of OXT in mice or of endogenous opioids in humans have been studied as mediator of observational learning as well (Haaker et al., 2017; Pisansky et al., 2017). In animals, e.g. in mice, the synchronized activity of the anterior cingulate and the amygdala is necessary for successful observational learning of pain associations (as shown by Jeon et al. (2010). Furthermore, learning by observation is also associated with individual human traits for social behavior such as autism traits of empathic abilities (Kleberg et al., 2015). It seems plausible and there is also emerging data to support the notion that safety learning in this context follows the same principles as fear learning (Golkar et al., 2015). Seeing somebody calm down in a specific context, or the mere presence of a close person in an aversive context, will very likely result in oneself feeling safe.

Remembering signals for safety, even non-verbal signals, is likely to help to avoid danger and to recognize a supportive conspecific (for review see Adolphs, 2003; Olsson and Phelps, 2007). In this line, adequate learning and memory of safety stimuli in a social context is possibly one central motivator to repeatedly seeking social contacts. While parents acting as a safety signal for their child might be a rather obvious example, this could also be true for adult couples or close friends.

5. Neural basis of safety learning

There is a large overlap between brain regions associated with safety learning and the neural fear circuitry, presumably because there rarely is safety learning without the *expectation of danger*. Based on the previous literature (Kong et al., 2014; Ochsner et al., 2009) about the neural processing of danger stimuli, which will be described in the following sections, it is plausible to expect that the presence of a safety signal will trigger a down-regulation of amygdala activity through the input of the prefrontal cortex (PFC) and the hippocampus.

5.1. The amygdala

The **amygdala** controls emotional processing, social behavior and danger detection, among a wide range of functions (reviews by Janak and Tye (2015); Phelps and LeDoux (2005). Its lateral (the primary sensory input site) and basal parts are involved in fear learning and its central nucleus (CeA) in the motor component of fear expression (for review, see LeDoux, 2000). Distinct dangerous stimuli are processed differently in the brain: as a summary, in fear conditioning to an auditory cue, inputs coming from either the auditory thalamus or the auditory cortex reach the lateral amygdala (LA), an area of convergence of CS and US information, whereas contextual fear conditioning, in which a chamber becomes CS, involves activation of both the amygdala and the hippocampus (for review, see LeDoux, 2003).

5.2. The prefrontal cortex

One important region for learning processes is the **prefrontal cortex (PFC)**, which, together with the amygdala, is a key structure for top-down and bottom-up emotion generation. Each of the two processes has its respective neural base: top-down responses are mainly

characterized by the activation of the prefrontal cortex, an area responsible for higher levels of cognitive interpretation, whereas bottom-up emotion generation activates mostly the amygdala and is related to the processing of perceptual and affective properties of stimuli (for overview see LeDoux, 2000); Ochsner et al., 2009). This prefrontal cortex-amygdala circuit is also crucially involved in fear extinction (for review, see Akirav and Maroun, 2007).

In humans, each PFC subdivision also exerts different effects on safety learning: e.g. the dorsolateral prefrontal cortex (DLPFC) is assumed to control the amygdala via projections to the ventromedial prefrontal cortex (VMPFC) (studies by Delgado et al., 2008; Jovanovic et al., 2013). This connectivity determines the intensity of anxiety in humans: at rest, subjects with high anxiety show negatively correlated amygdala and VMPFC activations, whereas individuals with low anxiety exhibit positive correlations between these regions (studied by Kim et al., 2011). In vicariously transmitted fear inhibition, the modulation of learned fear from extinction to the reinstatement phase was associated with a temporal shift in VMPFC activity in humans (Golkar et al., 2016). Furthermore, as previously mentioned, viewing attachment figures while receiving painful stimulation leads to reduced pain ratings, reduced pain-related neural activity and increased activation of VMPFC (Eisenberger et al., 2011), indicating involvement in safety signaling as well.

5.3. The hypothalamic pituitary adrenal axis and the sympathetic nervous system

On a neuroendocrine level, the anxiety and stress response is mediated by hormones of the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS). Both systems have their origins in the brain and from there under a regulated feedback send signals to the periphery (e.g. muscles, intestines, peripheral organs). More specifically, the HPA axis is characterized by the release of glucocorticoids from the adrenal cortex after an increase in blood levels of adrenocorticotropic hormone (ACTH), which is released by the anterior pituitary gland in response to the corticotropin-releasing hormone (CRH) from the hypothalamus (Bear et al., 2007). Several studies show reduced HPA axis stress responses in the presence of safety stimuli, for instance after social support, e.g. safety stimuli in both animal studies (Tuchscherer et al., 2016; Vogt et al., 1981) and in human studies (Apter-Levi et al., 2016; Tarullo and Gunnar, 2006).

6. Central nervous oxytocin signaling

Oxytocin (OXT) is an evolutionarily conserved neuropeptide which serves as a neuromodulator in the brain and as a hormone in the body (Meyer-Lindenberg et al., 2011). The central OXT system is composed of specialized neurons allocated in the hypothalamic nuclei, which widely project their axons through the forebrain and hindbrain regions (see Fig. 2). The axonal OXT release is now considered (Chini et al., 2017) as the most efficient mechanism of OXT signaling in the adult brain.

7. Oxytocin, fear- and safety-learning

During the past two decades, OXT has been the target of numerous studies exploring its role in social cognition and emotional learning see overviews by Eckstein and Hurlemann (2013); Grinevich et al. (2016). Early research was able to show that intranasal OXT facilitates learning with social feedback (Hurlemann et al., 2010) and memory for social contents (Unkelbach et al., 2008) on a behavioral level. Despite ongoing debates (Andari et al., 2017) on efficiency of passage of exogenous OXT through the blood brain barrier, these reports demonstrated that OXT impacts particularly social cognition and salience of social stimuli (as summarized by Bartz et al., 2011). In recent years, animal (Brill-Maoz and Maroun, 2016) and human studies (Cavalli et al., 2017; Eckstein et al., 2014a; Eckstein et al., 2016) showed that exogenous and endogenous OXT affects both basic fear learning and fear extinction processes, especially in a social context.

Furthermore, OXT has anxiolytic and stress-dampening effects when combined with social support, i.e. a safety signal (studies by Eckstein et al., 2014b; Heinrichs et al., 2003). In a most recent study investigating resting state brain activity, it has been shown that in fact the connectivity of limbic emotion regulation networks with specific amygdala subnuclei and prefrontal cortex is modulated by OXT (Eckstein et al., 2017): OXT increases connectivity of the centromedial and basolateral amygdala subregions with the cerebellar regions and also increases connectivity of the superficial and basolateral subregions with the prefrontal cortex. In addition, OXT decreases connectivity of the centromedial subregions with core hubs of the emotional face processing network in temporal, occipital and parietal cortical regions.

Our findings about OXT effects, fear learning and fear extinction (Eckstein et al., 2016) indicate that OXT enhances basic emotional learning processes (both acquisition and extinction of an emotional content) while simultaneously decreasing pain experiences. In addition, the functional connectivity within the neural emotion network is modulated by OXT in correlation with preclinical measures of depression and anxiety in a sense that modulatory effects of OXT are strongest in individuals with the least clinical load (Eckstein et al., 2017). Altogether, in humans, OXT influences neural and physiological learning (Eckstein et al., 2014b) as well as processing of danger and ambivalent visual social stimuli (Preckel et al., 2014).

It is important to note that anxio*genic* and stress-*promoting* effects of OXT in humans have been reported as well (Eckstein et al., 2014b; Grillon et al., 2013; MacDonald et al., 2013). These effects occurred especially in unsafe contexts and unfamiliar social environments or aversive laboratory settings. However, in combination with the data cited above, it is plausible that rather than acting as an anxiolytic per se, the effect of OXT depends on the safe context, suggesting that OXT might modulate perceived safety. Perceiving safety, in turn, has probably been learned during the individual's lifespan. Every positive contact with other persons, such as consoling or supporting friends and partners, might be interpreted as repeated exposure to a stimulus of perceived safety. From this perspective, understanding the anxiolytic properties of OXT would require a deeper understanding of OXT's impact on safety learning.

This notion is in line with OXT's involvement in attachment and romantic relationships. Specifically, OXT was shown (Ditzen et al., 2012; Ditzen et al., 2009; Kreuder et al., 2017) to improve positive affective behavior in romantic couples. In general, social touch and emotional and physical intimacy between partners play crucial roles in coping with negative effects (as shown by Ditzen et al., 2007). These social buffering effects became evident in peripheral psychophysiological measures and were assumed to be mediated through brain OXT mechanisms for review see Ditzen and Heinrichs (2014); Hurlemann and Scheele (2016). Studies with voles added further evidence indicating a key role of OXT in social buffering (Burkett et al., 2016; Smith and Wang, 2014).

With regard to social learning, the work by Engert et al. (2014) provided evidence that a transmitted emotional response in observers, examined as an increase in heart rate, is dependent on the emotional closeness between the stimulus person and the investigated subject. Likewise, it was shown that the stress-buffering effects of spousal handholding vary as a function of marital quality (Coan et al., 2006).

7.1. Oxytocin and CNS-mediated learning processes

The **amygdala**, especially its central nucleus (CeA), contains a high density of OXT receptors and axonal projections from OXT neurons (neuroanatomically studied by Boccia et al., 2013; Smith et al., 2017; Sofroniew, 1980). Endogenous OXT released into the CeA of rats induced by optogenetic stimulation decreased freezing responses in fear-

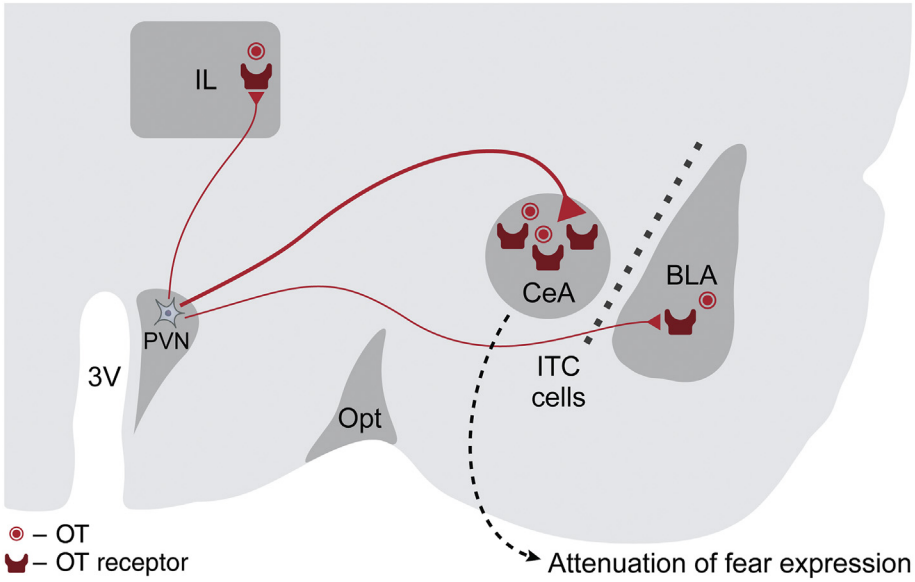

Fig. 2. Representation of OXT receptors distribution and axonal OXT projections from the PVN to extra-hypothalamic regions of rat brain involved in safety learning. The CeA contains higher number of OXT axonal terminals and OXT receptors, compared to the IL and BLA. The depicted brain areas, which are involved in the OXT-dependent fear attenuation, also mediate safety learning. Abbreviations: **3V**, 3rd ventricle; **BLA**, basolateral nucleus of the amygdala; **CeA**, central nucleus of the amygdala; **IL**, infralimbic cortex; **ITC**, intercalated cells; **Opt**, optic tract; **OT**, oxytocin; **PVN**, paraventricular nucleus. The representation of OXT axons and OXT receptors is in accordance to Knobloch et al. (2012), Nair et al. (2005) and Smith et al. (2017).

conditioned female rats (Knobloch et al., 2012). Additionally, an exposure of rats to swim stress caused OXT release, precisely within the CeA (Ebner et al., 2005).

Safety learning in relation to OXT has only been studied limitedly so far. In the only study on safety learning in mice, the in vivo electrophysiological recording of the lateral nucleus of the amygdala showed that safety conditioning decreased slope and amplitude of the CS-evoked field potential, thereby attenuating activity of this nucleus (Rogan et al., 2005). Moreover, in a study with rats, synapse size of LA decreased after safety learning, while it increased after fear conditioning (Ostroff et al., 2010). Lesioning the CeA in rats, however, was not sufficient to impair discrimination between safety and danger signals, although this led to reduced fear expression to both types of stimuli (Falls and Davis, 1995).

In contrast to the CeA, the **PFC** in rodents has relatively low density of OXT receptors and OXT fibers (shown by Smith et al., 2017). However, the microinfusion of synthetic OXT or its agonist into the infralimbic (IL) cortex – likely a homologue of the human ventromedial PFC (as discussed by Barker et al., 2014; Wallis, 2012) - facilitates fear extinction in conditioned rats (Lahoud and Maroun, 2013). In congruency, inactivation of the same cortical region impaired discrimination between safety and danger signals in rats (Sangha et al., 2014). In line with this observation, fear-conditioned rats with high IL neuronal responses to tone during fear extinction showed less freezing behavior than rats with a lower IL response (Milad and Quirk, 2002). Taken together, the emerging rodent studies underline the role of IL cortex in fear inhibition, both due to safety learning and fear extinction (see Fig. 3).

A large body of research indicates that OXT interacts with other neurotransmitters and hormonal systems, including gonadal hormones, rather than acting independently. Importantly, OXT significantly inhibits **HPA axis activity** at central and pituitary levels in response to stress (reviewed by Hostinar et al. (2014); Romano et al. (2015) and, in consequence, reduces cortisol levels. More specifically, OXT suppresses basal and stress-induced ACTH and glucocorticoid release in rats, although this outcome may depend on the neural region studied and the animals' state of activity (Neumann, 2002; Neumann et al., 2000a; Neumann et al., 2000b). Conversely, in rats, exposure to different types of stressors, such as the confrontation with a dominant conspecific (social defeat), shaker stress, osmotic stressor (administration of hypertonic saline) and immobilization triggers the release of intrahypothalamic and plasma OXT (Engelmann et al., 1999; Ježová et al., 1993; Nishioka et al., 1998). Results obtained in human studies remain controversial as data are mixed and, in some studies, psychological and social stress induced peripheral OXT release (de Jong et al., 2015; Pierrehumbert et al., 2010; Sanders et al., 1990), while in others it did not (e.g. Ditzen et al., 2007). Less is known about the interaction of OXT and SNS-outcomes, such as norepinephrine or epinephrine release (see mixed results in human studies by Burri et al., 2008; Grewen and Light, 2011).

Non-human studies demonstrated that **estrogens** are not only directly involved in OXT synthesis and its receptor (OXTR) expression (Dellovade et al., 1999), but also modulate the effects of OXT on social behavior (Caldwell et al., 1986) and social recognition (Choleris et al., 2004) and enhance the anxiolytic effects of OXT (McCarthy et al., 1996). Human research investigating the modulatory role of estrogens on OXT is scarce at this point. However, there is some evidence for the interaction between steroid hormones and OXT. For example, plasma OXT levels in women differ along the menstrual cycle, being higher around the time of ovulation when estrogen levels are the highest (Kumaresan et al., 1983; Salonia et al., 2005, although other studies failed to find any variation during the menstrual cycle, Feldman et al., 2010; Weisman et al., 2014). There are recent studies that report sexually dimorphic effects of OXT in various domains, including approach/avoidance behavior (Preckel et al., 2014; Scheele et al., 2012), amygdala reactivity (Domes et al., 2010), social cognition (Gao et al., 2016; Hoge et al., 2014), and moral decision-making (Scheele et al., 2014). These data suggest that naturally occurring higher levels of estrogens in females and testosterone in males might be involved in the sex-specific behavioral effects (Ditzen et al., 2012). Indeed, hormonal contraception was found to alter the OXT effects on reward-associated brain responses to the face of the romantic partner (Scheele et al., 2015; Scheele et al., 2013). Furthermore, opposite effects of testosterone to those of OXT on human social cognition and behavior have been hypothesized (Crespi, 2016). Thus, in order to understand the effects of OXT on social safety learning, it would be essential to further study sex differences and the interaction with gonadal hormones.

7.2. *The influence of context*

The HPA axis activity, however, varies according to timing, stressor and person features (for review, see Miller et al., 2007). Similarly, the effects of OXT, supposedly acting through anxiety reduction, perceptual selectivity and affiliative motivation, also depend on situational factors (e.g. task set difficulty, stimuli valence or opponent familiarity) as stated above (Bartz et al., 2011).

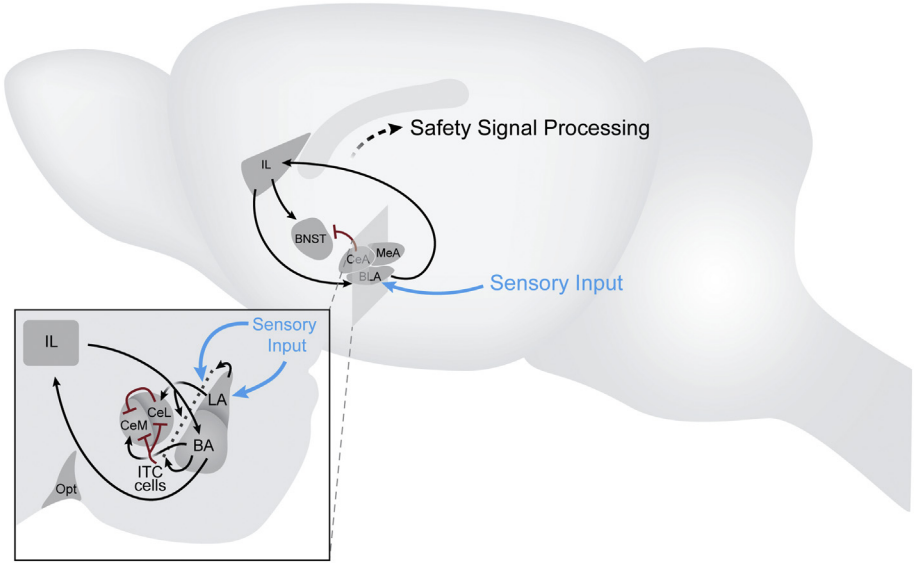

Fig. 3. The neural circuitries underlying safety learning in the rodent brain. As depicted, the BLA receives sensory input from the safety signals, then relays information to other nuclei of the amygdala as well as to the IL. In turn, the IL controls the activity of the BNST and amygdala in a top-down manner. Black and red arrows depict excitatory and inhibitory projections, respectively. The coherent activity of excitatory and inhibitory circuits leads to the reduction of fear expression mediated by the output from the CeM to the brainstem in the presence of safety signal. The inset shows the detailed connections between the nuclei of the amygdala and IL. Abbreviations: **BA**, basal nucleus of the amygdala; **BLA**, basolateral nucleus of the amygdala; **BNST**, bed nucleus of stria terminalis; **CeA**, central nucleus of the amygdala; **CeL**, lateral subdivision of CeA; **CeM**, medial subdivision of CeA; **IL**, infralimbic cortex; **ITC**, intercalated cells; **Opt**, optic tract. The schema was composed based on works of Kong et al. (2014), Pape and Pare (2010), and Tovote et al. (2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Examples of such contextual and individual factors, moderating OXT effects on social buffering in humans, are provided by data showing that intranasal OXT creates intergroup bias while pronouncing intra-group preferences (De Dreu et al., 2011). In the Coordination Game, for example, intranasal OXT increased cooperation between participants that had prior contact with each other, but reduced cooperation when they were unacquainted with each other (Declerck et al., 2010). Furthermore, OXT promoted trust and cooperation in healthy participants in the Assurance Game, but had the opposite effect in individuals with borderline personality disorder. In a recent study, intranasal OXT was found to increase charity donations in participants scoring low on xenophobic attitudes, while in participants with higher levels of xenophobia this effect was only observed if the OXT treatment was paired with peer-derived altruistic norms (Marsh et al., 2017). Therefore, OXT may promote social safety learning depending on the available social information, individual differences, and individual learning-history.

8. Clinical applications

The correct discrimination between safety and danger and the consequent ability to find rest in the presence of safety are crucial for mental health. When safety learning is impaired, it may lead to maladaptive behavior, chronic stress and mental disorders. Research in humans and animals has provided evidence that deficient safety learning is directly involved in Posttraumatic Stress Disorder (PTSD) and Depression.

8.1. Posttraumatic stress disorder

The most prominent example for fear conditioning and its consequences for psychopathology are trauma and post-traumatic stress responses to traumatic stress. According to the American Psychiatric Organization (APA) (2013), posttraumatic stress disorder (PTSD) is characterized by specific long-term reactions to trauma, including intrusive thoughts, negative thoughts and feelings, arousal and – as a consequence – avoidance of trauma-associated stimuli.

Different threat-related processes (and their deficits) were considered as underlying mechanisms of the disorder, such as fear conditioning, habituation (the decreased response after several US-CS pairing presentations) and extinction (for review, see Liberzon and Sripada, 2008; Rauch et al., 2006), which could potentially explain hypervigilance and hyperarousal. Impaired safety learning was also discussed as a potential explanation for PTSD symptoms, precisely for the inappropriate fear response in the presence of safety. In a human paradigm (Jovanovic et al., 2009), for instance, PTSD patients with high symptom load were not able to adequately discriminate between danger and safety stimuli, in comparison to patients with low symptom load or healthy controls. Moreover, PTSD is associated with increased amygdala activation (in response to potentially harmful stimuli, in the presence of emotionally expressive face stimuli or traumatic event reminders, or during fear acquisition) and decreased activation of areas associated with higher cognitive functions, such as the PFC, when exposed to traumatic event reminders or during fear extinction (studied by Bremner et al., 2005).

As a potential link between OXT and safety learning, Olff et al. (2013) reported that participants with PTSD who had experienced child maltreatment showed the highest levels of peripheral OXT, in comparison to those who had no history of maltreatment. This result led the authors to suggest that increased peripheral OXT could serve as a marker for the need of social affiliation (as proposed by Taylor, 2006), and that the combination of PTSD and childhood maltreatment could be related to particularly high levels of interpersonal distress and disconnection. In line with this, PTSD patients who received OXT intranasally showed decreased physiological responses during a personal combat imagery task (Pitman et al., 1993), normalized neural connectivity (Koch et al., 2016) and, in another study, intranasal OXT reduced anxiety and irritability, improved mood and lowered the intensity of recurrent thoughts about the traumatic event, in comparison to a placebo condition (Yatzkar and Klein, 2010).

Altogether, these studies suggest that OXT is a potential therapeutic agent to attenuate PTSD symptoms. Importantly however, higher doses of intranasal OXT may not necessarily produce better clinical outcomes: A recent functional magnetic resonance imaging kinetic study showed that 24 IU of OXT dampened amygdala responses to fearful faces in healthy men, while 48 IU of OXT had the opposite effect (Spengler et al., 2017).

8.2. Depression

Although the literature about safety learning is mostly linked to the study of fear, safety stimuli have also been considered a form of “behavioral antidepressant”. In safety-conditioned mice, safety stimuli reduced immobility in the forced-swim test and anhedonia caused

unpredictable chronic mild stress in the sucrose preference test (Pollak et al., 2008). Moreover, hippocampal neurogenesis, which is associated with the etiopathogenesis of major depression (Lee et al., 2013; Sahay and Hen, 2007), when ablated, impaired safety learning and inactivated the antidepressant effect of a safety signal (Pollak et al., 2008). Furthermore, safety stimuli had a reward value during a "CS-room preference" study in mice: in a room where the safety signal was heard, mice spent 80% of the time (on the following day of exposure), and only 20% in the room where no sound was presented (Rogan et al., 2005). As another potential association of OXT and safety learning in depression, the depressed patients with the highest scores in the Hamilton Depression Rating Scale (HDRS) had the lowest levels of plasma OXT, suggesting a strong association between OXT and mood in general (Scantamburlo et al., 2007, but see also Parker et al., 2010).

9. Outlook

In conclusion, in parallel to social fear learning (Olsson et al., 2005), animals and humans seem to be prone to social safety learning, and these processes are naturally enhanced through the experience of social resources from early on. In line with this in humans, reduced threat-related responses have been found to result from social interaction and social support (see for reviews, Ditzen and Heinrichs, 2014; Feldman, 2012). Social support and bonding in turn are known to be modulated by OXT. Therefore, it seems plausible to assume that OXT is involved in the long-term effects of social integration and repeated social support — experiences that serve as safety stimuli and modulate central and peripheral threat responses. From a psychotherapeutical or psychopharmacological perspective, this might have implications for the use of OXT as an augmentation treatment for learning based interventions, which include social resources (such as couple or family interventions). Notably in this context, differentiating between fear-extinction and initial safety learning may provide important insights into whether or when OXT might be of help: Many patients with psychiatric illnesses have experienced adverse (early) life social interactions and here the neural mechanisms of social fear extinction processes are relevant. In contrast, safety learning processes might explain why OXT had prosocial effects in studies with healthy participants and populations without major social impairment.

In this review, we have reviewed both the animal and human literature on safety processing and OXT and find parallels in species but also divergent findings due to the complexity of different species' neural systems and behaviors (for reviews, see Boll et al., 2017; Neumann and Slattery, 2016). With the advanced methods of optogenetic triggered OXT release in animals (Grinevich et al., 2016) and pharmacological brain imaging during complex behaviors in humans (Eckstein et al., 2014b), we are now able to design powerful translational studies in order to gain an elaborate insight into the neurobiological basis of safety learning and the inhibition of fear.

There are indications that the underlying neurobiological system is not only a single substance but rather an interacting system of many transmitters. For example, dopamine (DA) is known for its role in the pathophysiology of PTSD and depression (overview at Enman et al., 2015). Very novel data show that OXT stimulates DA neurons of the ventral tegmental area (Charlet and Grinevich, 2017). Since the administration of DA or its agonists to human patients may cause long-known and broad aversive side effects, the stimulation of DA signaling via OXT administration could be profitable for the treatment of PTSD and depression, in which both OXT and DA play significant roles. Thus, translational studies applying external OXT and the subsequent monitoring of the activity of the DA system, especially in primates, are required. In addition, serotonin (5-HT) is an agent involved in social bonding processes and interacts with OXT to mediate the rewarding properties of social contact (as shown by Dolen et al., 2013).

In conclusion, accumulating results suggest OXT effects on social behavior, stress-attenuation and interactions with gonadal hormones and the DA and 5-HT systems. These data point to a potential role of the OXT system as a promising therapeutic agent in major depressive disorders and in the chronic stress elicited by an impaired discrimination between safety and danger. To dissect the precise role of OXT in safety processing, we aim for future translational research in humans, primates and rodents with a broad methodological spectrum. The results would be of high relevance for clinical applications and might help to better understand how social relationships can improve individual health: through learned calm and safety from harm in the presence of others.

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Author contributions

A.A.M., M.E., D.S., and A.K. collected and preprocessed the existing literature, A.A.M., M.E., D.S., A.K., R.H., V.G. and B.D. wrote the paper.

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