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Odor-induced recall of emotional memories in PTSD-Review and new paradigm for research

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Review Article

Odor-induced recall of emotional memories in PTSD–Review and new paradigm for research

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ABSTRACT

It is clinically well known that olfactory intrusions in PTSD can be a disabling phenomena due to the involuntary recall of odor memories. Odorants can trigger involuntary recall of emotional memories as well have the potential to help diminishing emotional arousal as grounding stimuli. Despite major advances in our understanding of the function of olfactory system, the study of the relation of olfaction and emotional memory is still relatively scarce. Odor memory is long thought to be different than other types of memories such as verbal or visual memories, being more strongly engraved and more closely related to strong emotions. Brain areas mediating smell memory including orbitofrontal cortex and other parts of medial prefrontal cortex, hippocampus and amygdala, have been implicated in learning and memory and are part of a neural circuitry that is involved in PTSD. The olfactory cortex itself also plays an important role in emotional processing. Clinical observations support the notion that odor-evoked memories can play a role in the symptomatology of PTSD. This paper reviews a re-emerging body of science linking odor processing to emotional processing in PTSD using the calming and grounding effect of odors as well as the use of odors in augmented exposure therapy. This results in converging evidence that olfaction is an excellent model for studying many questions germane to the field of human emotional memory processing.

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1. Introduction

Odors have the ability to remind us of a far distant past, evoking a strong emotive connotation. A particular perfume or a specific scent can instantly conjure up long-forgotten scenes and emotions from the past. These so called odor-evoked memories can bring a person back to a specific time and context (Engen et al., 1973). This ecphory occurs when the recall of a past event is cued by a trigger, such as an odor. It is a central component of autobiographical memory, which allows us to travel mentally back in time and re-experience specific events from one's personal past. The most cited and famous anecdotal report of an odor serving a powerful cue for memory retrieval stems from Marcel Proust's recollection of the home of his aunt following the smell of a Madeleine that he had soaked in his tea (Proust, 1954). The power of odors to 'unlock' human emotion and memory has been celebrated in literature and popular anecdotes. It was a long held belief that magic to be maximally effective, must gain entrance through the nose (Malinowski, 1929). This so called "Proustian" view holds that odor memory is excellent for odors associated with significant autobiographical experiences. The relationship between olfaction and autobiographical memories appears to be stronger when the experiences are more significant and emotionally charged. Moreover, this relationship suggests that odors are more closely connected to affect and emotion than are other sensory experiences. While an abundance of animal studies have supported these notions, there is still little human empirical research and an almost complete absence of clinical studies in this field. Almost all human studies published to date pointed to the capacity for odors to serve as context cues, which are thought to underlie the formation and retrieval of content-dependent odor-evoked autobiographical memories.

Specific trauma-related smells (for example blood, napalm, diesel) have long been noted by clinicians to be precipitants of anxiety and fear-related memories in patients with posttraumatic stress disorder (PTSD) (Kline and Rausch, 1985, Vermetten and Bremner, 2003). Although odor stimulation can access limbic brain areas in as few as two synapses (Gottfried and Zald, 2005), odorants have rarely been introduced as probes for traumatic recall. Few papers report about this phenomenon and the prevalence of olfactory intrusions has not been studied systematically. On the other hand, it has become a clinical staple to use smells in exposure settings to keep patients grounded and re-orient them in case of strong intrusions or dissociative reactions.

Upon being exposed to the smell of diesel, a 28-year old woman, let's call her Jenny, reported a memory of herself waiting at a gas pump on way to school. It was hot, she was impatient, and she was hearing her sister's radio playing. The memory dated 10 years back and had little impact on her current emotional state. The same smell presented to a 54-year old Vietnam veteran, Jack, brought back a series of war scenes, and one scene in particular in which dead bodies were burnt using diesel. This recall upset him and made him anxious. Jenny reported the memory did not bother her, and that she had thought about it maybe a total of 5 times in her adult life. Jack, the veteran, had been bothered frequently by the smell and often could not get the associated picture out of his mind or the smell out of his nose. Since the war, he had tried to avoid places where he knew he otherwise would be exposed to diesel; he avoided gas stations and on the highway tried to stay away from trucks (see Vermetten and Bremner, 2003). These clinical examples illustrate that smells can elicit differential responses, varying from simple ecphory to high levels of emotional arousal that most likely are based upon prior experience.

The goal of this review is to revisit the literature on smell and memory, looking at plasticity of neural circuits subserving olfaction in emotion processing, recall of autobiographical memories by an odor, and review the importance of olfaction in trauma related disorders, in specific PTSD. An effort is made to link existing studies on memory for odors with current cognitive neuroscience and apply this to an understanding of the neural circuitry involved in olfactory memories. Finally, this review describes a new model for olfactory memory in PTSD providing a basis for olfactory experimentation as well as a novel use of odors in augmented exposure therapy for PTSD.

2. Why study olfaction and memory in trauma-related disorders?

The study of mechanisms for smell memory can provide insight into mechanisms of human emotion that can be applicable to both the understanding of normal emotions as well as mental disorders involving pathological emotional processing. PTSD is a disorder of particular interest since one of its psychobiological mechanisms involves failure of extinction of fear-conditioned emotional or traumatic reminders (Vermetten and Lanius, 2012, Yehuda et al., 2015). Odor memory is particularly relevant since it is strongly engraved and closely linked to intense emotions. In this respect it is different from other types of memories (such as visual and auditory memory). The olfactory function does not automatically engender verbal and/or visual representations, but is more likely to be evocative of affective states and significant episodes.

As researchers in the field of olfaction have noted there is a need for integration of preclinical findings stemming from animal studies with knowledge resulting from human cognitive sciences and clinical practice (Dudai, 1997a, b, Eichenbaum et al., 1983, Schab, 1991, Schab and Crowder, 1995, Schacter, 1996). In contrast to the extensive empirical literature on cognitive processing of verbal and visual memory, relatively few studies have examined olfactory memory in trauma-related disorders. Few studies have examined memory for odors per se, and the role of olfaction in emotional or traumatic memories (Vermetten and Bremner, 2003). An information processing approach commonly employs auditory and visual stimuli for the assessment of perception, and despite the fact that these involve similar processes as seen in olfactory memory (processing, encoding, consolidation, and retrieval), olfaction is rarely used to investigate them (Köster, 2005). This is interesting since it has long been known that the addition of a salient, olfactory cue during learning and retrieval facilitates recall over and above the presence of constant environmental cues (Morgan, 1996). To test the hypothesis that odors are the 'best' cues to memory, a series of cross-modal experiments have been conducted in which odors were compared with verbal, visual, tactile and musical stimuli as associated memory cues. In one study conducted by Herz (1998), odors were equivalent to other stimuli in their ability to elicit accurate recall, but odor-evoked memories were consistently rated as more emotional. Testing the hypothesis that emotional potentiation could be a key variable in the formation of odor-associated memory, Herz (1997) conducted a study in pre-exam students. She added a distinctive ambient odor (violet leaf 10%) in anxious and neutral mood during encoding. She found that word recall was higher in those groups where an ambient odor cue was available during both encoding and retrieval than in groups where no ambient odor was present. More importantly, subjects who were anxious during encoding and had an odor context cue available recalled significantly more words than subjects in any other group.

The results indicated that emotional potentiation could be a key variable in the formation of odor-associated memories. In conjunction, these data also suggested that heightened emotion experienced during encoding with an ambient odor could enhance the effectiveness of an odor as a cue to memory. Obviously, these studies are of great relevance to odor-induced recall of emotional memories in the clinical domain of patients suffering from PTSD.

3. Neural pathways in olfactory processing

In the last decade much progress has been made in understanding the function of the olfactory systems with important insights into the neural substrates of olfactory processing explaining how the brain recognizes and discriminates odors (for a review see [Lledo et al., 2005](#)). The olfactory system sits at the interface of the environment and the central nervous system. It is responsible for correctly coding sensory information from a wide range of odorous stimuli. To accomplish this, odor information has to be processed throughout distinct levels. Before reviewing the neural systems involved in olfactory processing we will first review the neural pathways.

The sense of smell is carried by olfactory receptors that lie deep within the nasal cavity. In humans, the receptors are confined to a specialized olfactory epithelium. This epithelium contains three types of cells: receptor cells as well as supporting and basal cells. The receptor cells are themselves bipolar neurons that have a short peripheral process and a long central process. The short peripheral process extends to the surface of the mucosa, where it expands into a small knob that gives rise to several cilia. These cilia form a dense mat at the mucosal surface and are thought to interact with odor-producing molecules. The longer central process, an unmyelinated axon, runs from the nasal cavity to the olfactory bulb. Three hundred fifty different olfactory receptors were identified in the human genome ([Zhang et al., 2007](#)), which is considerably less than the 1,100 different receptors expressed by rodents, likely reflecting a reduction of evolutionary pressure as humans depend less on olfaction for survival. However, the olfactory receptor genes represent one of the largest gene families in the human genome and in addition a single odorant may also bind at several receptors ([Malnic et al., 2004](#)).

The olfactory receptors have a turn-over of 60 days, formed from precursor basal cells. The olfactory neurons are capable of mitotic division in adult life. Neuroblasts differentiate into interneurons after having migrated from the subventricular zone into the olfactory bulb ([Whitman and Greer, 2009](#)). A newly formed dendrite will migrate toward the mucosal surface and its axon in the opposing direction to synapse appropriately in the olfactory bulb.

The olfactory bulb consists of five layers ([Shepherd, 1972](#)), with different spatial subregions representing different odors. In contrast to other sensory systems, the central relays have no topographical relation to the receptive sheet; the receptive sheet of olfaction has no intrinsic spatial map. Directional smelling exclusively mediated by the olfactory nerve does not exist: we can only localize olfactory stimuli by turning our head to detect temporal differences between intensity patterns of the stimuli that reach the nostrils ([Kobal et al., 1989](#)). The bulb and higher centers use their own neural space to order the representation of different basic odors. Again, in this respect the olfactory system differs from other sensory systems that have spatial coordinates to represent a topographical relation to the physical world.

The unmyelinated neurons in the olfactory receptor neurons terminate in the bilateral olfactory bulbs, which are the first relay of the olfactory system. In most mammals, the olfactory bulbs consists of two parts: the main olfactory bulb (MOB) and an accessory olfactory bulb (AOB) (for a review see [Meisami and Bhatnagar, 1998](#)). The AOB is smaller than the MOB and stems directly from the vomeronasal organ, which is involved in pheromone detection. The major afferent input to the AOB stems from the bed nucleus of the stria terminalis, the nucleus of the accessory olfactory tract, and median and posteromedian cortical

nuclei of the amygdala. Some afferents are common with the MOB, especially with respect to cholinergic and serotonergic inputs. Interestingly, the AOB has direct projections to the amygdala and the ventromedial hypothalamus. The status of the AOB in humans and great apes is not completely understood. The AOB seems to be either completely absent ([Meisami et al., 1998](#)) or not well developed ([Halpern and Martinez-Marcos, 2003](#)), although some recent research is suggestive of its presence ([Stoyanov et al., 2016](#)). The regions innervated by the output of the MOB are generally referred to as primary olfactory cortex ([de Olmos et al., 1978](#)). The MOB can also mediate autonomic responses through the amygdala and hypothalamus.

The primary olfactory cortex consists of five parts, (1) the anterior olfactory nucleus (AON, a complex and significant structure, actually more a cortical than a nuclear structure which connects the two olfactory bulbs through a portion of the anterior commissure), (2) the olfactory tubercle, (3) the prepyriform cortex (considered to be the main olfactory discrimination region), (4) the amygdala, (5) the lateral entorhinal area, which projects to the dentate gyrus and CA fields of the hippocampus ([Brunjes et al., 2005](#)). The entorhinal cortex is anatomically closely related to the hippocampus. In establishing these neural connections, the olfactory tract divides into two main striae, departing from the posterior edge of the orbital gyrus, (a) the lateral olfactory tract (LOT) that enters the prepyriform cortex and entorhinal cortex; (b) the medial olfactory striae pass superiorly and medially toward the subcallosal area. The LOT serving the amygdala acts as a relay center that connects the olfactory cortex to the hypothalamus and the tegmentum of the midbrain. In doing so it mediates the affective component of odoriferous stimuli. The piriform and olfactory tubercle both also project to the thalamus. The olfactory information that reaches the thalamus projects to the orbitofrontal cortex (OFC), as this is involved in the conscious perception, discrimination, and recognition of smell.

For many years it was thought that the olfactory pathway, as all sensory systems, passed through first-order, sensory thalamic nuclei. However, this is not the case. The olfactory system is different from all other sensory information systems, with direct and indirect connections serving as a dual relay system with direct connections to the olfactory cortex that bypass the thalamus ([Shepherd, 2005](#)).

However, there is some evidence in rodents that the dorsomedial thalamic nucleus acts as a higher-order thalamic relay that drives attentional processing, reward and valence as well as associative learning ([Courtillot and Wilson, 2014](#), [Kay and Sherman, 2007](#), [Plailly et al., 2008](#)). It is thus currently unknown how perception of odors could arise without the participation of the thalamus and what this would tell us about the presumably critical role that the thalamus plays for the conscious state in other sensory systems.

4. Olfactory memory is stored in the emotional brain

The cortical olfactory structures relay to regions that have a general function to (1) integrate olfactory information so that responses to olfaction can be elicited at the conscious memory level, (2) process the information so that odors can be recognized, distinguished, and flavors appreciated, (3) initiate motor, affective and or visceral responses to odors, and (4) memorize the odorant. We review the key anatomical structures and their relevance in olfactory processing.

4.1. Amygdala

4.1.1. Emotional processing and conditioning effects

Electrophysiological responses to odorants in patients that underwent amygdalotomy have contributed to our understanding that there is a distinct pattern of frequency components that is important in the coding mechanism ([Hughes and Andy, 1979](#)). The amygdala is placed at a relatively high level of sensory integration for olfactory stimuli. It plays a critical role in modulating associative learning that produces conditioned behavioral responses in the first postnatal period

(Poulos et al., 2014, Sullivan and Wilson, 2003). The amygdala has long been implicated in conditioned fear (Davis, 1986), and also has a role in influencing memory-storage processes in other brain regions, such as the hippocampus, striatum, and neocortex (reviewed in Cahill and McGaugh, 1998, Duvarci and Pare, 2014, Hermans et al., 2014). Conditioned fear, in which pairing of a neutral ('conditioned') stimulus to a fear-inducing ('unconditioned') stimulus results in fear responses to the neutral ('conditioned') stimulus alone, has been used as a probe of amygdala function (LeDoux, 2000, Pitman et al., 2012). Acute psychological stress occurs when a rat is exposed to a cat scent, a response that is mediated by the amygdala and which can be modified in experimental settings to assess effects of pharmacological intervention (Cohen et al., 2010). Lesions of the central nucleus of the amygdala have been shown to completely block fear conditioning (Hitchcock and Davis, 1986, Hitchcock et al., 1989). Because odors can be independently classified in terms of valence and intensity, they have been employed to clarify the necessary stimulus properties to engage the amygdala as a brain area key to processing emotive stimuli (Zald, 2003). Amygdaloid discharges are accompanied by an increase in odor intensities (Zald and Pardo, 1997), while the intensity of an olfactory stimulus is greatly reduced by lesions in the amygdala (Anderson et al., 2003). This impairment of odor differentiation and identification is relatively long lasting, whereas the impairment for the rudimentary detection is short lasting (Andy et al., 1975). Zald and Pardo (1997) investigated the neural correlates of odor aversiveness using fMRI. Exposure to an aversive odorant produced strong regional cerebral blood flow (rCBF) increases in both amygdalae and in the left OFC. Exposure to neutral odorants produced rCBF increases in the OFC, but not in the amygdala. Furthermore, the activity within the left amygdala was associated significantly with subjective ratings of perceived aversiveness. These findings provided evidence that the human amygdala participates in the emotional processing of olfactory stimuli.

Instinctive reactions to danger are paramount to the perpetuation of most species. Olfaction thus is a critical sensory system for most animals. Different species have fundamental similarities in the organization of the olfactory pathway, from the function of the odorant receptor proteins to the organization of the olfactory central nervous system (CNS; Ache and Young, 2005). For instance, predator odor induced fear has been studied widely and involves the basolateral and medial amygdala as one of the gateways for fear processing. Lesions of the basolateral and the medial amygdala have been shown to reduce unconditioned and conditioned fear-related behavior in response to predator smell, with the basolateral areas possibly involved in fear memory consolidation, but not memory retrieval and medial areas involved in retrieval, but not consolidation (Takahashi et al., 2007, Takahashi, 2014). In addition to the basolateral nucleus of the amygdala, other limbic structures have been associated with specific aspects of processing unconditioned olfactory fear stimuli such as the bed nucleus of the stria terminalis (Fendt et al., 2003, Rosen, 2004, Wallace and Rosen, 2001). Protective reactions in response to the detection of predator odors seem to be mediated by the activation of a specific area of the olfactory cortex, the amygdalo-piriform transition area (AmPir). This region in turn then induces stress hormone responses via signaling to hypothalamic corticotropin releasing hormone (CRH) neurons (Kondoh et al., 2016).

Anderson et al. (2003) tried to map the contribution of valence and intensity in olfaction in the brain with functional Magnetic Resonance Imaging (fMRI). Different neural networks seem to contribute to these dimensions, as amygdala activation was exclusively associated with intensity of odors, while activity in the OFC was associated with valence independent of intensity. However, these results were only partially replicated by Winston et al. (2005), who showed that the amygdala responds robustly to odor intensity for pleasant and unpleasant smells when valence is held constant, but that it does not show similar reactivity for neutral smells. Rosen and Donley concluded in their review that the amygdala might be involved in the evaluation of fear and

uncertainty as it is less activated at exposure to neutral stimuli than to stimuli with positive or negative valence at high levels of concentration (Rosen and Donley, 2006).

4.2. Hippocampus

4.2.1. Representation of odor memory

The hippocampus plays a unique role in mediating new learning and memory (explicit recall), emotional memory related to a stressor, and modulation of neurobiological systems, such as the HPA axis (Herman and Cullinan, 1997). Molecular biological studies demonstrated that the hippocampus is a primary target for ligands that reflect body physiology, including ion balance and blood pressure, immunity, pain, reproductive status, satiety and stress (Lathe, 2001). The hippocampus is also particularly vulnerable to stress. Its role in memory may be ancillary to physiological regulation. It is suggested that the hippocampus operates, in parallel with the amygdala, to modulate body physiology in response to environmental stimuli. Hippocampal outputs are predominantly inhibitory on downstream neuroendocrine activity; increased synaptic efficacy in the hippocampus (for example long-term potentiation) could facilitate throughput inhibition. This may have implications for the role of the hippocampus and long-term potentiation in memory. Lesions of the hippocampus have been shown to block the acquisition of conditioned fear responding to the context (i.e. the box) of a stressor (i.e. electric footshock), emphasizing the role the hippocampus plays in memory for the emotional context of a stressor (Kim and Fanselow, 1992, Phillips and LeDoux, 1992, Ross et al., 1984). The hippocampus is not essential to memory for single odors, but is critical for forming the representations of relations among odor memories, and for the expression of odor memories in novel situations. While it has been established that hippocampal lesions produce memory deficits, the exact function of the hippocampus remains obscure. The noted case H.M., who was rendered amnesic following bilateral temporal lobectomy that included uncus, amygdala, and the anterior two thirds of hippocampus, was reported to perform normally on measures of absolute olfactory sensitivity although he performed poorly on measures of odor discrimination, identification, and recognition (Eichenbaum et al., 1983). These findings suggest that the hippocampus plays a role in smell memory, in addition to its better known role in the mediation of verbal memory. Consistent with this, several disorders with known hippocampal pathology are associated with deficits in olfaction (for example Alzheimer's disease, Parkinson's disease, Huntington's disease as well as schizophrenia). However, many areas of the olfactory system, not just the hippocampus, are affected by neurodegenerative diseases (Saiz-Sanchez et al., 2016). Although lesions of central nodes of both the memory encoding network (such as inferior frontal cortex and hippocampus (Kim, 2011)) as well as the memory retrieval network (such as primary sensory cortices, posterior parietal cortices, and the hippocampus (Butler and James, 2011)) can produce rapid forgetting of visual, auditory, or tactile stimuli without disrupting perception, lesions of the same centers disrupt the capacity for more elementary aspects of odor perception (Mair et al., 1995). As Schab and Crowder (1995) report, there is no compelling evidence for a separate odor memory system, in other words, smell memory is not stored in a fundamentally different way than verbal or visual memory (Lehn et al., 2013). However, odor recognition memory is particularly vulnerable to the effects of healthy aging, which has been associated with less activation of brain regions subserving memory recall across modalities (Cerf-Ducastel and Murphy, 2009).

4.3. Orbitofrontal cortex

4.3.1. Discrimination

The OFC has been characterized as a multimodal sensory cortex. Direct, reciprocal connections have been demonstrated between all or parts of the olfactory cortex and the orbitofrontal cortex (Illig, 2005),

amygdala (Majak et al., 2004), and perirhinal areas such as the entorhinal cortex (Kerr et al., 2007). These connections add to the richness of information available to the olfactory cortex, in terms of context, hedonic valence, reward, and expectation. Evidence is lacking for conscious discrimination of odors in these structures. Olfactory information eventually makes its way to the neocortex through the thalamus. Studies in monkeys have given evidence for odor discrimination in the lateral and posterior part of the OFC. Individual cells located here are thought to respond to only one odor (Takagi, 1984). The transmitters are not known, but glutamate seems most likely involved since it has been found in almost all thalamic projection cells of the piriform cortex (Kaneko and Mizuno, 1988). In humans, the OFC has direct outputs to the amygdala (which adds emotional valence to memory) as well as cerebral cortex and hippocampus (Jones et al., 1997). The OFC is the only region of the prefrontal cortex that possesses a strong relation with the amygdala. In humans the OFC is one of the major areas targeted by olfactory stimulation.

5. Odors as conditioned fear stimuli

5.1. Preclinical studies

Exposure to predator odor has long been used as an animal model for traumatic stress as it elicits unconditioned fear responses mediated by the extended amygdala, more specifically distinct neuronal populations of the amygdala proper as well as in the bed nucleus of the stria terminalis (Butler et al., 2012, 2016, Masini et al., 2009, 2010, Rosen et al., 2015). Whether hard-wired, unconditioned olfactory threat-cues also exist in humans is yet to be determined (for a discussion see Cortese et al., 2015a, 2015b). While responses to such unconditioned odors are highly informative regarding the neural pathways of odor processing in the context of fear, their explanatory power regarding the close link exposure to odors and the recall of emotional memories is limited. The paradigm that seems most informative for odor-cued memory recall such as seen in PTSD and emotion processing disorders is olfactory fear conditioning, i.e. the repeated pairing of a neutral odor with a stressor. Reliable recall of emotional memories cued by exposure to a specific, fear-conditioned odor seems to be a pre-disposition of the brain, further facilitated by epigenetic adaptation (Dias et al., 2015, Klengel et al., 2016). During conditioning, a pattern of neuronal activity in one brain area becomes functionally joined or linked to a previously unrelated pattern in a second area so that the occurrence of one pattern reconstructs the other. This process is known as hetero-associative learning and recall. For example, the first time a rabbit smelled a fox, the distributed pattern of neuronal firing evoked in the olfactory cortex was defined in large part through the associative linkages that developed with emotion from the chase, the visual image of the fox, etc. Subsequently, the odor of the fox could elicit fear and visual memory, and the sight of a fox could likewise elicit odor memory and other associations. This is a function of bidirectionally connected pattern correlation networks (also referred to as ‘reciprocal feed-forward correlation architecture’; Haberly, 2001).

Cohen et al. (2009) investigated the impact of trauma on response adequacy in a rodent model. Exposure to traumatic stressors resulted in freezing when the rats were exposed to an odor that previously only elicited freezing when presented in combination with certain contextual cues. While the rats showed a modulated response before the trauma, this modulation was disrupted by exposure to severe stress. Interestingly, a conditioned odor-cue can elicit such reactions even in the absence of explicit memory of the original pairing with the traumatic event, i.e. when the subjects is amnesic for the situation in which the cue was conditioned (Poulos et al., 2014). Exclusively parameters essential for survival such as the attachment to the mother in a newborn can prevent conditioned fear learning and paradoxically result in the odor-cue originally paired with traumatic events being processed as cues for safety (Perry and Sullivan, 2014).

The primary sensory receptive field maps of the olfactory system remain malleable from development through adulthood as indicated by learning-dependent structural plasticity (Jones et al., 2008). Olfactory fear-conditioning results in plastic adaptations both in the olfactory bulb as well as limbic brain regions. More specifically, olfactory fear-conditioning induces increased release of neurotransmitters from olfactory sensory neurons (Kass et al., 2013), higher expression of brain-derived neurotrophic factor within the basolateral amygdala (Jones et al., 2007) as well as anatomical changes within the olfactory bulb due to increased odorant-specific receptor representation in the main olfactory epithelium and in glomeruli in rodents (Dias et al., 2015). Interestingly, such anatomical adaptations to fear-conditioned odorants are reversible, i.e. successful extinction learning leads to a reduction of odor-specific representations (Morrison et al., 2015). In the absence of extinction learning, however, conditioned responses even get passed down to the following generation via epigenetic modulations. Increased behavioral sensitivity to fear-conditioned odors have been shown in up to two generations of offspring of the odor-exposed parent in rodents (Dias and Ressler, 2014). In humans, it has been shown that fear-conditioning of an odor lowers the concentration threshold at which this specific odor can be detected, indicating increases in absolute sensory sensitivity. In the absence of active extinction learning, these levels returned to baseline over the following 8 weeks, indicating a high functional flexibility of the olfactory system in humans (Ahs et al., 2013). In addition, exposure to the conditioned odor elicits enhanced activation in fear processing areas in frontal, temporal, occipito-parietal and limbic brain regions, including the amygdala (Moessnang et al., 2013).

Such high plasticity of the sensory receptive fields as well as the limbic areas associated with processing of emotionally-relevant odorants were evolutionary highly adaptive, but likely also constitute the neural foundation of involuntary and uncontrollable recall of emotional memories triggered by odorants as observed in trauma-exposed subjects.

5.2. A close link between emotion and olfaction

It is becoming increasingly clear that emotions are not exclusively evoked via visual or linguistic channels (de Groot et al., 2014), and that olfactory fear signals can serve as potent triggers. Croy and co-workers asked their participants which basic emotions they could evoke through inhaling a specific smell. Two-thirds reported being aware of an odor that would instantly induce a feeling of fear in them (Croy et al., 2011). This is not surprising given the dominance of first associations with odors over subsequent perceptions associated with enhanced hippocampal activation (Yeshurun et al., 2009). Subjects characterized by high trait anxiety experience a stronger feeling of being taken back in time when confronted with an odor (Masaoka et al., 2012), are faster in detecting both pleasant and unpleasant odors (La Buissonniere-Ariza et al., 2013), but a different study found that both state and trait anxiety is negatively correlated with absolute detection thresholds (Takahashi et al., 2015). Conversely, odors that elicit positively-valenced autobiographical memories are known to reduce the subjective experience of anxiety in conjunction with a decrease of heart rate and levels of immune-signaling molecules (Matsunaga et al., 2011). Tanida et al. (2008) demonstrated a long-term modulation of stress-induced PFC activity by exposure to a positive-hedonic odor, confirming a privileged representation for olfactory associations. New insights into the close interrelation between emotion and olfaction stems from a laboratory study using anxiety induction to study correlated changes in olfactory functioning in humans (Krusemark et al., 2013). While resting in an MRI scanner, subjects were exposed to an odor twice, once before and once after an anxiety induction procedure. Changes in state anxiety were assessed to ascertain that the mood manipulation was successful. Odors that were perceived as neutral before the anxiety induction were rated as slightly aversive afterwards. This shift in subjective experience was accompanied by a shift in the neural correlates of odor processing, with a region in the OFC showing higher

activation as well as a closer functional connectivity with the amygdala after the anxiety induction. These results are very preliminary, but nevertheless illustrate well how flexible the brain adjusts to both external sensory stimuli and internal mood states.

Taking this close link between olfaction and emotional experience into account, it is not surprising that alterations in olfaction have long been associated with several disorders of emotion processing. Smell is of interest to anxiety and disorders of emotional processing because primitive brain structures that are involved in fear processing also mediate smell (Etkin and Wager, 2007). One can say that olfaction has a tradition of being studied in the context of mental disorders (Martzke et al., 1997). Olfactory deficits are well documented in psychiatric disorders, particularly in schizophrenia and depression, and alterations may serve as neuropsychiatric markers (Atanasova et al., 2008, Buron et al., 2015, but also see Gill et al., 2014, Turetsky et al., 2008). For example, Lombion-Pouthier et al. (Lombion-Pouthier et al., 2006) claim that depressive patients have a poor odor sensitivity and detection abilities but over-evaluate the pleasantness of odors; anorectic patients have a high sensitivity, over-evaluate the intensities of the odors but under-evaluate their pleasantness; and alcoholic/drug addicted patients showed impairments in identification. Interestingly, in patients suffering from panic disorder, exposure to their own sweat odor (associated with the experience of panic states) elicited a hyperactivation of the vmPFC, which in turn was associated with symptom severity (Wintermann et al., 2013).

6. Recall of autobiographic memories cued by an odor

Preliminary evidence indicates that the odor-cued recall of autobiographic memories seems to differ from the recall cued by verbal or visual stimuli (for a recent review see Larsson et al., 2014). A feature of olfactory perception that distinguishes it from other sensory perceptions is its dependence on respiratory activity. Odors that trigger the recall of autobiographic memories lead to slower and deeper breathing as well as to more subjective experiences of emotional arousal than control odors (Masaoka et al., 2012a, 2012b).

Matsunaga and coworkers investigated the neural correlates as well as peripheral circulating cytokines of odor-induced autobiographical memory recall accompanied by positive emotions using positron emission tomography (PET). The levels of peripheral tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ) were significantly reduced after experiencing odor-evoked autobiographic memories. Subtraction analysis of PET images showed that the mOFC and precuneus/posterior cingulate cortex (PCC) were significantly activated during experiences of odor-evoked autobiographic memory. A negative correlation was found between activities of the mOFC and precuneus/PCC with IFN- γ concentration indicating that the neural networks including the precuneus/PCC and mOFC might regulate the secretion of peripheral proinflammatory cytokines during the experience of odor-evoked autobiographic memories accompanied with positive emotions (Matsunaga et al., 2013).

In a recent functional MRI study, recall cued by an odor seemed to elicit significantly less activation in prefrontal brain regions subserving intentional searching and selecting of a memory and thus seemed to be associated with direct, effortless retrieval of a specific autobiographic memory (Arshamian et al., 2013). This is in line with research indicating that odor-cued recall of autobiographic memories is associated with faster reaction times (Zucco et al., 2012). Autobiographical memory recall cued by odors also seems to evoke a stronger activation of the hippocampus and emotion-processing brain regions, such as the amygdala (Arshamian et al., 2013, Herz et al., 2004a, 2004b, Masaoka et al., 2012). This might explain why odor-related autobiographical memories are reported to be more vivid and elicit a stronger subjective experience of going back in time (Herz, 1998, Herz et al., 2004a, 2004b, Willander and Larsson, 2006). As such, odor-cues have also been reported to help retrieve more specific details of a certain event (Chu and

Downes, 2002), which seems to be particularly true for highly emotional events (Saive et al., 2014, Toffolo et al., 2012) as well as odors that activate not only the olfactory nerve but also the trigeminal nerve (Czerniawska et al., 2013).

7. Olfaction and memory in trauma-related disorders

Intrusive reliving, a core symptom of PTSD, has traditionally been described through mechanisms of classical fear-conditioning (Pitman et al., 2012, Vermetten and Lanius, 2012). A life-threatening situation can prime the limbic system and set the stage for an indelible learning trial in which an external cue is associated with a state arousal or anxiety. When the cues related to the original exposure are re-encountered, the fear response may be re-elicited. In 100 refugees attending a psychiatric clinic, 45% described experiencing olfactory-triggered panic attacks during the preceding month. Of these, 58% experienced at least one instant of intrusive reliving during an olfactory-triggered panic attack (Hinton, et al., 2004). PTSD patients respond strongly to trauma-related danger cues even in objectively safe environments, seemingly unable to adjust their responses according to the contextual cues present.

One Vietnam veteran reported he was doing fine until many years after the war a Vietnamese restaurant started business next to his house. He could not stand the smell of *muchoi*, a typical sauce that in Vietnam is commonly put on fish and he hence had smelled repeatedly during his time in Vietnam. The smell brought back memories of his war experiences, and he attributed to this smell feeling uneasy, with a strange sensation of blood and a feeling of being torn apart. It was not so much his liking or disliking the smell, but the associated memories that made him uneasy. The repetitive exposure to this penetrative smell was a factor he could not avoid, for it was always there when he came home. He could smell the odor inside his house when next door the kitchen was opened, and ultimately he felt had no other choice than to move to another apartment. An information processing approach commonly employs auditory and visual stimuli for the assessment of perception, and despite the fact that these involve similar processes as seen in olfactory memory (processing, encoding, consolidation, and retrieval), the processes involved in olfactory memory are rarely investigated (Köster, 2005). Research in the field of olfaction is lacking an integration of preclinical findings of animal studies with knowledge in areas of human cognitive sciences (Dudai, 1997a, 1997b, Schab, 1991, Schab and Crowder, 1995, Schacter, 1996). However, there is a noticeable overlap between brain regions known to be altered by traumatic experience and the projection areas of the olfactory system, including the amygdala, OFC, insula and hippocampus.

PTSD is associated with both structural (Daniels et al., 2013b, Karl et al., 2006, Kuhn and Gallinat, 2013) and functional alterations (Daniels et al., 2013a, 2013b, Hayes et al., 2012, Patel et al., 2012) that span several neural networks (Daniels et al., 2013a, Kim et al., 2011). Although much work has investigated the contribution of brain regions such as the amygdala, hippocampus, and prefrontal cortex to the processing of fear learning and memory, fewer studies have examined the role of the olfactory system in the detection and perception of cues involved in fear conditioning and fear memory. As this review has already outlined, the study of mechanisms for smell memory can provide insight into mechanisms of human emotion that can be applicable to both the understanding of normal emotions as well as mental disorders involving pathological emotional processing.

A key symptom of PTSD is the inability to differentiate properly between former experiences of danger and the present situation, with conditioned sensory associations not showing the expected habituation. The neural circuitry of olfaction indicates that it is different from that of other senses in that it has direct projections to brain structures that are involved in emotion (amygdala) and learning and memory (hippocampus), justifying its relevance for the study of emotional and trauma-related disorders such as PTSD. For example, our group has shown deficits in verbal declarative memory in patients with extreme stress

and the diagnosis of PTSD using standardized measures of verbal declarative memory (Bremner et al., 1993, 1995), which we hypothesized was related to stress-related hippocampal damage. However we also noticed clinically that smell memory was altered in these patients, and often strongly linked to emotional memories. The smell of sexual discharge may then remind an incest victim of childhood trauma, which in turn may explain why many of these individuals have therapy-resistant sexual dysfunction (O'Driscoll and Flanagan, 2015). In this way, odors can serve as state-dependent cues for prior emotionally charged memories (Aggleton and Waskett, 1999, Vermetten and Bremner, 2003). However, despite the common sense knowledge of the power of odors to 'unlock' human memory, only few empirical studies have been performed to explore this in more detail, and there is a deficiency of instruments available to assess declarative memories for smell.

We therefore measured neural correlates of olfaction in PTSD by exposing veterans with and without PTSD to a set of smells. We tested changes in regional cerebral blood flow (rCBF) induced by exposure to diesel smell (related to traumatic memories of combat), vanilla/cocconut, and hydrogen sulfide (H_2S) (respectively, a traumatic, positive, and negative hedonic, non-traumatic smell) as well as odorless air during a PET scan. PTSD patients rated diesel as unpleasant and distressing, resulting in increased PTSD symptoms and anxiety in PTSD versus combat controls. In comparison to neutral air, diesel resulted in significantly more fearful responses in the PTSD group compared to the differences in these two conditions in the combat control group. Also the appraisal of the hedonic tone of the diesel was significantly higher to neutral air than the difference in these conditions in the control group. Diesel also resulted in higher subjective units of distress scores. In the imaging results exposure to diesel resulted in an increase in rCBF in amygdala, insula, medial prefrontal cortex, and anterior cingulate cortex, and decreased rCBF in lateral prefrontal cortex in PTSD in comparison to combat controls (Vermetten et al., 2007) (Fig. 1). Exposure to H_2S showed similar regional changes like diesel, although the differences between patients and controls were less pronounced. Vanilla and diesel showed similar increases in regional cerebral blood flow in the right anterior and posterior cingulate gyrus and medial PFC, although this was stronger with diesel. Diesel differed in inducing a decrease in rCBF in lateral PFC (BA 22, 47) in PTSD group only (Fig. 2). These data are in line with the notion that PTSD patients in general are more sensitive to any novel stimulus in comparison with a control population (stress sensitized), and are specifically responsive to traumatic reminders (fear-conditioned). A caveat in this type of smell experimentation can be the bimodality of aversive odorants. While vanilla is considered to be a unimodal odorant (meaning that it induces the olfactory cortex solely, without trigeminal nerve

involvement), both diesel and H_2S are not considered to induce trigeminal activity when presented at relatively low concentration levels as used in this study.

Convergently, veterans with, but not those without, PTSD reported that a limited number of odors relevant to the combat scene (gunpowder, fuel, blood and burning hair) elicited significantly higher levels of distress upon exposure (Cortese et al., 2015a, 2015b), likely due to olfactory fear conditioning (Li, 2014). The presence of olfactory elements in nightmares might actually be an indicator of encoding depth or the extent of re-consolidation of the traumatic memories as it was associated with poorer treatment response in veterans with PTSD (Harb et al., 2012). These data support the hypothesis that in PTSD trauma-related smells can serve as strong emotional reminders. The findings indicated the involvement of a neural circuitry that shares olfactory elements and memory processing regions when exposed to trauma-related stimuli. However, as is always the case when studying the effects of PTSD, one needs to tease apart those alterations induced by the experience of traumatic stress and those associated with the pathological reaction to such traumatic stress in the form of PTSD. To date, empirical data indicate that alterations in odor processing are evident in subjects with PTSD, but might also arise solely due to the exposure to traumatic stress in the absence of its pathological processing. In a few studies, trauma exposure seems to be associated with impairments in smell identification and/or a higher threshold for odor detection, potentially mediated by structural changes in the olfactory bulb or the piriform cortex. Vasterling et al. (2000) assessed odor identification in trauma-exposed Vietnam veterans with and without PTSD as well as 17 healthy, non-trauma-exposed veterans. Relative to veterans without PTSD, those diagnosed with PTSD were less proficient in odor identification and verbal learning but not in other cognitive tests sensitive to dorsolateral prefrontal and mesial temporal functioning. Following the same argument that neuropsychological dysfunctions of the OFC are predominant in PTSD, Dileo et al. (2008) aimed to explore olfactory identification as a probe of putative OFC dysfunction. In their study comparing veterans with PTSD with age-matched healthy controls, the PTSD sample exhibited significant deficits in odor identification compared to controls, despite uncompromised performance on cognitive measures. A recent study indicated that trauma exposure, independent of the development of PTSD, might be associated with a reduced sensitivity emotionally-neutral odors, necessitating higher absolute concentrations for detection of the odor (Cortese et al., 2014). Convergently, in one sample exposure to childhood maltreatment was related to a significantly reduced olfactory detection and identification ability, with the volume of the olfactory bulb reduced to 80% of that of non-exposed controls

Fig. 1. Areas of increased blood flow in diesel and PTSD patients (top row) and combat controls (bottom row) in different horizontal sections through the brain (slice 31 and 32: $z = -12$; slice 44 and 45: $z = 6$; slice 49 and 50: $z = 26$). Brain sections were chosen to illustrate the relevant activations. Between brackets are Brodmann areas. PAG = periaqueductal grey. (Z Score > 3.09 , $p < 0.001$).

(Reprinted with permission from Medworks Media, in Vermetten et al., 2007).

Fig. 2. Areas of greater increases (left column) and greater decreases (right column) in blood flow in vanilla (top), diesel (middle) and hydrogen sulfide (bottom) in PTSD compared to combat controls ($z = 0$ and $z = 14$). Brain sections were chosen to illustrate the relevant activations. Between brackets are Brodmann areas. nc = n caudatus (Z Score > 3.09 , $p < 0.001$). (Reprinted with permission from Medworks Media, in Vermetten et al., 2007).

(Croy et al., 2013). However, in a separate study no significant difference in olfactory functioning between subjects exposed or not exposed to childhood maltreatment was reported in reaction to unpleasant odors, while a significant correlation between severity of PTSD symptoms and preferential processing of unpleasant odors emerged (Croy, 2010). Evidence for functional and structural plastic adaptations of the olfactory system to trauma exposure is still preliminary. In healthy, unexposed subjects a significant correlation between olfactory acuity and grey matter volume in both the right orbital sulcus and the olfactory bulb has been established (Seubert et al., 2013). Combat veterans with and without PTSD differ regarding the volume in anterior piriform (primary olfactory) and orbitofrontal (secondary olfactory) cortices with veterans with PTSD exhibiting smaller volumes. Testing specifically for the odor of burning rubber, which has been reported repeatedly by veterans to be trauma-associated, a negative correlation between grey

matter volume in the piriform cortex and trauma memories elicited by the smell of burning rubber was established (Cortese et al., 2015a, 2015b). In addition, subjects with a history to childhood maltreatment exhibited increased activation of prefrontal and parietal brain regions upon exposure to a neutral and pleasant odor as compared to controls (Croy, 2010). Animal studies and some human studies show that smell can be used as a probe of the amygdala, as well as orbitofrontal and medial prefrontal cortex, areas of interest in PTSD (Herz et al., 2004a, 2004b, Kessler et al., 2012). These regions are target areas of olfactory stimulation (Zatorre et al., 1992). Imaging studies of brain function in PTSD are consistent with dysfunction of the orbital and medial prefrontal cortex during presentation of traumatic cues (Hayes et al., 2012, Patel et al., 2012). Smell can elicit conditioned responses that most probably are mediated by limbic and neocortical brain areas, i.e. amygdala and orbitofrontal cortex.

Fig. 3. Different applications of odorants in clinical and experimental setting in PTSD.

8. The role of olfactory stimuli in clinical applications and experimental psychotherapy research

8.1. Grounding - exploiting the calming influence of odors

Therapists have known for a long time that olfactory cues can be used to help ground a patient when he or she is overwhelmed with emotional memories (s. Fig. 3, first line). Ground coffee beans in a small sachet, or some vanilla over the upper lip has been used in therapy settings when trauma exposure was the focus of therapy (personal communication Southwick, Loewenstein, 2012). There are two alternative pathways how the exposure to odors in clinical settings may result in calming the patient:

The grounding effect observed in clinical practice could stem from the odor serving as a very salient distractor. Redirecting parts of the attention away from the overwhelming emotionally charged reliving of a traumatic memory could in itself lead to a calming effect. In fact, distraction has been studied as an effective form of intentional emotion regulation (Dorfel et al., 2014) and is known to regulate emotional arousal faster than other strategies (Uusberg et al., 2014) and result in a larger reduction of amygdala activity (Dorfel et al., 2014, McRae et al., 2010), at least for a short time (Lamke et al., 2014, Walter et al., 2009).

Alternatively, odorants may directly modulate the physiological arousal elicited by strong emotions, possibly via altered secretion of neurotransmitters in the brain. Investigations in rodents revealed that exposure to vanillin elevated both serotonin and dopamine levels in brain tissue (Xu et al., 2015) and exposure to lavender exerts an anxiolytic effect (de Sousa et al., 2015), which is not dependent on the conscious perception of the odor (Chioca et al., 2013). In humans, exposure to lemon, lavender, or peppermint odors has been associated with a reduced heart rate and lowered blood pressure, both systolic and diastolic, as compared to controls, with lemon inducing the strongest anxiolytic effect (Dong and Jacob, 2016). Convergently, inhalation of bergamotte essential oil, which also emits a citric odor, has been associated with a reduction of cardiovascular arousal symptoms (for a review see Navarra et al., 2015, Ni et al., 2013). Tanida et al. (2008) demonstrated a long-term modulation of stress-induced PFC activity

by exposure to a positive-hedonic odor, thus highlighting possible neural underpinnings of these effects.

In clinical samples such as patients with disorder of emotion processing however, the available data on the effects of aromatherapy is inconclusive (Perry and Perry, 2006). While most, but not all, studies reported positive effects, effects sizes were typically very small (Lee et al., 2011). However, oral administration of some essential oils such as lavender has been reported to have similar effects, presumably indicating a pharmacological rather than psychological modulation (Kasper et al., 2014, Uehleke et al., 2012).

If odors can indeed elicit strong enough direct modulations of acute emotional arousal as seen during exposure treatment in patients with PTSD is thus still unclear. To maximally exploit the calming properties of odors Abramowitz and Lichtenberg (2009, 2010) developed a technique which they call hypnotherapeutic olfactory conditioning in which the patient associates pleasant scents with a sense of security and self-control during induced hypnosis. Importantly, a scent is chosen which for the individual patient is already associated with positive, calming memories and imagery. Subsequently, the conditioned odor is used to prevent overwhelming intrusive memory recall during psychotherapeutic treatment. Preliminary evidence indicates that this approach may be effective for patients with PTSD who experience frequent episodes of odor-cued intrusive reliving: In a trial involving 36 patients with PTSD significant improvement was noted, with 58% of the patients reporting a reduction of at least 50% in symptom severity (Abramowitz and Lichtenberg, 2010). Future studies need to test if these rates are indeed higher than in standard trauma-focused treatment approaches using randomized trials.

8.2. Odors in augmented exposure therapy for PTSD

Clinicians working in the field of PTSD are well aware that olfactory cues can bring back memories of trauma with associated affect even years after the original event (Pointer and Bond, 1998). While many sensory and cognitive cues are known to elicit intrusive reliving in PTSD patients, smell can have distinctive characteristics that make evocation of vivid olfactory memories particularly likely (Herz and Cupchik,

1995; Vermetten and Bremner, 2003). Odorants have rarely been introduced in clinical contexts as probes for traumatic recall (s. Fig. 3, second line), yet odor stimulation can access limbic brain areas in as few as two synapses (Gottfried and Zald, 2005).

As recent research on exposure therapy for anxiety disorders indicates, the inclusion of many diverse sensory elements in the exposure setting might boost the effect of exposure treatment and delay return of fear (Craske et al., 2008, 2014, Janak and Corbit, 2011, Rescorla, 2006). As such, combining standard exposure techniques with the presentation of an odor, which for the patient is closely related to the traumatic experience, might augment therapy outcomes. However, to our knowledge the use of exposure to trauma-associated smells in the treatment of PTSD has not been studied systematically to date.

During sleep, patterns of brain activity elicited during learning are spontaneously reactivated, a process called consolidation, which is thought to make memories stronger and more enduring (for a review of the neurobiological mechanisms see Abel et al., 2013).

Recent approaches to PTSD treatment have set out to investigate if this process of consolidation might open a window in which memories can be modified. Different research groups are thus studying the effect of combining psychotherapeutic treatments with pharmacological agents that are thought to alter the emotional arousal to modulate the consolidation of trauma memories during sleep (for a recent review see Giustino et al., 2016).

Interestingly, recent studies have indicated that the brain is quite receptive for olfactory cues even during sleep, and that the presentation of odors during sleep can modulate associated memory traces (“targeted memory reactivation”; for recent reviews see Oudiette and Paller, 2013, Shanahan and Gottfried, 2014).

Presentation during slow wave sleep of an odor, which was present while subjects were learning during the day, was accompanied by enhanced hippocampus activation and subsequently resulted in improved recall the following day (Rasch et al., 2007). If strong emotional memories can be specifically targeted and modified during sleep is currently unknown. Should this be possible, this would open new pathways to target trauma memories via exposure to odors. A recent investigation of fear conditioning did indeed indicate that fear extinction can be enhanced by exposure to a fear-associated odor during sleep (s. Fig. 3, third line): In an odor context, humans subjects learned face-shock paired fear conditioning. During a subsequent nap, subjects were re-exposed to the contextual odor, without being exposed to the fear-conditioned face. Results indicate that this promoted extinction learning, although the subject did not consciously learn to dissociate the stimuli. Interestingly, this was associated with less activation of the hippocampus and the amygdala upon exposure to the conditioned stimulus (Hauner et al., 2013). Translated to the situation of PTSD treatment this would indicate that exposure to a trauma-related odor during sleep might result not only in dissociating the odor from the traumatic event, but possibly also weaken the conditioned fear reaction elicited by exposure to visual, tactile and auditory stimuli present during the traumatic event. This, of course, is only true if the odor itself does not elicit the recall of trauma memories in the form of nightmares. Preliminary evidence indicates that both dream content as well as the associated emotions can to a small degree be elicited by environmental cues such as odors presented during sleep (Schredl et al., 2009). If the use of conditioned odors for fear extinction is viable therefore still needs to be carefully explored. Alternatively, the introduction of a new odor during fear extinction might pose a safer way of garnering the positive effects of enhanced extinction due to sleep-related memory consolidation without the risk of symptom exacerbation (s. Fig. 1, last line).

9. Conclusion

Olfaction is an excellent model for studying many questions germane to the field of emotional memory processing in humans. There is still a need for a comprehensive theory of odor memory in cognitive

neurosciences. This field can be enriched from studies in clinical populations with specific application to the affective components in trauma-related disorders such as PTSD. Odor-induced flashbacks are common in PTSD and exposure to trauma-associated odors has shown to result in increased activation of areas involved in emotion processing and emotion regulation. PTSD subjects are characterized by decreased ability to consciously identify odors appropriately, possibly indicating diminished functionality of top-down regulatory circuits implicated in emotion regulation.

This review has outlined various windows to using olfaction as a system for emotional memory that allows anatomical, physiological and behavioral data to be collected and integrated across levels of analysis. Based on classic contributions in literature, it described the olfactory pathways and circuits into the limbic structures implicated in human olfactory memory processing (Dolan, 2002, Herz et al., 2004a, 2004b). This review has also explored using olfaction as a probe of emotional memory challenge in a neuroimaging condition. Neuroimaging with PET or fMRI seems to be a promising, non-invasive approach to further our understanding of the relation between olfaction, memory and emotion.

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