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Review

Odorants: a tool to provide nonpharmacological intervention to reduce anxiety during normal and pathological aging

Benedicte Ballanger [a,b,c], Kevin G. Bath [d,1], Nathalie Mandairon [a,b,c,*,1]

[a] INSERM, U1028; CNRS, UMR5292; Lyon Neuroscience Research Center, Neuroplasticity and Neuropathology of Olfactory Perception Team, Lyon F-69000, France
[b] University Lyon, Lyon F-69000, France
[c] University Lyon 1, Villeurbanne, F-69000, France
[d] Department of Cognitive, Linguistic, and Psychological Sciences, Brown University, Providence RI 02912, United States

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ABSTRACT

Anxiety disorders represent 1 of the most common classes of psychiatric disorders. In the aging population and for patients with age-related pathology, the percentage of people suffering of anxiety is significantly elevated. Furthermore, anxiety carries with it an increased risk for a variety of age-related medical conditions, including cardiovascular disease, stroke, cognitive decline, and increased severity of motor symptoms in Parkinson's disease. A variety of anxiolytic compounds are available but often carry with them disturbing side effects that impact quality of life. Among nonmedicinal approaches to reducing anxiety, odor diffusion and aromatherapy are the most popular. In this review, we highlight the emerging perspective that the use of odorants may reduce anxiety symptoms or at least potentiate the effect of other anxiolytic approaches and may serve as an alternative form of therapy to deal with anxiety symptoms. Such approaches may be particularly beneficial in aging populations with elevated risk for these disorders. We also discuss potential neural mechanisms underlying the anxiolytic effects of odorants based on work in animal models.

1. Introduction

Anxiety disorders (including generalized anxiety, panic disorder, social anxiety disorder, post-traumatic stress disorder, and specific phobias) represent 1 of the most common classes of psychiatric disorders, impacting nearly 4% of the global population (Kroenke and Michaelis, 2015; Lépine, 2002; Martin, 2003), and disproportionately affecting females (~2x greater risk relative to males) (Altemus et al., 2014; McLean et al., 2011). In the United States alone, nearly 18% of adults will be affected by an anxiety disorder, costing nearly $42 billion dollars, nearly a third of the money spent on mental health (Greenberg et al., 1999). This likely underestimates the true cost of this disorder, as there is significant underdiagnosis in multiple populations, including aged individuals (Palmer et al., 2007). As many as 2/3 of those afflicted by anxiety disorders do not seek treatment and are not likely to be counted in epidemiological studies (Kroenke et al., 2007; Kroenke and Michaelis, 2015). Although a variety of treatment options exist, including cognitive behavioral therapy and a panoply of pharmacological interventions, a significant percentage of individuals seeking treatment will not respond effectively to a given intervention (Bystritsky, 2006; Taylor et al., 2012). Thus, development and application of novel therapeutic approaches have the potential to fill a large unmet need for individuals suffering from these disorders.

Targeted development of new therapeutics has been difficult, as the neurobiological underpinnings of anxiety-related disorders remain poorly understood. This is in part due to heterogeneous presentation of these disorders over the lifespan (Costello et al., 2005), their high comorbidity with other neuropsychiatric and neurological disorders (Brown and Barlow, 1992; Kaye et al., 2004; Kroenke et al., 2007; Pini et al., 1997; Regier et al., 1998), and the evolutionary beneficial origins of anxiety (Bateson et al., 2011; Hofer, 1995; Marks and Nesse, 1994; Willers et al., 2013). Anxiety, including vigilance, has evolved to protect the individual from harm and is a normal part of everyday life. It is only when this signal becomes engaged in inappropriate contexts or exaggerated in its degree or persistence that it becomes pathological.

* Corresponding author at: Centre de Recherche en Neurosciences de Lyon Inserm U1028-CNRS UMR5292, Neuroplasticité et neuropathologie de la perception olfactive Centre Hospitalier Le Vinatier Bâtiment 462, Neurocampus 95 boulevard Pinel, Bron Cedex 69675, France. Tel.: +33 (0)4 81 10 65 17; fax: +33 (0)4 72 13 89 51.
E-mail address: nathalie.mandairon@cnrs.fr (N. Mandairon).
[1] Contributed equally to this article.

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In the hopes of developing more targeted approaches to treat anxiety disorders, recent studies have attempted to identify key brain regions involved in anxiety using a multitude of approaches, including resting state functional connectivity (Fig. 1) (Xu et al., 2019), imaging, postmortem approaches, and animal models. Some of the earliest studies included lesioning of brain regions such as amygdala as well as parts of the medial temporal lobe (Klüver and Bucy, 1937; LeDoux, 1992; Maren and Fanselow, 1996; Prather et al., 2001), which resulted in what was later termed Klüver-Bucy syndrome. Loss of the amygdala led to a near complete loss of aggression, docility, lack of social anxiety, and inability to identify the emotional importance of events (Hayman et al., 1998; Klüver and Bucy, 1937). Although many early studies have clearly linked the amygdala with emotional regulation, signal detection of threat, and gating social approach, this may be in part due to its role as a principal modulator of engagement of the hypothalamic-pituitary-adrenal (HPA) axis for gating the fight or flight response. However, anxiety is likely far more than mere engagement of sympathetic arousal or activation of the amygdala (LeDoux and Pine, 2016; Pine and LeDoux, 2017). In an attempt to map the circuits underlying defined aspects of threat assessment, such as learning and responding to specific threat associations, several labs have used "fear" conditioning paradigms (Pare et al., 2004). Through this work, multiple nodes including the amygdala, thalamus, hippocampus, and associated regions have been identified as regulator of the detection, generation, and maintenance of freezing behavior in response to threat conditioning (Fig. 1) (Maren and Fanselow, 1996; Orsini and Maren, 2012; Pare et al., 2004; Quirk et al., 1996). Still others have begun mapping out the roles of regions of basal ganglia and medial extended amygdala, which may serve to guide more complicated types of threat assessment, including social approach and social avoidance after stress or defeat (Bath et al., 2017; Dulka et al., 2018; Goode and Maren, 2017; Saga et al., 2019).

One common feature of many of the brain regions identified in anxiety and threat assessment is their intimate association with the reception and processing of olfactory inputs. Inputs from the main and accessory olfactory bulb have direct monosynaptic connections that impinge on the amygdala, bed nucleus of the stria terminalis, and entorhinal and piriform cortices and entirely bypass the thalamus (Fig. 1). The significant enmeshment of chemosensory processing and regions implicated in social approach/avoidance and anxiety-related behaviors is likely due to the evolutionarily old reliance on chemosensory cues for detection of threat and regulation of sociosexual behaviors. Lesioning of nodes within the medial extended amygdala, including the basolateral amygdala, bed nucleus of the stria terminalis, periaqueductal gray, and medial preoptic area alters the processing of olfactory and pheromonal cues to impact social approach, copulation, and aggression. Given the significant overlap in circuits mediating the chemical senses and threat assessment, the chemosensory system may represent a novel and evolutionarily old means of manipulating activity of brain centers implicated in threat assessment and anxiety disorder.

2. Anxiety with aging and aged-related disorders

Approximately 20% of elderly individuals go on to develop anxiety disorders (Himmelfarb and Murrell, 1984; Wolitzky-Taylor et al., 2010). However, this actual percentage may be even higher than estimated as anxiety disorders are often under-recognized in older adults and erroneously attributed to a normal consequence of the aging process (Fuentes and Cox, 1997; Lauderdale and Sheikh, 2003; Waxman et al., 1984). Yet, with an increasing percentage of the population being elderly individual (>65 years), anxiety disorders are becoming a growing public health concern, impacting the overall quality of life and increasing mortality (de Beurs et al., 1999; Murphy et al., 1987).

In parallel, anxiety is a risk factor for many age-related medical conditions, including cardiovascular disease (Allgulander, 2016; Emdin et al., 2016; Esch et al., 2002; Grippo and Johnson, 2009), stroke (Bowen et al., 2000; Lambiase et al., 2014); see also (Perez-Pinar et al., 2017) for a review), cognitive decline (Gulpers et al., 2019), and dementia ((Becker et al., 2018; Gimson et al., 2018; Santabarbara et al., 2019); see also (Ford et al., 2018) for a recent review). In both animals and humans, an association has been well documented between anxiety symptoms and reduced cognitive

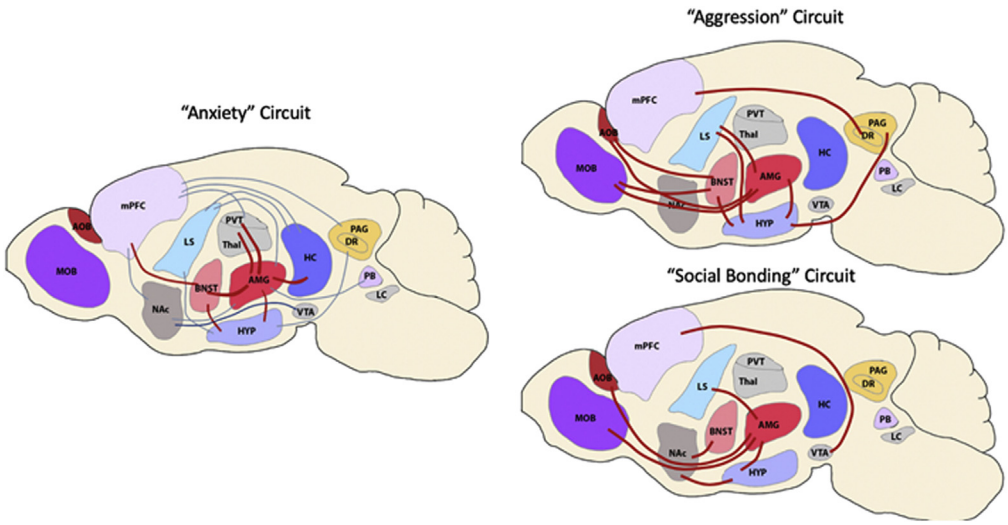

Fig. 1. Map of brain regions involved in the development, learning, and expression of anxiety and threat assessment in rodent models (Figure adapted from Calhoon and Tye, 2015, Nature Neuroscience). There is significant overlap between these regions and the chemosensory pathways mediating sociosexual behaviors, including aggression and social bonding (adapted from Ko, 2017, Frontiers in Neural Circuits). This high degree of overlap likely has its roots in the use of chemical signals to detect threat and social signals and the ability to modulate approach/avoidance of the sources of those signals. Thus, the unique ability of the chemosensory system to directly modulate key centers involved in threat assessment makes it a unique candidate for treating anxiety-related pathology. Abbreviations: MOB, main olfactory bulb; AOB, accessory olfactory bulb; LS, lateral septum; NAc, nucleus accumbens; BNST, bed nucleus of the stria terminalis; PVT, periventricular thalamus; Thal, thalamus; AMG, amygdala; HYP, hypothalamus; HC, hippocampus; VTA, ventral tegmental area; PAG, periaqueductal gray; DR, dorsal raphe; LC, locus coeruleus; mPFC, medial prefrontal cortex; PB, parabrachial nucleus.

functions (mainly memory and executive functions) in older individuals without dementia (Potvin et al., 2011; Yochim et al., 2013).

Furthermore, anxiety symptoms often accompany neurodegenerative diseases in the aging population. This is the case in Alzheimer's disease in which anxiety symptoms have been observed more frequently in individuals with mild cognitive impairment than in cognitively intact elderly individuals and were associated with a significant increase in risk of progression from mild cognitive impairment to Alzheimer's disease at 3-year follow-up (Palmer et al., 2007). In the same vein, the likelihood of developing Parkinson's disease (PD), the second most common neurodegenerative disease, is greater in anxious individuals (Lin et al., 2015). Actually, anxiety is highly prevalent in PD (~20-25% that can reach 60%; (Aarsland and Kramberger, 2015; Broen et al., 2016; Chen and Marsh, 2014; Schapira et al., 2017), yet frequently underdiagnosed and undertreated. Nevertheless, interest in anxiety is growing as it negatively impacts the quality of life in those patients (Broen et al., 2016; Pontone et al., 2009) by contributing to the severity of motor symptoms (Leentjens et al., 2012), cognitive (specifically memory) impairment (Dissanayaka et al., 2017), as well as compulsive behavior and depressive symptoms (Rutten et al., 2017). In parkinsonian patients, anxiety symptoms can manifest as generalized anxiety, panic attacks, and social phobia, similar to what is observed in the general population (Han et al., 2018). Finally, anxiety in PD is also directly related to therapeutic response fluctuations with increasing anxiety when the effect of dopaminergic mediation wears off (Leentjens et al., 2011; Stephens et al., 2018). Strengthening the relationship between dopaminergic dysfunction and anxiety, imaging studies showed that lower striatal dopaminergic transporter uptake is associated with higher levels of anxiety (Picillo et al., 2017) and are in agreement with work in non-PD individuals with anxiety disorders (Mathew et al., 2001) as well as with pharmacological studies showing a positive effect of dopaminergic treatment on anxiety (Stacy et al., 2010). Nevertheless, the role of other neurotransmitters (i.e., GABA (Cryan and Kaupmann, 2005), serotonin (Lucki, 1998; Ramboz et al., 1998; Munafo et al., 2006; Stein et al., 2006), or noradrenaline) cannot be overlooked. For instance, anxiety symptoms have also been associated with a loss of noradrenergic innervation in the limbic system (Remy et al., 2005), as well as functional polymorphisms in the serotonin transporter gene (Menza et al., 1999). A first line of treatment for anxiety disorders in older adults is pharmacological medications. Among those, benzodiazepines constitute the most frequently prescribed anxiolytic drugs despite notable potential adverse effects (such as cognitive decline) in the geriatric population that should warrant consideration ((Lenze et al., 2009) see also (Picton et al., 2018) for a recent review). The serotonergic antidepressant medications such as venlafaxine (Katz et al., 2002) or the selective serotonin reuptake inhibitors such as escitalopram (Lenze et al., 2009), citalopram (Lenze et al., 2005), and sertraline (Schuurmans et al., 2006) have also been shown to be effective pharmacological treatments for older adults with anxiety disorders. Nevertheless, those therapeutics cause a robust set of side effects including weight gain, constipation, cognitive disorders, as well as sleep and sexual disorders (see Table 1). Finally, chronic treatment with buspirone, a serotonin 1A (5-HT_{1A}) receptor agonist, has been shown to produce an anxiolytic-like effect although reports on the effect of its acute administration are inconclusive (Barrett and Vanover, 1993; Lowry et al., 2005). However, known side effects associated with buspirone include headaches, nausea, and somnolence. Accordingly, due to the numerous side effects of traditional anxiolytic treatments, there has been increasing interest in the use of alternative therapies.

To date, nonpharmacological treatments have included the use of physical activity to attempt to stem symptoms (Ruscheweyh et al., 2011). Recently, lifetime exercise has been associated with increased neurogenesis and reduced anxiety, an effect that was most efficacious in young adult female mice (Morgan et al., 2018). In addition, nutritional intervention, such as caloric restriction, has been shown to reduce anxiety in aging mice (Parikh et al., 2016) as well as in aged Rhesus monkey (Willette et al., 2012). Furthermore, cognitive behavioral therapy has been shown to be efficacious as an evidence-based treatment for older adults with generalized anxiety disorders (Stanley et al., 2003, 2009) with greatest benefit when performed in combination with selective serotonin reuptake inhibitor treatments (Rosnick et al., 2013). Then, relaxation training has also been reported as having a positive effect in reducing geriatric anxiety (Thorp et al., 2009) and interventional studies on choral singing initiatives (Coulton et al., 2015). Finally, among nonpharmacological approaches, aromatherapy or odor diffusion has also been investigated. In this review, we highlight the emerging perspective suggesting that use of odorants may reduce anxiety symptoms or at least potentiate the effect of other anxiolytic approaches and may serve as an alternative form of therapy to deal with anxiety symptoms, including in the aging population.

3. Anxiolytic effect of odorants

Although the effect of anxiety on olfactory perception (threshold, memory, discrimination) has been well documented (Chen and Dalton, 2005; Havlicek et al., 2012; La Buissonniere-Ariza et al., 2013; Pollatos et al., 2007), we will focus here on the effect of odor exposure on stress and anxiety, and when possible, age.

3.1. Behavioral effects of odor exposure in humans

Odorants or essential oils have been used as alternative treatments for medical purposes since ancient times (Kuriyama et al., 2005). Aromatherapy proposes that essential oils have the ability to influence mood, perceived well-being, emotional states, and behavior (Carvalho-Freitas and Costa, 2002; Cooke and Ernst, 2000; Diego et al., 1998; Herz, 2009; Komori et al., 1995; Lehrner et al., 2000; Perry et al., 2012; Tsang and Ho, 2010; Woronuk et al., 2011). Beyond essential oils, more generally, odorants are universally recognized as effecting behavior and physiology. In many cultures, as well as animals, odorants have been considered a powerful elicitor of emotions, possibly due in part to direct connections between olfactory relay neurons and the amygdala, a key node in regulation of arousal. In the last few decades, a growing scientific literature has documented a wide array of emotional effects to odors, including fear, anxiety, aversion, pleasure, or relaxation (for reviews, see e.g., (Ehrlichman and Bastone, 1992; Herz and Schooler, 2002). The positive and negative affects induced by odorants can be assessed in humans using self-rating, autonomic parameters, cerebral activity analysis on electrophysiological recording, or neuroimaging (Bensafi et al., 2001).

To assess the emotional effect of odor diffusion, some authors have tested subjects in a stressful context such as a dental office. They have shown that patients who were exposed to ambient odor of orange or lavender showed a lower level of anxiety compared with the patients in control condition. They further found that exposure to music in a dentist's waiting room has an intermediate effect. This finding is consistent with a growing body of evidence showing that odorants have a strong capacity to change emotional states (Lehrner et al., 2000, 2005) and decrease anxiety related feelings and behavior in humans (Diego et al., 1998; Kritsidima et al., 2010; Lehrner et al., 2000, 2005; Linck et al., 2010; Perry et al., 2012; Tsang and Ho, 2010; Umezu et al., 2006). For instance, administered orally, the essential oil derived from the petals and stamens of *Citrus aurantium* reduced the preoperative

Table 1
Potential mechanisms, limitation, and uses of the current therapeutics for anxiety disorders

Medications	Actions	Limits	Conditions
Selective serotonin reuptake inhibitors			
Fluoxetine	Inhibit SERT (but also DAT and NET at supratherapeutic doses [Koch et al., 2002]) Inhibit CYP2D6 activity Inhibit 5-HT_{2C} receptors at high concentrations (Pälvimäki et al., 1996)	CYP2D6-dependent metabolism => intraindividual variability in tolerability and response Adverse effect: sexual dysfunction (Clark et al., 2013)	Panic disorder (Michelson et al., 2001; Cavaljuga et al., 2003)
Paroxetine	Inhibit SERT (but also NET)	SSRI withdrawal symptoms due to its short half-life CYP2D6-dependent metabolism => intraindividual variability in tolerability and response	GAD (Pollack et al., 2001; Rickels et al., 2003; Bielski et al., 2005)
Escitalopram	Inhibit SERT Inhibit CYP2D6 activity	Relatively good acceptability (Slee et al., 2019 for a recent meta-analysis)	GAD (Goodman et al., 2005; Allgulander et al., 2006; Stein et al., 2018) Late-life GAD (Lenze et al., 2011) SAD (Baldwin et al., 2016; Faria et al., 2017)
Selective serotonin-norepinephrine reuptake inhibitors			
Venlafaxine	Inhibit SERT and NET	CYP2D6-dependent metabolism => intraindividual variability in tolerability and response Side-effects: Suicide and discontinuation syndrome (Haddad, 2001)	GAD (Sheehan, 2001; Rickels et al., 2000, 2013; Gelenberg et al., 2000; Zullino et al., 2015)
Duloxetine	Inhibit SERT and NET	Acceptable tolerated (Li et al., 2018 for a recent meta-analysis)	GAD (Koponen et al., 2007; Carter and McCormack, 2009 for review)
Multimodal antidepressant			
Vortioxetine	Inhibit SERT 5-HT_3 and 5-HT_7 receptor antagonist, 5-HT_{1B} partial agonist and 5-HT_{1A} receptor agonist (Orsolini et al., 2016)	Nausea with high dose (Fu et al., 2016)	GAD (Bidzan et al., 2012; Rothschild et al., 2012; Christensen et al., 2018; Pae et al., 2015 for a recent meta-analysis but see also Fu et al., 2016 for opposite results) SAD (Liebowitz et al., 2017)
Benzodiazepines	Enhance the effect of GABA at the GABA-A receptor	Poorly tolerated: Somnolence, fatigue, increased sweating, dependence	Efficacy in the short-term management of GAD and panic disorder (Martin et al., 2007; Stevens and Pollack, 2005; McIntosh et al., 2004)
Caloric restrictions	Enhances ATP production and neuronal and CBF (hippocampal and frontal) levels Increased DA and 5-HT blood levels (Lin et al., 2017)	No apparent negative effects	Reduced anxiety in aging mice (Parikh et al., 2016) and aged Rhesus monkeys (Willette et al., 2012) Reduced anxiety in patients with metabolic syndrome (Perez-Cornago et al., 2014)
Physical activity	Increase in BDNF (Asmundson et al., 2013; Stroghle et al., 2010) Improve autonomic system functioning by increasing the heart-rate variability (Hsu et al., 2015) Increase levels of GABA in the striatum (Dishman et al., 1997) Inhibits NE activity (Soares et al., 1999) Reduced 5-HT levels in the amygdala (Greenwood et al., 2012) Increase the number of 5-HT_{1A} autoreceptors (Greenwood and Fleshner, 2011)	No apparent negative effects	Rodents (Nguyen et al., 2013; Sciolino and Holmes, 2012) Reduced anxiety in adults older than 50 years (McDowell et al., 2018), in midlife and older women (Martinez-Dominugez et al., 2018), and in obese individuals (Vancini et al., 2017).
Cognitive behavioral interventions	Reduce cortisol levels Reduction in afternoon cortisol levels Reduced hyperactivity of the dorsolateral prefrontal cortex, parahippocampal gyrus (Paquette et al., 2003) insula, and anterior cingulate cortex (Straube et al., 2006)	No apparent negative effects	Younger and middle-aged adults with anxiety disorders (Brand et al., 2011) Individuals with GAD (Tafet et al., 2005)

Key: SERT, serotonergic transporter; SSRI, selective serotonin reuptake inhibitor; DAT, dopaminergic transporter; NET, noradrenergic transporter; GAD, generalized anxiety disorder; SAD, social anxiety disorder; CBF, cerebral blood flow; CYP2D6, cytochrome P450 2D; ATP, adenosine tri-phosphate; 5-HT_{1A}, serotonin 1A.

anxiety of patients scheduled for surgery (Akhlaghi et al., 2011). To further determine the characteristics of odorants that modulate mood, the authors considered hedonic tone. Indeed, they assumed that odor hedonics are important in the determination of the effects on emotion and, thus, it is likely that odorants perceived as pleasant tend to induce positive moods, whereas unpleasant odorants tend to induce negative moods (Schiffman et al., 1995a,b). In this context, Knasko (1995) found that exposure to an ambient smell of chocolate or baby powder caused people to report being in a better mood as compared with a no odor condition (Knasko, 1995). Ludvigson and Rottman (1989) demonstrated that presentation of lavender, an odorant rated as pleasant, affected mood in a positive direction (Ludvigson and Rottman, 1989). This is in line with prior studies showing that pleasant odorants significantly decreased tension,

improved mood, and reduced report of depressive feelings in middle-aged and elderly women (Abriat et al., 2007; Schiffman et al., 1995b). Thus, it seems that pleasant odors make people feel good, with positive effects being observed in aged populations. The behavioral effects provoked by pleasant and unpleasant odorants have been linked with changes in autonomic tone: such as altered heart rate or skin conductance, which are used as physiological indices of an emotional response (Bensafi et al., 2002a,b,c; Heuberger et al., 2001; Robin et al., 1999; Sano et al., 2002).

3.2. Behavioral effects of odor exposure in animal models

To better understand potential neural mechanism underlying modulation of mood, animal models may provide unique and important insights. Although animal models do not provide direct access to subjective mood state, behavioral assays have been developed to index approach and avoidance behaviors that index anxiety-like behavior and hedonic valuation of stimuli.

Some well-characterized behavioral paradigms used to assess anxiety-like behavior in rodents include the open field, elevated plus maze, or the light/dark chamber. These tests place animals in a conflict setting where they have the opportunity to explore a novel, often mildly aversive environment. The pattern of exploration is often used to index levels of anxiety, with high levels of exploration often being characterized as low anxiety state, and restricted patterns of exploration being characterized as a more anxious phenotype. These tasks were developed to have both face validity and construct validity, meaning that novel mildly aversive environments should induce higher levels of anxiety, and the use of drugs that diminish anxiety alter the pattern of behavior in these settings in a way that is consistent with an anxiolytic response.

Several studies using mice and rats have successfully demonstrated anxiolytic effects of certain essential oils, lending support to the use of these oils as aromatherapies to treat anxiety symptoms (Faturi et al., 2010). For instance, the effects of *Citrus sinensis* essential oil (sweet orange) have been evaluated on rodents using the elevated plus-maze and light/dark paradigm. An increase of exploration time in the open arms of both the elevated plus maze and the lit chamber of the light/dark paradigm after exposure to orange is strongly suggestive of an anxiolytic effect of this essential oil. Similar behavioral results have been found for linalool, lavender, lemon, *Citrus aurantium,* or rose (Buchbauer et al., 1993; Ceccarelli et al., 2004; Cryan and Sweeney, 2011; de Almeida et al., 2004; Linck et al., 2010; Umezu, 1999, 2000) and also with green leaf volatiles *Z*-3-hexen-1-ol (leaf alcohol) and *E*-2-hexenal (leaf aldehyde) termed "green odor" (Nakatomi et al., 2008; Tokumo et al., 2006; Watanabe et al., 2011). This last odor has received greater attention and in multiple studies has been found to have powerful anxiolytic and antidepressant-like effects in rodents when compared with conventional anxiolytic and antidepressant pharmaceutical drugs (Nakatomi et al., 2008; Tokumo et al., 2006; Watanabe et al., 2011).

3.3. Neural mechanisms underlying the anxiolytic effect of odorants

Odorants activate olfactory receptor neurons in the nasal epithelium, which synapse with relay neurons in the olfactory bulb, and send this signal directly to cortical regions, where the odor is perceived, as well as to subcortical brain regions that modulate sympathetic arousal and in turn affective state (regions such as the amygdala) (de Almeida et al., 2004; Faturi et al., 2010; Herz, 2009; Souto-Maior et al., 2011). Unlike all other sensory systems, olfactory information bypasses the thalamus, with direct connections to both cortical and limbic brain centers. This architecture may be a remnant of the evolutionary age of this sensory modality, or be a function of the high reliance of many species of animals on olfaction for navigation, communication, and threat detection. Thus, olfactory information may have a more privileged connection to cortical and emotional centers and promote more rapid detection and processing of these signals. Anatomically, the olfactory system also shares a great deal in common with the vomeronasal system, which is critical for sensing pheromones and driving robust changes in physiology and behavior, including reproductive and escape behaviors.

Given the architecture of the olfactory system, odorants that alter anxiety would be expected to do so by acting on brain regions that have been implicated in the expression of anxiety-like behavior, threat learning, or on systems that are the target of anxiolytic drugs. It is well known that exposure to "stressful" stimuli engage the HPA axis and drive sympathetic arousal, leading to a stereotyped fight or flight response. This response includes increased blood pressure, increased respiration, and elevations in plasma concentrations of adrenocorticotropic hormone and corticosterone (CORT) (DiMicco et al., 2006; Smith and Vale, 2006). It is hypothesized that anxiolytic odorants should dampen the response of the HPA axis to otherwise stressful stimuli.

To test this hypothesis, some authors have mapped brain activity in response to stressful stimuli using c-fos expression, an immediate early gene that is elevated in cells after increased activity. Exposure to a stressor induces an increase in c-fos–positive neurons in the hypothalamic paraventricular nucleus (PVN), the amygdala, the hippocampus, and the paraventricular thalamic nucleus (Chowdhury et al., 2000; Dumont et al., 2000; Kurumaji et al., 2003; Linden et al., 2004; Spencer et al., 2004; Viau and Sawchenko, 2002). Modulation of c-fos expression in these particular regions of the brain has been shown with anxiolytic drugs, including the benzodiazepines that are used as a pharmacological validation tool (Cryan and Sweeney, 2011; Lister, 1987; Nicolas and Prinssen, 2006). The use of odorants, such as the lavender or green odor, which decrease anxiety, reduced stress-associated increases in c-fos expression, in the PVN, paraventricular thalamic nucleus, and the amygdala (Ito et al., 2009; Kim et al., 2005). Green odor has also been shown to attenuate the response of the HPA axis to a variety of types and intensities of stressors without affecting basal hormone concentrations (Nikaido et al., 2011). It has also been found to attenuate stress-induced elevations in plasma adrenocorticotropic hormone and reduce the stress-associated elevations in plasma CORT and stress-induced activation of PVN neurons (Ito et al., 2009). In addition, green odor was also able to block the hypertrophy of the adrenal glands after repeated stress (Fukada et al., 2007). These results suggest that odorants that reduce anxiety may decrease the activity of brain regions involved in moderating the stress responses, including the HPA axis, limbic centers, and activation of the sympathetic nervous system (Fukada et al., 2007; Ito et al., 2009; Nikaido et al., 2011).

The main molecular target of benzodiazepine is the GABA/benzodiazepine complex (Rudolph and Knoflach, 2011). This drug increases inhibitory GABAergic neurotransmission by binding to the benzodiazepine site on GABA-A receptors (Rudolph and Knoflach, 2011). In animal models of anxiety, antagonists of GABA (picrotoxin and bicuculline) and benzodiazepine (flumazenil) are used to assess whether the anxiolytic effects of drugs or agents involves GABA/benzodiazepine complex (Baretta et al., 2012; Dombrowski et al., 2006). It is in this context that 1 of the mechanism underlying the anxiolytic effect of lavender has been revealed with a potentiation of the effect of GABA at GABA-A receptors (Aoshima and Hamamoto, 1999), suggesting that the anxiolytic effect of lavender implies GABAergic modulation (Tsang and Ho, 2010). Using similar approaches, other studies suggested that serotonin, in particular its 5-HT_{1A} receptors, is another neurotransmission frequently associated with anxiety and anxiolytic drugs (Fogaca et al., 2014; Gardner, 1988; Leonard, 2005; Nutt and

Stein, 2006; Xiang et al., 2017). Indeed, the 5-HT_{1A} partial agonist (buspirone) is clinically effective in reducing anxiety symptoms in patients with anxiety disorder (Koen and Stein, 2011). Moreover, preclinical studies have shown that 5-HT_{1A} agonists exhibit anxiolytic effects in animal models, and 5-HT_{1A} antagonists block the anxiolytic-like effects of some drugs, such as cannabidiol (Campos and Guimaraes, 2008). Interestingly, it has been demonstrated that odorants such as lavender present similar action to reduce anxiety that involves the serotonergic system (Chioca et al., 2013). In particular, the anxiolytic-like activity of *Citrus aurantium* is suggested to involve 5-HT_{1A} receptors (Costa et al., 2013), whereas increased 5-HT and DA synthesis was observed in the prefrontal cortex and hippocampus of mice after inhalation of lemon oil vapor associated with reduced anxiety (Komiya et al., 2006).

Odorants have thus demonstrated their efficiency on stress and anxiety, thanks to their action on the central nervous system in the same way that anxiolytic drugs do, by acting at GABA-A receptors and serotoninergic transmission, and thus may represent a powerful nonpharmacological anxiolytic tool to reduce anxiety, including in aging population.

4. Proposed neural anxiolytic mechanism of odorants' action in aging

Taken the aforementioned results together, we propose that the use of odorants might be beneficial in counteracting the deleterious effects of the anxiety observed with aging or with certain neurodegenerative diseases as well as the cognitive impairment associated to these diseases. In particular, the hippocampus participates in the regulation of stress response by inhibiting most aspects of HPA activity, preventing the occurrence of elevated levels of glucocorticoids associated with anxiety (Sapolsky et al., 1985) (Fig. 2). However, this structure is vulnerable to the aging process as demonstrated by smaller hippocampal volumes in the elderly due to a decrease in the number of hippocampal neurons and a concomitant reduction in neurogenesis within the hippocampal dentate gyrus (Geinisman et al., 1995; Persson et al., 2012). Moreover, alterations in hippocampal structures have been associated with abnormalities in the functioning of the HPA axis (i.e., persistent activation and exacerbated stress response (Frodl and O'Keane, 2013)) evidenced by increased cortisol response in older compared with younger adults (Otte et al., 2005). In parallel, excessive levels of glucocorticoids have been linked to hippocampal atrophy and dysfunction in elderly humans (Anacker et al., 2013; Lupien et al., 1998), which may accelerate the aging process. Due to tight connections between the olfactory cortex and the hippocampus (Aqrabawi and Kim, 2018; Cenquizca and Swanson, 2007; Haberly and Price, 1978; Swanson and Cowan, 1977; van Groen and Wyss, 1990), 1 possibility is that odorant exposure could lead to changes in hippocampal activity, leading to a decreased response of the HPA axis driven more specifically by the activation of 5-HT_{1A} receptors (Fuss et al., 2013). This cascade of events would explain the

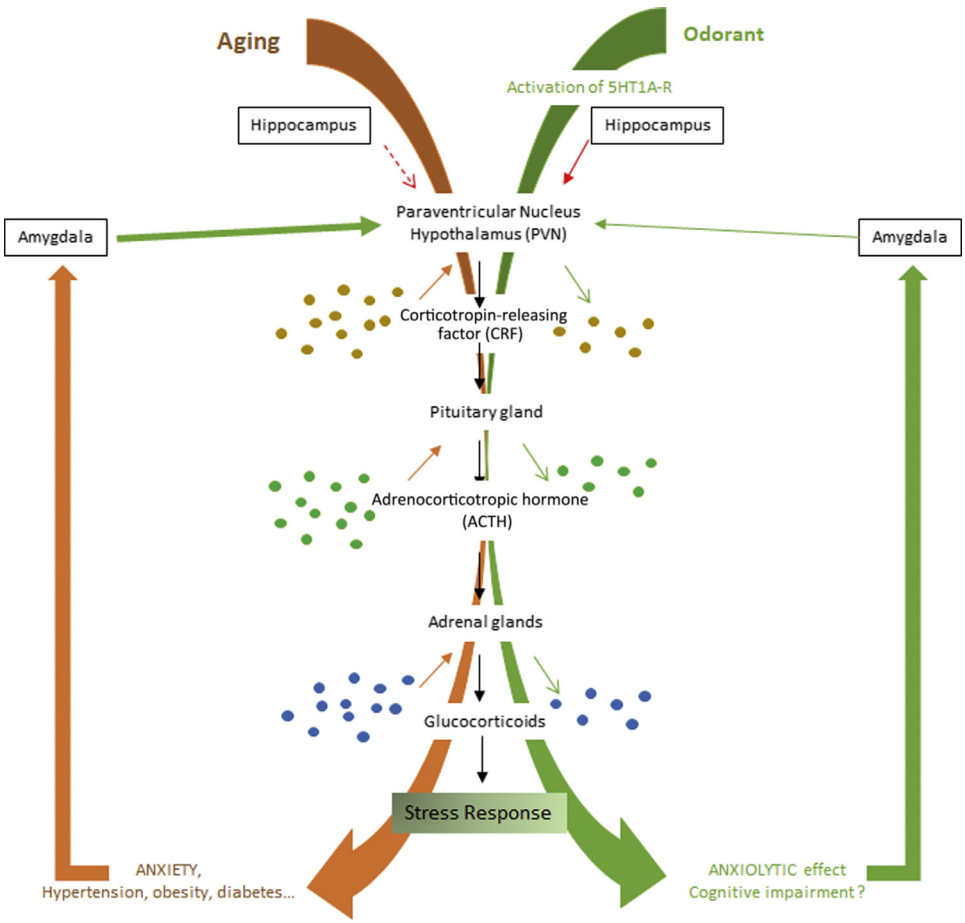

Fig. 2. Hippocampus and amygdala participate in the regulation of the stress response by acting on the paraventricular nucleus, which releases corticotropin-releasing factor (CRF), initiating a cascade of events that culminate in the release of glucocorticoids from the adrenal cortex. Aging alters the activity of the hippocampus and amygdala, as well as the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, altering basal glucocorticoid levels and release during stress response. Odor exposure could be an efficient mean to decrease the hyperactivity of the HPA axis and glucocorticoid release, given the intimate connections between the olfactory system and the hippocampus and amygdala.

anxiolytic-like effect of odorant exposure. It is tempting to speculate that this effect may also have an impact on delaying cognitive decline associated with both normal and pathological aging as well as anxiety disorders (e.g., (Coles and Heimberg, 2002; Croisile et al., 2009; Mohlman et al., 2013). Indeed, deterioration of cognitive functions is a well-established feature of normal aging, with particularly marked negative effects of age in the hippocampal-dependent memory domain (Salthouse, 2011), which is exacerbated to a greater degree in neurodegenerative disease such as AD (Apostolova et al., 2012). Interestingly, several studies have reported an association between elevated cortisol levels and both worse memory performance in the healthy older population (Almela et al., 2012; Gulpers et al., 2019; Hidalgo et al., 2016; Lenze and Wetherell, 2011; Montoliu et al., 2018) and anxiety (Almela et al., 2011; Hidalgo et al., 2014; Mantella et al., 2008). Of note, higher levels of cortisol are a well-established feature of AD, although the mechanism responsible for HPA axis hyperactivity is unknown (Gil-Bea et al., 2010; Peskind et al., 2001). Work in developing rodent models and humans have shown that stress or exogenous CORT administration can drive accelerated aging (Bath et al., 2016; Ridout et al., 2018; Sullivan and Holman, 2010), with implication for cognitive and emotional pathology (Bath et al., 2017; Goodwill et al., 2018, 2019). Accordingly, cortisol-reduction strategies, such as odorant exposure, may be one pathway to reducing accelerated cognitive and health-related burdens of anxiety and the aging process. In the same vein, the effect of odorants exposure on amygdala activity has to be elucidated, given its connectivity with both the hippocampus and the olfactory bulb, along with its well-known hyperactivity associated with anxiety disorders (Drevets, 2000). Like the hippocampus, the amygdala modulates the activity of the HPA axis (Jankord and Herman, 2008). Nevertheless, although hippocampal neurons exert an inhibitory effect on the activation of the HPA axis, the activity of the amygdala exerts a significant facilitatory effect (Feldman et al., 1995; Gray et al., 1989). Interestingly, it has been recently reported a serotonergic modulation of the amygdala with a decrease of its activity through activation of the $5HT_{1A}$ receptors (Sengupta et al., 2017). Furthermore, projection neurons of this region form reciprocal synapses with GABA inhibitory interneurons, which dampen neural activity of the amygdala. With age, the number of inhibitory interneurons declines, leading to increased drives of the HPA axis (for reviews see Prager et al., 2016; Nuss, 2015). Finally, the connectivity of the amygdala has been related to cortisol levels (e.g., (Burghy et al., 2012; Gee et al., 2013; Veer et al., 2012) as corticosteroid can induce weakening of amygdala connectivity (Henckens et al., 2012). Olfactory stimulation could counteract these effects and restore the activity (Fig. 2).

Altogether, these results suggest that olfactory stimulation or training could improve negative affective states observed in older subjects or patients with neurodegenerative diseases. Because behavioral markers of olfactory function are impaired in these populations (Murphy et al., 2002; Pinto et al., 2014; Vennemann et al., 2008), one can ask how olfactory training can be efficient if there is disruption in odor processing. One argument toward the efficiency of olfactory training is that it improves olfactory function in patients with impairments in olfactory sensory function (Damm et al., 2014; Hummel et al., 2009; Konstantinidis et al., 2013; Sohrabi et al., 2012), and significantly improves general well-being and decreases depressive symptoms in aged people (Birte-Antina et al., 2018). Similar efficiency of odor stimulation in adult patients suffering from depression has also been reported (Komori et al., 1995). These studies have shown efficiency of olfactory training through the use of daily short-term exposure to odors over a period of several weeks (5–20 weeks) (Birte-Antina et al., 2018; Damm et al., 2014; Hummel et al., 2009; Komori et al., 1995; Konstantinidis et al., 2013). The nature of odorants that have been used differs between studies. It seems that older people are less sensitive to heavy molecules, which suggests the use of light-weight molecule odors (Poletti et al., 2017). However, lemon, eugenol, eucalyptus, phenyl ethyl alcohol, and orange, which are a mix of heavy and light molecules, are often retrieved in efficient olfactory training protocols (Birte-Antina et al., 2018; Damm et al., 2014; Hummel et al., 2009; Komori et al., 1995; Konstantinidis et al., 2013). Therefore, the strategy may be to vary the nature of odorants and ensure that, if some odorants are familiar, they have a positive association or rating by the subject, as well as to train subjects with short exposures over extended periods of time.

5. Conclusions

Anxiety disorder leads to the loss of friends and relatives, decreased mobility, greater isolation, increase stressful situation, or changes in food intake that are further exacerbated with aging. These contribute to a decrease in the quality of life and possibly more rapid decline in cognitive and emotional function associated with aging, and possibly accelerated aging. Indeed, people with anxiety disorder have shorter telomeres than those without a mental health disorder, which has been used as an index of cellular aging (Verhoeven et al., 2015). Treatment against anxiety in late life is a challenge, given concerns about medication side effects, frail patients, and medically ill patients due to other treatments (for Alzheimer's or Parkinson's disease for instance). The use of odor therapy to accompany or potentiate the pharmacological treatment against anxiety in normal and pathological aging can be step forward to a better health care of patients.

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