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

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Abstract

Anxiety disorders represent one 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. Further, 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 non-medicinal 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.

Keywords: Anxiety, Normal Aging, Odorants, Neurodegenerative disorders

1. Introduction

Anxiety disorders, (including generalized anxiety, panic disorder, social anxiety disorder, post-traumatic stress disorder, and specific phobias) represent one of the most common classes of psychiatric disorders, impacting nearly 4% of the global population (World Health Organization), and disproportionately affecting females (~2x greater risk relative to males). In the U.S. 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 (ADAA Journal of Clinical Psychiatry). This likely underestimates the true cost of this disorder, as nearly 2/3 of those afflicted by anxiety disorders do not seek treatment, and are likely not counted in epidemiological studies. Furthermore, while a variety of treatment options exist, including cognitive behavioral therapy and panoply of pharmacological interventions, a significant percentage of individuals seeking treatment will not respond effectively to a given intervention. 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 heterogeneity of the disorder, their high co-morbidity with other neuropsychiatric and neurological disorders, and the likely evolutionary origins of anxiety. Anxiety, including vigilance, has likely evolved to protect the individual from potential harm, and is normal part of everyday life. It is only when this signal become engaged in inappropriate contexts or exaggerated in its degree or persistence that it becomes pathological. Thus, imaging and post-mortem approaches to identify the neural basis of feelings of anxiety will likely need to be focused on identifying magnitude and contextual/situational regulation of the complex circuit underlying this state. Further, given the diversity of triggers and

subjective differences in feelings of anxiety, the neural underpinnings of these feelings are likely to differ markedly across individuals.

To understand the neurobiological basis of anxiety-like behaviors some have looked to animal models. Some of the earliest studies include lesioning of brain regions such as amygdala as well as parts of the medial temporal lobe. The result was what was later termed Kluver-Bucy syndrome (Afifi and Bergman, 1998), where, along with other symptoms, there is a near complete loss of aggression, docility, lack of social anxiety, and inability to identify the emotional importance of events (Bourtchouladze, 2004). While many early studies clearly link the amygdala with emotional regulation, this may be in part due to its role as a principle modulator of engagement of the hypothalamic-pituitary-adrenal (HPA)-axis for the fight or flight response. However, anxiety is likely far more than mere engagement of sympathetic arousal (LeDoux and Pine, 2016). In an attempt to map out 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, medial prefrontal cortex, thalamus, hippocampus and associated regions have been identified as regulator of the detection, generation, and maintenance of freezing behavior in response to threat conditioning (Pare et al., 2004; Quirk et al., 1996). Still others have begun mapping out the roles of regions of basal ganglia, frontal cortex, and medial extended amygdala, which may serve to guide social approach and social avoidance following repeated social defeat (Bath et al., 2017; Takahashi et al., 2018). These studies have helped to inform work in humans, including neuroimaging, post-mortem, and PET studies, and to reify that anxiety disorders are not likely to be able to be reduced to disturbance in single region, receptor, or even sub-circuit within the brain. More work will be needed, including work to understand the underlying basis of sex differences in risk, the

reason for high comorbidity between anxiety disorders and other neurological and neuropsychiatric conditions, and the effects of aging on emergence of pathology.

2. Anxiety with aging and aged-related disorders

Approximately 15% of elderly individuals go on to develop anxiety disorders. 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. However, they are often under-recognized in older adults and erroneously attributed to a normal consequence of the aging process.

Anxiety is a risk factor for many age-related medical conditions, including cardiovascular disease, stroke, and cognitive decline. In both animals and humans, an association has been documented between anxiety symptoms and reduced cognitive functions (mainly memory and executive functions) in older individuals without dementia (Potvin et al., 2011; Yochim et al., 2013). In mice, anxiety is correlated with impaired spatial learning and memory (Wang et al., 2014). In a sample of older individuals without dementia, anxiety symptoms were associated with memory loss and predicted both cognitive decline and impairment in daily-life functioning after 3 years (Sinoff and Werner, 2003).

Longitudinal studies have shown that risk factors for anxiety include sex and comorbidity with physical disease. Moreover, personal circumstances including coping style and prior stressful life events, also play a role in moderating risk for pathology. Further, anxiety symptoms occurred more frequently in individuals with mild cognitive impairment (MCI) than in cognitively intact elderly individuals and were associated with a significant increase in risk of progression from MCI to Alzheimer's disease at 3-year follow-up (Palmer et al., 2007). Finally, anxiety symptoms often accompany co-morbid psychiatric as well as neurodegenerative diseases in the aging population. For instance, the likelihood of developing

Parkinson's disease (PD) was greater in patients with anxiety than patients without anxiety, and the severity of anxiety correlated with the risk of PD (Lin et al., 2015). In parallel, anxiety disorders are common in PD (with an estimated prevalence ~40%) and are an important determinant for quality of life (Pontone et al., 2009; Broen et al., 2016). Indeed, anxiety disorders contribute to the severity of motor symptoms (Leentjens et al., 2012) and have recently been associated with more severe cognitive (specifically memory) impairment (Dissanayaka 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. Strengthening the relationship between dopaminergic dysfunction and anxiety, a recent cross-sectional analysis showed that lower caudate dopaminergic transporter uptake is associated with higher level of anxiety (Picillo et al., 2017), and are in agreement with work in non-PD individuals with anxiety disorders (Mathew et al., 2001). 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, are anxiolytic medications. Currently, anxiolytic drugs such as benzodiazepines (one of most frequently prescribed anxiolytic drugs) are often used in treatment of anxiety despite loss of efficacy with repeated use and side-effects such as withdrawal symptoms and drug dependence (Lenze et al., 2009). Due to the side effects of traditional anxiolytic treatment, 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). Additionally, 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). Further, cognitive behavioral therapy (CBT) has been shown to be efficacious as an evidence-based treatment for older adults with generalized anxiety disorders (Stanley et al., 2003; Stanley et al., 2009) with greatest benefit when done in combination with SSRI treatments (Rosnick et al., 2013). Finally, among non-pharmacological 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

While the effect of anxiety on olfactory perception (threshold, memory, discrimination) has been well documented (Pollatos et al., 2007; Chen and Dalton, 2005; Havlicek et al., 2012; La Buissonniere-Ariza et al., 2013), 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 to 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; Lehrner et al., 2005) and decrease anxiety related feelings and behavior in humans (Diego et al., 1998; Lehrner et al., 2000; Perry et al., 2012; Tsang and Ho, 2010; Lehrner et al., 2005; Umezu et al., 2006; Kritsidima et al., 2010; Linck et al., 2010). 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; Schiffman et al., 1995b). 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 (Schiffman et al., 1995b; Abriat et al., 2007). 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 (Robin et al., 1999; Heuberger et al., 2001; Sano et al., 2002; Bensafi et al., 2002a; b; c).

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. While 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 as well as 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 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 or rose (Linck et al., 2010; Umezu, 2000; 1999; Cryan and Sweeney, 2011; de Almeida et al., 2004; Ceccarelli et al., 2004; Buchbauer et al., 1993) and also with green leaf volatiles *Z*-3-hexen-1-ol (leaf alcohol) and *E*-2-hexenal (leaf aldehyde) termed “green odor” (Tokumo et al., 2006; Nakatomi et al., 2008; 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 (Tokumo et al., 2006; Nakatomi et al., 2008; 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) (Herz, 2009; Faturi et al., 2010; de Almeida et al., 2004; 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 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 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, odorant 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 (ACTH) 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 following 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 (PVT) (Chowdhury et al., 2000; Dumont et al., 2000; Viau and Sawchenko, 2002; Kurumaji et al., 2003; Linden et al., 2004; Spencer et al., 2004). 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, PVT and the amygdala (Kim et al., 2005; Ito et al., 2009). 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 ACTH 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 following repeated stress (Fukada et al., 2007). These results suggest that odorants that reduce anxiety and 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 (Ito et al., 2009; Nikaido et al., 2011; Fukada et al., 2007).

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 one 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 with its 5-HT_{1A} receptors is another neurotransmission frequently associated with anxiety and anxiolytic drugs. Indeed, 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). Chioca et al (2013)

demonstrated that odorants such as lavender present similar action to reduce anxiety that involves the serotonergic system (Chioca et al., 2013).

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 GABAA receptors and serotonergic transmission, and thus may represent a powerful non-pharmacological anxiolytic tool to reduce anxiety, including in aging population.

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

Taken the above 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)(Figure 1). 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 to younger adults (Otte et al., 2005). In parallel, excessive levels of glucocorticoids have been linked to hippocampal atrophy and dysfunction in elderly humans (Lupien et al., 1998; Anacker et al., 2013), which may accelerate the aging process. Due to tight connections between the olfactory cortex and the hippocampus, one possibility is that odorant exposure could lead to changes in hippocampal activity, leading to a decreased

response of the HPA-axis and explaining its anxiolytic-like effect. This effect could be driven more specifically by the activation of 5HT_{1A} receptors that have been involved in anxiety disorders (Fuss et al., 2013). Of interest, this effect may also have an impact on delaying cognitive decline associated with both normal and pathological aging. 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). We propose that the use of odorants might reduce the impact of aging by promoting a neuroprotective response, as this has been already reported for physical exercise and/or cognitive stimulation (Kempermann et al., 1997; van Praag et al., 2000; Rosenzweig and Bennett, 1996).

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. 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 dampens 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). Olfactory stimulation could counteract these effects and restore the activity (Figure 1).

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 or Parkinson 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.

Disclosure statement

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Figure Legend

Figure 1. 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 HPA axis, altering basal glucocorticoid levels and release during stress response. Odor

exposure could be an efficient mean to decrease the hyper-activity of the HPA axis and glucocorticoid release given the intimate connections between the olfactory system and the hippocampus and amygdala.

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