



Review

Olfactory markers of depression and Alzheimer's disease



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ABSTRACT

Depression and Alzheimer's disease are two common and closely intertwined diseases in the elderly. Bio-markers for their early diagnosis would be helpful for clinicians. The brain areas involved in depression, Alzheimer's disease and in olfactory processing overlap, leading to suggestions that olfaction could constitute a potential marker of these diseases. Here, we review the literature in the relevant clinical and olfactory fields, and consider which olfactory measures and factors could serve as markers of these diseases. It has been reported repeatedly that there is an alteration of odor identification in Alzheimer's disease but not in depression. These observations provide strong arguments that this olfactory marker may serve as a complementary tool for the early screening of patients. Odor threshold detection and odor hedonic aspect may constitute complementary markers of the efficacy of depression therapy. However, there are numerous contradictory data and innovative methods are required to investigate whether investigations of olfaction can usefully contribute to routine clinical practice.

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Contents

1. Links between depression and Alzheimer's disease	262
2. Reasons for investigating olfactory function in cases of depression and AD	263
2.1. A mutual relationship	263
2.2. Neuro-anatomical links	263
2.2.1. The olfactory bulb	263
2.2.2. Amygdala	263
2.2.3. Hippocampus	264
2.2.4. Frontal cortex	264
3. Olfactory deficits in depression and AD	264
3.1. Odor threshold	264
3.2. Odor identification	264
3.3. Odor recognition memory	265
3.4. Odor hedonicity	267
3.5. Odor intensity evaluation and discrimination	267
4. Conclusion	267
References	268

1. Links between depression and Alzheimer's disease

Depression and Alzheimer's disease (AD) are both common diseases in the elderly. Depression is also a major public health issue. Almost 1 in 5 of the United States population experience

a depressive episode during their lifetime (Kessler et al., 2003); and it has been reported that 1 to 2% of people aged over 65 have major symptoms of depression and 13 to 27% minor symptoms of depression (Olin et al., 2002). AD is the commonest cause of dementia (Sun et al., 2008). Clinicians and researchers have observed close links between these two diseases, although the link between depression and AD is not easy to characterize: is depression a risk factor for, a symptom of, or a stress reaction to, AD?

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Depression is the non-cognitive symptom most frequently associated with AD (Aalten et al., 2007), mostly expressed as minor symptoms of depression (Janzing et al., 1999). Depression affects 15 to 25% of AD patients (Cummings, 1997) and 80% of these patients have neuropsychiatric symptoms including affective symptoms (Robert and Benoit, 2010).

Depression could be considered to be a risk factor of AD. The neurotoxic effects of depression (Krishnan and Nestler, 2008) could lead to long-term neurological lesions which could lead to AD. These neurotoxic effects include atrophy of hippocampal cells due to oversecretion of cortisol or abnormally low concentrations of neurotrophic factors including BDNF (Brain-derived neurotrophic factor). Little is known about such interactions. However, a recent review suggests a model including the hypothalamic–pituitary–adrenal (HPA) axis and serotonergic system: substantial release of glucocorticoids due to abnormal functioning of the HPA axis in depression may alter receptors and lead to structural modification of the limbic system such that it becomes more vulnerable to AD neurodegeneration (Sierksma et al., 2010). Dysfunction of the HPA axis has been observed in AD, leading to abnormally high cortisol levels and this may influence the production of amyloid plaques (Lee et al., 2009). Besides, serotonin disfavoring the production of A β (Nitsch et al., 1996), and an abnormally low abundance of serotonin receptors have been observed in the hippocampus and the frontal cortex of AD patients (Reynolds et al., 1995). This model is consistent with findings that a history of depression may increase the risk of developing AD (Ownby et al., 2006). Another study reported an increase of amyloid plaques and neurofibrillary tangles in the hippocampus of depressed patients (Rapp et al., 2006). Also, a study with twins showed that the risk of developing dementia was three times higher for subjects with than without a history of depression (Brommelhoff et al., 2009).

All these various studies illustrate how depression and AD are closely intertwined; early detection and discrimination between them can therefore be difficult. Appropriate bio-markers for early diagnosis would be clinically valuable. Some researchers have suggested that various olfactory characteristics may constitute markers of these two diseases (Atanasova et al., 2008; Djordjevic et al., 2008). This review article presents arguments in favor of this hypothesis, describes the state-of-the-art concerning olfactory disorders associated with these two diseases and considers which olfactory features could be used to differentiate between depression and AD.

2. Reasons for investigating olfactory function in cases of depression and AD

2.1. A mutual relationship

Numerous studies indicate that there is a relationship between olfaction and depression. On the one hand, symptoms of depression are more prevalent among patients with olfactory loss than the healthy population (Deems et al., 1991; Seo et al., 2009). For example, a study comparing 374 patients with olfactory loss to 362 controls matched for gender and age found that the patients had higher scores than healthy subjects on a depression scale (Beck Depression Inventory) (Deems et al., 1991). Also, depressive symptoms have been observed in 60% of patients with olfactory loss in the months after the beginning of olfactory deficits (Faulcon et al., 1999). On the other hand, olfactory deficits have been described in depressed patients. This point will be considered in more detail later in the paper. Are olfactory deficits a consequence or a cause of depression? A recent study suggests that olfactory disorders could cause depression (Oral et al., 2013): animals with olfactory bulbs

lesions display neural degeneration in habenular nuclei, a phenomenon associated with depressive symptoms in animals. Nevertheless, there is currently insufficient evidence or data to resolve this issue definitively, and further experimental works are required.

Reciprocity between olfactory disorders and the risk of AD have been reported. Olfactory impairment has been observed in patients who were genotyped for the presence of the ApoE epsilon4 allele (Bacon et al., 1998; Handley et al., 2006) and in those with mild cognitive impairment (Djordjevic et al., 2008). Also, a Japanese study has shown that among patients who have a genetic risk of developing AD, the risk is five times higher for those who are anosmic (Graves et al., 1999).

2.2. Neuro-anatomical links

We are not aware of any study that has investigated olfactory receptor integrity in depressed patients. However, numerous abnormalities in peripheral olfactory system have been observed in patients at the first stage of AD (Davies et al., 1993; Talamo et al., 1989).

Numerous brain areas including the olfactory bulb, hippocampus, amygdala, anterior cingulate cortex, orbito frontal cortex and habenula, which are altered in depression and in AD are also involved in olfaction processing.

2.2.1. The olfactory bulb

The olfactory bulb is the first relay for olfactory information. Bilateral olfactory bulbectomy in rodents leads to immune and endocrine alterations similar to those observed in cases of major depression (Song and Leonard, 2005). Stress, a predictive factor for depressive episodes in vulnerable subjects, can not only lead to typical symptoms of depression, including decreased neurogenesis in the hippocampus, but also decreased neurogenesis in the olfactory bulb (Mineur et al., 2007). The olfactory bulb volume has been found to be smaller in depressed patients than controls, and there is a negative correlation between olfactory bulb volume and depression scores (Negoiias et al., 2010). The authors suggested that this indicates a possible link between depression and decreased of neurogenesis in this brain area.

Dopaminergic neuron numbers in the olfactory bulb have been reported to increase (Mundiñano et al., 2011; Thomann et al., 2009) and the volume of the olfactory bulb decrease (Thomann et al., 2009) in AD patients. A higher level of beta-amyloid has been also observed in neocortex and hippocampus in bilateral olfactory bulbectomy rodents model (Aleksandrova et al., 2004). Moreover, a positive correlation between olfactory bulb volume and performance in the Mini Mental State test (MMS) (Folstein et al., 1975) has been shown for AD patients (Thomann et al., 2009).

Thus, the alteration of the olfactory bulb in both depression and AD could explain the impairment of the odor threshold (as described below) in these diseases.

2.2.2. Amygdala

The amygdala is involved in odor intensity perception, odor hedonic judgment and odor memorization tasks (Pouliot and Jones-Gotman, 2008). Anderson et al. (2003) has showed that the amygdala is specifically activated in response to odor intensity and does not depend on odor valence.

Numerous studies have reported abnormal amygdala activity in depression. However, there are contradictory data: some studies provide evidence of increased activity (Van Eijndhoven et al., 2009) whereas others indicate decreased activity of this brain area (Kronenberg et al., 2009) in depression. Some authors suggest that the volume of the amygdala could be decreased in patients without treatment and increased in patients receiving treatment (Hamilton et al., 2008).

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