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Long-term odor recognition memory in unipolar major depression and Alzheimer's disease



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ABSTRACT

Major depression and Alzheimer's disease (AD) are often observed in the elderly. The identification of specific markers for these diseases could improve their screening. The aim of this study was to investigate long-term odor recognition memory in depressed and AD patients, with a view to identifying olfactory markers of these diseases. We included 20 patients with unipolar major depressive episodes (MDE), 20 patients with mild to moderate AD and 24 healthy subjects. We investigated the cognitive profile and olfactory memory capacities (ability to recognize familiar and unfamiliar odors) of these subjects. Olfactory memory test results showed that AD and depressed patients were characterized by significantly less correct responses and more wrong responses than healthy controls. Detection index did not differ significantly between patients with major depression and those with AD when the results were analyzed for all odors. However, MDE patients displayed an impairment of olfactory memory for both familiar and unfamiliar odors, whereas AD subjects were impaired only in the recognition of unfamiliar odors, with respect to healthy subjects. If preservation of olfactory memory for familiar stimuli in patients with mild to moderate AD is confirmed, this test could be used in clinical practice as a complementary tool for diagnosis.

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1. Introduction

Major depression and Alzheimer's disease (AD) are often observed in the elderly. There is a partial overlap between the symptoms of these two diseases. Indeed, the anxiety, somatic and memory disturbances often observed in the elderly may make diagnosis difficult. It also remains unclear whether depression is a risk factor (Copeland et al., 2003; Fuhrer et al., 2003; Gabrylewicz et al., 2007), prodromal, a stress response or a symptom of AD (Aalten et al., 2007). Given the close anatomical links between the olfactory system and the brain circuits involved in memory (Savic et al., 2000) and emotion (Anderson et al., 2003) – two cognitive features frequently affected in subjects with AD and depression – the characterization of olfactory dysfunctions in these diseases

might potentially have clinical implications. Many recent studies (presented below) have investigated olfactory deficits in major depression and AD and have reported conflicting results. Olfaction is processed sequentially at two levels: peripherally, in the nasal epithelium (evaluation of odor detection threshold) and centrally (evaluation of odor identification, short- and long-term recognition memory, discrimination, intensity, familiarity and pleasantness). These last four central olfactory parameters have been investigated only occasionally in these two diseases. Two comparative studies have been carried out on odor identification in AD and major depression (Solomon et al., 1998; Pentzek et al., 2007). They reported a deficit for this parameter only in AD patients. The authors suggested that the identification test could be used as a complementary tool for differentiating between these two diseases in the elderly.

Two key characteristics of olfactory recognition memory make it a prime candidate for the study of affective and memory disorders. Firstly, olfactory memory is more emotional than visual and auditory

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memories (Herz, 2004). Secondly, olfactory memory tends to extend further back in time than the memories created by other types of sensory stimuli (Chu and Downes, 2002). Numerous studies have shown olfactory deficits in AD (for review, see Hawkes, 2003; Kovács, 2004) and more precisely concerning memory deficits in these patients (Gilbert and Murphy, 2004; Luzzi et al., 2007; Moberg et al., 1997; Niccoli-Waller et al., 1999; Nordin and Murphy, 1998; Razani et al., 2010). Besides, some authors have reported that odor recognition task could help screen patients at risk of developing AD (Murphy et al., 2009). Concerning depression, olfactory deficits have been well documented (Lombion-Pouthier et al., 2006; Negoias et al., 2010; Pause et al., 2001; Swiecicki et al., 2009); however, only one recent study (Zucco and Bollini, 2011) has reported a deficit in odor-recognition memory in major depressive (MD) patients. The authors have demonstrated that this deficit depended of the disease's severity and concluded that their odor-recognition task could be used as an additional tool for discriminating between patients with major depressive episodes (MDE) of different severities. However, authors used a short-term memory task: each target odor was presented during 4 s and 3–4 s later, each participant had to smell four test tubes (one target odor and three competitors) one by one. Subject had to choose the correct tube between the fourth. Given that the long-term episodic memory is impaired in both MD and AD patients, we thought that the study of long-term olfactory memory can bring new insights concerning the functioning of memory in these diseases. Indeed, our study investigated for the first time the comparison of long-term olfactory memory performances in AD and MD patients.

Olfactory recognition memory tests require a time interval to be left between the learning and recognition phases. In long-term olfactory memory tests, this time interval is generally a few minutes to a few hours and may even be as long as several months or years. To our knowledge, no study has yet compared long-term odor recognition memory in subjects with AD and depression. Furthermore, previous studies have used mainly common and household odors, making it impossible to differentiate between the contributions to test the performance of the subject's previous knowledge of the odor and their memory from the test exposure. Finally, if learning is explicit during the first odor presentation session of the memory test, subjects often try to identify odors (verbalization strategies), thereby improving the quality of restitution during the second, odor recognition phase of the memory test (Rabin and Cain, 1984). This phenomenon biases the results and deviates from the real conditions in which odors are learnt.

In this study, we investigated long-term olfactory memory in depressed patients and patients with AD, comparing the performances of these two groups. We also developed an original olfactory test, using both familiar and unfamiliar odors, including incident learning reflecting fortuitous encoding. Our test also prevents the use of verbalization-based learning strategies, thereby providing a more realistic assessment. In this test, the familiar odors were odors encountered in everyday life. The unfamiliar odors were created such that they would be unknown to the participants, to reflect a new learning. Our recognition test corresponds to the restoration of certain items of information to determine whether or not an item has been encountered before. It does not require the active recovery of information, such as temporo-spatial context or odor identification. Moreover, as previous studies have demonstrated a loss of smell in the elderly (Doty, 1991; Schiffman, 1997), we compared the olfactory performances of the patients recruited in our study with those of healthy elderly controls. Given the long-term memory deficits previously reported in depressed subjects (Gupta and Kar, 2012), we predicted that these patients would fail to recognize odors. Subjects with mild to moderate AD are characterized by impaired learning of new information. We therefore predicted a deficit of long-term olfactory memory only for unfamiliar odors in these patients.

2. Methods

2.1. Subjects

Twenty-eight subjects with mild to moderate AD (McKhann et al., 2011) and thirty patients with unipolar major depression episodes (MDE) were recruited at the hospital (in Tours, France). Eight patients with AD and ten with MDE were excluded from the study due to ineligibility (psychotic features, eating disorders or addictions) or protocol violations (missing data, serious medical problems). We finally included 20 patients with AD, 20 with MDE and 24 healthy controls.

All of the subjects were over the age of 50 years. Patients with MDE (mean age: 64.9 ± 11.2) were included on the basis of a diagnosis, according to DSM-IV criteria (1994), of acute unipolar MDE (a single or recurrent episode). The inclusion criterion for depressed patients was a MADRS (Montgomery and Asberg, 1979) score of more than 20/60 (mean MADRS score: 29.2 ± 7.7). All MD patients included in this protocol were treated with antidepressant treatments (escitalopram, venlafaxine, paroxetine, seropram) which are the inhibitors of serotonin reuptake or the inhibitors of serotonin–norepinephrine reuptake. In addition, four patients had anxiolytic treatment, two had antihypertensive therapy, two had an antidiabetic treatment, and another had an antihistamine treatment. Half the patients had a commonly prescribed treatment in AD (memantine). Besides, five MA patients were treated with antidepressants (escitalopram, mianserine). These antidepressant treatments were prescribed to treat anxiety but none of the MA patients had a diagnosis of major depression episode.

Subjects with AD (mean age: 73 ± 11.2) were included according to the criteria of McKhann et al. (2011), including clinical findings, neuropsychological evaluations and brain imaging. The Mini Mental State Examination score (Folstein et al., 1975) for AD subjects exceeded 15/30 (mean MMSE score: 19.4 ± 3.1) and, for inclusion in this study, an absence of MDE was required for AD patients.

A control sample of 24 healthy volunteers (mean age: 67 ± 12.7) with no history of mental or neurodegenerative illness was included. These subjects were matched with the patients for age, educational level and smoking status.

The severity of depressive symptoms and the global efficiency of all participants were evaluated with the Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979) and the MMSE.

The exclusion criteria for all subjects included head injury, current substance abuse, odor allergy, current cold or any alteration to their sense of smell. The participants were selected on the basis of an absence of anosmia to the odorants used in this study.

The characteristics of the groups are presented in Table 1.

2.2. Procedure and experimental design

This study was approved by the local ethical committee board (Comité de Protection des Personnes Tours Ouest-1, France) and was conducted in accordance with good clinical practice and the Declaration of Helsinki. This study was prospective and observational.

The experimental procedure was clearly explained to all participants, who provided written informed consent before participating. The participants were informed that they were free to discontinue testing at any time.

Before testing, the participants were informed that they were going to undergo olfactory tests. However, the term “olfactory memory” was never used.

A classic method was used to investigate the long-term olfactory recognition memory. It is based on a yes–no-recognition task, in which a first set of stimuli is presented (odor exploration, encoding), followed by a second set of stimuli comprising mixed stimuli from the first set with novel stimuli interleaved

Table 1

Demographic and clinical characteristics of the three groups of subjects (S.D.: standard deviation).

	Depressed patients (n=20)	AD patients (n=20)	Healthy controls (n=24)
Female/male ratio	15/5	14/6	17/9
Mean age (years) (S.D.)	64.9 (11.2)	73.0 (11.2)	67 (12.7)
Age range (years)	50–98	53–87	51–98
Non smokers/smokers ratio	16/4	15/2	24/2
MMSE, mean score (S.D.)	24.9 (3.0)	19.4 (3.1)	28.5 (1.0)
MADRS, mean score (S.D.)	29.2 (7.7)	8.6 (6.3)	3.3 (2.9)
Socio-educational level, mean score ^a	2	1.75	1.88

^a Socio-educational level was calculated on a three-level scale (1, 2 and 3 correspond to primary, middle and high school levels, respectively).

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