

Year : 2014
Volume : 1
Issue Number : 2
Doi Number : 10.5455/JNBS.1395921963

Article history:

Received 28 March 2014
Received in revised form 15 May 2014
Accepted 10 July 2014

IS DETECTING EARLY ONSET OF ALZHEIMER'S DISEASE IS GAINING A "NEW IDENTITY"? OLFACTORY DYSFUNCTION AS AN ERP BIOMARKER OF ALZHEIMER'S DISEASE.

ALZHEİMER HASTALIĞINDA ERKEN TANI YENİ BİR KİMLİK Mİ KAZANIYOR? ALZHEİMER HASTALIĞINDA BİR ERP BİYOMARKERİ OLARAK KOKU DİSFONKSİYONU

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Abstract

The olfactory system is vital mechanism for our survival to interact with the environment, influencing not only on odor detection but also on nutrition, social behavior and well-being. Current findings suggest that before the onset of any cognitive decline reflecting early sign of dementia, dysfunction in the areas processing olfactory information is present at the early stages of Alzheimer's disease (AD). Behavioral test including thresholds, odor identification, recognition memory tasks are the most common types of odor measurement. However, recent neuroimaging techniques using measures of brain response, including Olfactory Event Related Potentials (OERPs) suggested the potential for detection of AD at the early preclinical stage. The importance of olfactory event related potentials and their relation with AD appear to be very promising.

Keywords: Olfactory Event Related Potentials (OERPs), Alzheimer's disease, Age, Olfaction, Apolipoprotein E

Özet

Koku alma sistemi bizim çevre ile etkileşimimizde hayatta kalmamız sağlayan, sadece koku algılamayı değil aynı zamanda beslenme, sosyal davranış ve iyi olma halini etkileyen hayati bir mekanizmadır. Güncel bulgular, koku bilgi işleme alanlarında fonksiyon bozukluğunun, Alzheimer hastalığının (AH) erken aşamalarında, erken bunamayı yansıtan herhangi bir bilişsel gerileme başlamadan da mevcut olduğunu göstermektedir. Koku eşikleri, koku tanımlama, tanıma bellek görevleri koku ölçümü için kullanılan en yaygın davranış testi türleridir. Ancak, beyin yanıt ölçülerini kullanan yeni nörogörüntüleme teknikleri Alzheimer hastalığının klinik öncesi aşamasında, Koku Olaya İlişkili Potansiyeller'in (KOİP), hastalığın tespitinde önemini vurgulamaktadır. Koku olaya ilişkin potansiyeller'in (KOİP) Alzheimer hastalığı ile ilişkisi ve önemi çok umut verici görünmektedir.

Anahtar Kelimeler: Koku Olaya İlişkili Potansiyeller (OERPs), Alzheimer Hastalığı, Yaş, Koku Alma, Apolipoprotein E

1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disease, related with early cognitive and behavioral dysfunctions, particularly in memory domain (Chapman et al., 2011). Although the disease mostly seen in the elderly, it can occur in middle to late adult life. This irreversible and progressive disorder insidiously destroys short – term memory, and finally goes further to destroy long term memory accompanied by cognition loss and functional decline; thinking, deterioration of language, perceptual and motor skills, mood instability (DSM-IV). AD worsens as it progresses, unresponsiveness occur in advanced stages followed by severe loss of

mobility and control of bodily functions, and eventually leads to death (National Institute of Aging). According to NHS (National Health Service), the worldwide prevalence of Alzheimer's disease was 26.6 million in 2006. Current therapeutic advances and preventive approaches have small impact on the progression of the disease, yet can significantly contribute to delay in the global burden of AD (Brookmeyer et al., 2006). However, such contributions do not give significant outcomes, since the causes of AD are not yet known and postmortem autopsy and brain biopsy are the primary features for a definite diagnosis (Morgan and Murphy, 2012; Brookmeyer et al., 2006).

Genetic studies have confirmed that 10 percent of cases

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begin before the age of 60 are emerging as a result of a genetic mutation which is called the Apolipoprotein (ApoE) $\epsilon 4$ allele: a genetic risk factor for AD (Bertram and Tanzi, 2005; Teter et al., 2002; Farrer et al., 1997; Blacker, 1997). Being carrier of even a single the Apolipoprotein (ApoE) $\epsilon 4$ increases the emergence of the disease by a factor of three in men and four in women (Morgan and Murphy, 2012; Blacker, 1997; Combarros et al., 2002; Bertram, 2005; Farrer et al., 1997). Presence of the allele is associated with olfactory deficit accompanied by dysfunction in olfactory threshold sensitivity, odor identification, odor recognition memory, and odor fluency (Morgan and Murphy, 2012). Neuroimaging studies have found that degenerative changes in the olfactory system can be detected with using Olfactory Event Related Potentials (OERP) before the onset of any cognitive decline reflecting early sign of dementia, dysfunction in the areas processing olfactory information is present at the early stages of Alzheimer's disease (AD).

2. The Olfactory System

The olfactory system is vital mechanism for our survival to interact with the environment, influencing not only on odor detection but also on nutrition, social behavior and well-being (Huart et al., 2013; Ozdener and Rawson, 2004). These regions involved in olfactory system are located in medial temporal areas which are essential for conscious memory for facts (Squire et al., 2004). Odor identification is particularly sensitive to several cognitive changes with dementia (Morgan and Murphy, 2012). During the preclinical stage, although there is no any alarming cues about dementia, toxic changes, particularly in olfactory system, take place in the brain, and during this latent period, these areas undergo early neuropathological change in Alzheimer's disease (Squire et al., 2004; Murphy, 1999; National Institute of Aging). It was shown that abnormal accumulation of proteins that form amyloid plaques and tau tangles known as a primary marker of Alzheimer's disease throughout the brain (Huart et al., 2013; National Institute of Aging). This process causes neurons to work less efficiently, and eventually losing their ability to function, communicate with each other, and eventually ends in death (National Institute of Aging; Huart et al., 2013). Figure 1 shows Alzheimer type degenerative changes in the olfactory system, depicting the accumulation of neurofibrillary tangles (a protein as a primary marker of Alzheimer's disease).

Odor molecules reach the olfactory cleft, stimulating the olfactory receptor neurons that synapse with neurons at the olfactory bulb. The olfactory information is then carried to the primary olfactory cortex, including piriform cortex, located in the telencephalon and relates to the perception of smell (Piredda et al., 1985); entorhinal cortex which is located in the medial temporal lobe and functioning as center in a widespread network for memory and navigation (Hafting et al., 2005); periamygdaloid cortex located in the rhinencephalon; anterior olfactory nucleus, olfactory tubercle (Ozdener and Rawson, 2004). The information is then projected via primary olfactory cortex, among other areas, including the orbitofrontal cortex located in the frontal lobe, involved in the cognitive processing of decision-making (Kringelbach, 2005); the insular cortex located within the lateral sulcus, involved in consciousness

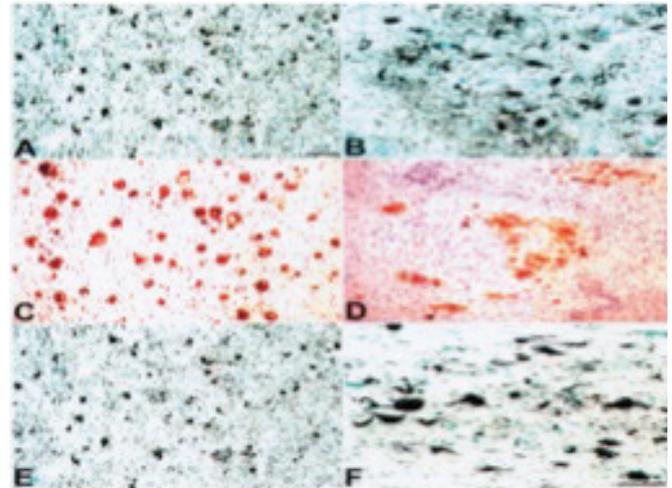


Figure 1. Photomicrographs illustrating the AD-type degenerative changes in the olfactory system in Alzheimer's disease (AD), depicting the accumulation of neurofibrillary tangles (a protein as a primary marker of Alzheimer's disease) in the frontal cortex (A) and in the olfactory bulb (B) (Gallyas silver technique). C and D also present amyloid β deposition in senile plaques of the frontal associative cortex and olfactory bulb, respectively. E/ F depict an accumulation of neurofibrillary tangles in the frontal associative cortex (E) and anterior olfactory nucleus (F) showing degenerative changes of the olfactory system in the case of a young familial Alzheimer's disease. Adapted from Christen-Zaech and et al. 2003.

and related to emotion (Phan et al., 2002) or the regulation of the body's homeostasis (Oppenheimer et al., 1992); thalamus situated between the cerebral cortex and the midbrain, playing roles in the relaying of sensory and motor signals to the cerebral cortex (Sherman, 2006), and regulation of sleep and alertness; Hippocampus, a major component of the brain located in the medial temporal lobe and part of limbic system, having vital functions including the consolidation of information from short-term memory to long-term memory and spatial navigation (Kheirbeck and Hen, 2011). Additionally, it is the one of the first regions of the brain that shows a disruption as one of the earliest signs of Alzheimer's disease, leading a memory loss and disorientation (Hampel et al., 2008; Prull et al., 2000). Hypothalamus is the last destination where the information is processed for further analysis, and it is located below the thalamus. It has several major functions, including the regulation of hormone secretion, body temperature and some activities of the autonomic nervous system; hunger, thirst, fatigue, sleep, and circadian rhythms, as well it plays role on important aspects of parenting and attachment behaviors (Blair et al., 2006; Saper and German, 1987). Figure 2 shows a significant correlation between Alzheimer type cortical changes and the density of neuropil threads (loss of axon, dendrites and synapses), neurofibrillary tangles and senile plaques (extracellular deposits of beta amyloid in the gray matter of the brain) in the olfactory system.

Taking into consideration the fact that studies of the functional processes of the olfactory system will shed light on early diagnosis and prevention of Alzheimer's disease and may lead to new therapeutic approaches in the treatment of AD.

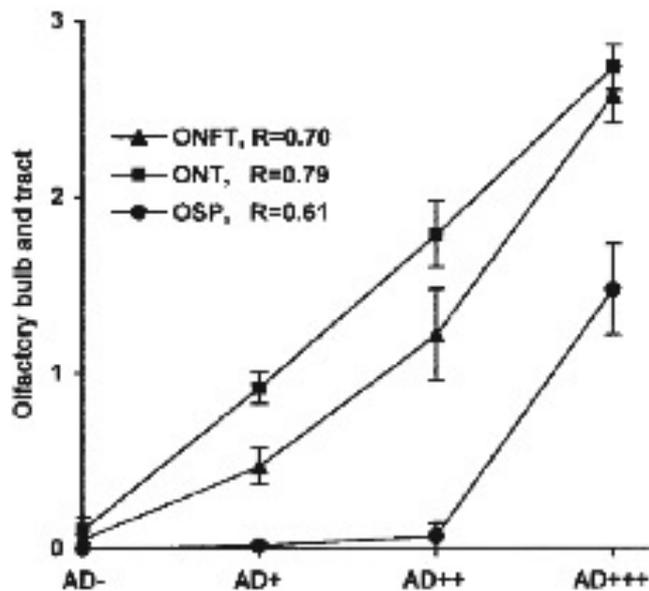


Figure 2. Early Olfactory Involvement in Alzheimer's disease. The severity of the changes in the olfactory system are significantly associated with the densities of neurofibrillary tangles (ONFT), neuropil threads (ONT) and senile plaques (OSP) in the olfactory system in the groups: without Alzheimer's disease (AD-), with discrete (AD+), moderate (AD++) and with severe (AD+++) cortical involvement, progressively increased with the severity of the cortical involvement. Adapted from Christen-Zaech et al., 2003.

3. The Olfactory event related potentials

There are many ways to measure olfaction. Behavioral test including thresholds, odor identification, recognition memory tasks are the most common types of odor measurement. However, recent neuroimaging techniques using measures of brain response, including fMRI and Event Related Potentials suggested the potential for detection of AD at the early preclinical stage (Bondi et al., 2005; Morgan and Murphy, 2012; Peters et al., 2003). Depending on ApoE status, recent OERP studies have found significant brain activity during odor identification, however fMRI studies revealed mixed results showing increased activation in ApoE+ individuals (Han et al., 2007; Bookheimer et al., 2000; Lind et al., 2006) or reduced activation in ApoE+ carriers (Lind et al., 2006) (Morgan and Murphy, 2012). Backman et al. demonstrated that individuals who were positive for the genetic risk factor the ApoE+ showed greater activation in the left and medial frontal gyrus, bilateral fusiform gyri, left pyramis and the parietal cortex (1999; Morgan and Murphy, 2012). Peters et al. also demonstrated electrophysiological findings of individuals with AD and with mild cognitive deficit, showing significantly lower olfactory functioning than healthy age-matched comparison group (Peters et al., 2003). More recently, Morgan and Murphy indicated that individuals

with the ApoE+ showed different ERP latency with the onset of olfactory stimuli, however visual stimuli did not elicit any significant ERP component (2012). One of the robust findings from their study was to show significant different olfactory event related responses (OERP) based on ApoE+ condition and interactions with the age for each group. ApoE+ individuals produced significantly longer N1 and P2 latencies in comparison with ApoE- individuals.

A few previous studies using olfactory event-related potentials have demonstrated contradictory results. Despite the absence of psychophysical dysfunction of olfactory system, Sakuma et al. (1996) reported abnormal potentials, however, although the individuals odor identification scores were abnormal Hawkes and Shepard (1998) found normal event related potentials (Peters et al., 2003).

Despite few contradictory studies, a major effort is emerging to identify ERP biomarker of AD during odor identification. The most common peaks examined in OERP research are the N1, P2, and N2 are early exogenous components (stimulus driven activation) of the olfactory event related responses (OERP) that are associated with odor threshold and odor identification (See Figure 3) (Tonoike et al., 1990; Murphy, 1994, Morgan and Murphy, 2012; Krauel et al., 1998). These OERPs are more sensitive than classical behavioral methods measuring odor identification, and show higher specificity to ERPs obtained in other domains e.g. auditory or visual (Wetter and Murphy, 2001). A recent fMRI study revealed that behavioral tests showed no significant differences between male and female individuals, however increasing age correlated with a decline in odor identification performance (Evans et al., 1995). A significant correlation has been found between P2 latency and the generation of olfactory processing. Age related decline has been observed in N1-P2 inter-peak amplitude (Evans et al., 1995). It was also demonstrated that when the visual stimuli were demonstrated individuals with the ApoE+ showed different OERP latencies for identification of olfactory stimuli but not visual stimuli (Murphy and Morgan, 2012; Wetter & Murphy, 2001). ApoE+ individuals correctly identified and quickly responded to picture identification task, whereas the same ApoE+ individuals showed difficulties at odor identification.

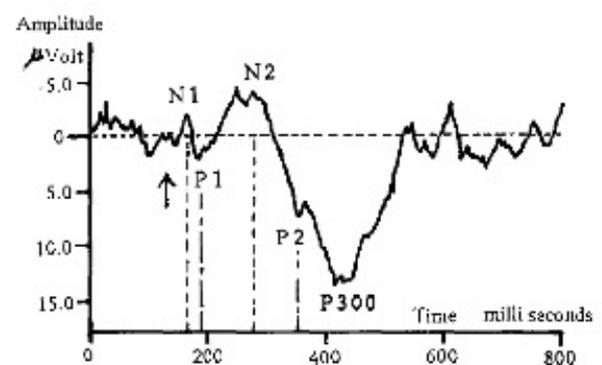


Figure 3. An illustration of the Olfactory Event Related Potentials (OERP) waveform with labeled peaks: The early major negative components N1 and N2 are followed by second late positive component P2 and P3 as endogenous potential with a latency of 250-600 msec reflecting processes involved in stimulus evaluation or categorization. Adapted from Tonoike et al., 1990.

In another OERPs study, when the N1, P2, and N2 OERPs were compared to traditional olfactory psychophysical testing in an age related study, they found that when the odorant stimulus presented to the individuals the older participants showed smaller peak latencies and also longer ISIs (Inter-Stimulus-Intervals). Peak amplitudes also increased with longer ISIs for older males (Morgan et al., 1997; Morgan and Murphy, 2010, 2012). The P3 component reflecting cognitive processing; classification speed, evaluation of the stimuli is also used in OERP studies (Polich, 2007). The findings revealed that P3 peak latency correlates with neurophysiological test, measuring memory and classification speed (Covington et al., 1999; Murphy and Morgan, 2012).

Forecasting the early onset of AD, Chapman et al. used OERP to compare individuals with Mild Cognitive Impairment (MCI) (2007). Several different ERPs related memory storage and stimuli relevancy and P3 component obtained in a perceptual/cognitive paradigm. MCI individuals were separated into two groups: AD progress and stable groups, indicating the disease is progressing and there is no progress, respectively. They demonstrated that MCI progress individuals showed smaller P3 amplitude to relevant stimuli than MCI stable groups, implying that difficulty in evaluating and discriminating of relevant and irrelevant stimuli may predict AD-like cognitive decline (Chapman et al., 2011).

Current findings suggest that before the onset of any cognitive decline reflecting early sign of dementia, dysfunction in the areas processing olfactory information is present at the early stages of AD (Doty, 1994; Murphy, 1999). Furthermore, although the olfactory alterations related to AD may appear together with agedness, individuals at the early stage of AD with mild dementia show poor performance on olfactory identification task than age-matched control group (Peters et al., 2003; Geisler et al., 1999; Doty et al., 1987). Overall, the results suggest that compared with other methods, olfactory event related potentials (OERPs) reflecting online measures of olfactory processing with fine-grained temporal resolutions are more sensitive to changes in the olfactory system (Morgan and Murphy, 2012; Luck, 2005). The importance of olfactory event related potentials and their relation with AD appear to be very promising. Further researches on this topic are rewarding and may deepen our understanding of the nature of AD. Finally, this method may give opportunity to capture the early onset of dementia at the very earliest stages and yet enhance diagnosis of AD.

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