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Auditory post-processing in a passive listening task is deficient in Alzheimer's disease

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HIGHLIGHTS

- Auditory post-processing in the form of a diminished late negative frontal wave is reduced in patients with Alzheimer's disease compared to age-matched healthy controls.
- Physiological aging does not affect auditory post-processing as measured activity does not differ between young and elderly healthy controls.
- The amplitude of the late negative frontal wave predicted short-term memory capacity deficits in the patients with Alzheimer's and could represent a valuable marker for these impairments.

ABSTRACT

Objective: To investigate whether automatic auditory post-processing is deficient in patients with Alzheimer's disease and is related to sensory gating.
Methods: Event-related potentials were recorded during a passive listening task to examine the automatic transient storage of auditory information (short click pairs). Patients with Alzheimer's disease were compared to a healthy age-matched control group. A young healthy control group was included to assess effects of physiological aging.
Results: A bilateral frontal negativity in combination with deep temporal positivity occurring 500 ms after stimulus offset was reduced in patients with Alzheimer's disease, but was unaffected by physiological aging. Its amplitude correlated with short-term memory capacity, but was independent of sensory gating in healthy elderly controls. Source analysis revealed a dipole pair in the anterior temporal lobes.
Conclusion: Results suggest that auditory post-processing is deficient in Alzheimer's disease, but is not typically related to sensory gating. The deficit could neither be explained by physiological aging nor by problems in earlier stages of auditory perception. Correlations with short-term memory capacity and executive control tasks suggested an association with memory encoding and/or overall cognitive control deficits.
Significance: An auditory late negative wave could represent a marker of auditory working memory encoding deficits in Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is characterised by a severe and progressing deterioration in patients' delayed recall, short-term memory capacity and executive functions. The precise neural mechanisms underlying the cognitive impairments in Alzheimer's

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disease (AD) are still not fully understood. An excellent method to image cognitive processes with a high temporal resolution is multi-channel EEG. When source analysis is performed, a reasonable separation of different event-related potential (ERP) components becomes possible and conclusions can be drawn about their generators in the cortex.

The actual encoding of short auditory stimuli takes place after stimulus offset and after initial auditory perception during auditory post-processing. Ruchkin et al. (2003) suggested that this 'post-processing' of auditory information is specifically characterised by a long-lasting negativity over bilateral frontal areas. Patients with AD present with reduced activation of frontal and temporal cortices during the encoding of verbally presented information (Peters et al., 2009). The authors suggested that both frontal executive control processes and language-related processing in temporal areas could contribute to the encoding deficits in AD. We recently found that such modality-specific late negative slow waves occur even after passive perception of single stimuli and are enhanced during active short-term memory tasks (Bender et al., 2010).

To the best of our knowledge, no studies have yet examined if and in which way the cognitive deficits present in AD are related specifically to changes in stimulus encoding during auditory post-processing (as measured by the late negative slow wave) and not in basic auditory perception per se. Passive listening without the necessary involvement of active executive control facilitates the examination of auditory processing contributions to encoding deficits which are not simply based on executive control problems. Despite not being directly relevant to a task, passively presented auditory stimuli still capture the subjects' attention and are automatically encoded (Kramer et al., 1995). Also, modality-specific late negative slow waves even occur in response to passively perceived stimuli (Bender et al., 2010).

The inhibition of irrelevant information (sensory gating) is another basic mechanism of focusing that makes efficient cognitive processing possible by restriction to potentially meaningful or salient material. Neuropsychological correlates of sensory gating are predominantly measures of attention (Potter et al., 2006; Thomas, 2010; Wan et al., 2008) and frontal executive function (Thomas, 2010; Wan et al., 2008) including working memory (Lijffijt et al., 2009; Thomas, 2010). The gating out of auditory stimuli has previously been found to be deficient in Alzheimer's disease (Ally et al., 2006; Cancelli et al., 2006; Jessen et al., 2001; Thomas, 2010). This deficit has been linked to a deficit in cholinergic transmission and to a dysfunction of the nicotinergic alpha7 ACHR (Koike et al., 2005; Olincy et al., 2006).

P50 sensory gating could be diminished as a consequence of a more rapid decrease of the late post-processing traces in AD patients, with the second stimulus not being filtered out efficiently because the neuronal representation of the first stimulus decays too quickly and thus has already vanished when the second stimulus is perceived. Even though P50 sensory gating reflects pre-attentional filtering, the strength of the late post-processing memory trace of the first stimulus could directly influence or correlate with the filtering of the second stimulus. On the other hand, sensory gating and post-processing could also represent two independent parameters. To investigate whether the sensory gating deficit is related to later automatic auditory processing stages in healthy participants and patients with AD, we examined whether auditory post-processing (as reflected by the auditory late negative wave) would correlate with sensory gating of P50.

We therefore aimed to examine whether a more rapid decay of the auditory late negative wave would occur in patients with AD in a passive listening task (dual click paradigm).We hypothesised that P50 sensory gating would positively correlate with the amplitude of the frontal negativity occurring during auditory post-processing. Based on the reduced P50 gating in patients with AD (Thomas, 2010) and our hypothesis of a reduced post-processing frontal negativity in this patient group (Peters et al., 2009), we assumed that this positive correlation would be weaker in the AD group. Source analysis was used to examine the hypothesis that bilateral sources in the auditory cortex could account for such automatic auditory post-processing traces. We hypothesised that the activity of these sources would be reduced in patients with AD. To gain hints about a possible functional significance of such auditory post-processing deficits in AD, we examined the correlations to the participants' performance in separately conducted tasks of short-term / working memory and executive function. Even though obtaining these neuropsychological data independently of the EEG data and using a passive listening task instead may have its disadvantages, we deliberately selected this approach since a passive listening task can be completed regardless of general disease severity or any existing executive control deficits and could provide a useful marker for auditory post-processing deficits. Similar to studies reporting that auditory processing potentials such as the P300 can be a useful diagnostic measure for AD (van Deursen et al., 2009; Filipović and Kostić, 1995; Jackson and Snyder, 2008; Papaliagkas et al., 2010), specific reductions in auditory post-processing may have a certain diagnostic value in this respect.

To examine these questions, we recruited patients with AD and a control group of healthy elderly participants. To account for possible aging effects, we further included a group of young healthy volunteers.

2. Methods

2.1. Subjects

22 Patients with AD were recruited from the memory clinic of the Department of Psychiatry, Heidelberg University. The diagnosis was made according to the NINCDS-ADRDA criteria (McKhann et al., 1984) and included patient's and caregiver's interviews, neurological and psychiatric examinations as well as neuroimaging (e.g. MRI), cerebrospinal fluid markers and neuropsychological testing. Patients completed the CERAD battery (Welsh et al., 1994), including the mini-mental state examination (MMSE) and tests of immediate as well as delayed verbal memory and verbal fluency (Morris et al., 1989). Moreover, digit spans and the logical memory subscale from the Wechsler Memory Scale (as described in Barth et al. (2005)) were applied. Disease severity was rated by the global deterioration scale (GDS) (Reisberg et al., 1988). Patients did not have a history of additional neurological or psychiatric diseases and did not receive antipsychotic medication except for three patients who used pipamperone for sleep induction. Two patients received a serotonin reuptake inhibitor.

23 healthy elderly control subjects were recruited from a local senior citizen program. No signs or history of neurological or psychiatric disorders were present. Elderly controls underwent the same thorough neuropsychological testing as the patients with AD (Supplementary Table S1). Three elderly control subjects had to be excluded because of mild cognitive deficits detected by the neuropsychological evaluation. One elderly control subject reported a first-degree relative with schizophrenia and was excluded from the study. In two elderly controls and three AD patients the ERP data could not be evaluated because of technical artefacts. Finally, 19 patients with AD (age: 75.2 ± 5.01 years; range: 66–84; 11 males; MMSE score: 20.9 ± 5.1) and 17 elderly controls (age: 72.3 ± 5.1 years; range: 66–82; 6 males; MMSE score: 29.5 ± 0.6) were included. The two groups did not differ from each other with regards to gender distribution ($t(32) = 1.02$, $p = 0.32$), whereas MMSE scores did differ significantly ($t(34) = 6.9$; $p < 0.0001$; both