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Research article

Mismatch negativity as a potential neurobiological marker of early-stage Alzheimer disease and vascular dementia

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HIGHLIGHTS

- A significant abnormality in MMN measurements has been found between the patients groups and the controls in the frontal-central area.
- No significant differences were found in MMN components between P-AD and P-VD group.
- No significant differences were found in the temporal areas.

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ABSTRACT

Alzheimer's disease (AD) and vascular dementia (VD) are serious, irreversible forms of cognitive impairment, which means that an early diagnosis is essential to slow down their progression. One potential neurophysiological biomarker of these diseases is the mismatch negativity (MMN) event-related potentials (ERP) component, which reflects an automatic detection mechanism at the pre-attentive stages of information processing. We evaluated the auditory MMN response in individuals from two patient groups: those in the prodromal stages of AD (P-AD) and those in the prodromal stages of VD (P-VD). Thirty patients (15 P-AD patients and 15 P-VD patients) and 30 age-matched controls were recruited to undergo electrophysiological recordings during the presentation of an auditory deviant-standard-reverse oddball paradigm that was used to elicit genuine MMN responses. We show that over the frontal–central area, the mean amplitude of the MMN was significantly reduced in both the P-AD ($p = 0.017$) and P-VD groups ($p = 0.013$) compared with controls. The MMN peak latency in P-VD patients was significantly shorter than in controls ($p = 0.027$). No MMN response differences between the P-AD and P-VD were found in either the frontal–central or the temporal areas. These results indicate that P-AD and P-VD patients exhibit impaired pre-attentive information processing mechanisms as revealed by the frontal–central area MMN response, which is associated with sensory memory and cognitive deficits.

1. Introduction

Alzheimer's disease (AD) and vascular dementia (VD) are the main causes of severe cognitive impairment in elderly people. AD is currently considered a prototypical form of dementia and accounts for approximately 50% of all dementia cases [1], whereas vascular dementia is the second most common cause of acquired cognitive impairment in elderly people [2,3]. Dementia causes chronic and progressive cognitive impairment and cannot be cured. The disease's slow progression makes it difficult to diagnose, highlighting the importance of identifying dementia early on, especially during the preclinical period. Mild cognitive impairment (MCI) is considered to be a transitional state between normal aging and the clinical

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features of dementia [4]. An early diagnosis of MCI may allow for therapeutic intervention that could slow the progression of the disease towards dementia and, therefore, substantially increase the probability of therapeutic success [5,6].

Single-domain amnestic MCI is considered as the prodrome of AD (P-AD). P-AD has been described as an episodic memory impairment with deficits that are greater than expected for an individual's age and education level, but that do not notably interfere with the activities of daily life [7]. Multiple-domain amnestic MCI is considered as the prodrome of VD (P-VD). P-VD mainly consists of deficits in attention, memory and executive functions, whereas other cortical functions are preserved. P-AD and P-VD both have high rates of morbidity in older people, and carry an important risk of developing into dementia. However, there are currently no available clinical biomarkers that sensitive and reliable enough to identify these diseases early on. The use of event-related potentials (ERP), a non-invasive and relatively inexpensive technique to measure brain activity, has been suggested as a possible tool for widespread clinical application given its potential for identifying electrophysiological markers of cognitive impairment [8,9]. Using a variety of different paradigms, several ERP studies have revealed neurophysiological features that are associated with cognitive functions in older normal, MCI, and dementia subject groups [10–13]. However, previous ERP studies studying cognitive impairment have typically have used an active cognitive paradigm that depends on the conscious processing of stimuli. Similarly, previous studies have mainly focused on the midline scalp electrodes that reflect fronto-central brain functioning [14]. In the present study, we sought to address these gaps by investigating the usefulness of passive cognitive paradigms and effects measured at other scalp electrodes.

The mismatch negativity (MMN) ERP component is a negative deflection that occurs approximately 100–250 ms after the onset of an infrequent (deviant) stimulus embedded in a train of repeated (standard) stimuli [15]. The MMN results from a temporal and a frontal generator. The temporal generator is thought to reflect the processing of auditory information, whereas the frontal generator is linked to the reorientation of attention [16]. The MMN can be elicited in the absence of directed attention, reflecting an automatic change detection system operating in the pre-attentive stages of information processing [17]. Pre-attention information processing is an initial and essential component of perception and cognition in humans. Successful processing of task-relevant information relies on effective pre-attention mechanisms, and deficits in the early stages of sensory information processing may reflect impaired complex cognitive functions [8,18] that underlie some of the clinical symptoms of MCI [19,20]. Furthermore, the MMN has a distributed neural architecture with high test-retest reliability and can serve as a reliable probe of auditory and sensory network dysfunction [21]. Therefore, the investigation of pre-attentive sensory information processing in P-AD and P-VD patients can provide valuable information regarding their cognitive functions.

In this study, we used the deviant-standard-reverse oddball paradigm [22] to elicit genuine MMN responses. In general, MMN components are usually derived from the subtraction of the ERP waveforms elicited by standard stimuli from those elicited by deviant stimuli. However, the negative deflection relevant to deviants, in this case, can also be confounded with low-level physical differences between the deviant and standard stimuli. In addition, the standard stimuli are typically presented more frequently than the deviant stimuli, which means that the neuronal processing of standard stimuli can produce more refractory effects than the processing of deviant stimuli. Therefore, the MMN paradigm in some studies may reflect differences in the refractory effects between standard and deviant stimuli instead of pre-attentive and memory-based change-detection mechanisms. The MMN obtained using a deviant-standard-reverse method is similar to the MMN observed in an equal-probability sequence; however, differences in the physical attributes of the standard and deviant stimuli no longer influence the MMN. Furthermore, the MMN can still be elicited with few neuronal refractory effects using a deviant-standard-reverse method with a deviant stimulus presentation probability of 15% [23]. Therefore, the aim of the present study was to investigate and compare the auditory MMN response in P-AD and P-VD patients using the deviant- standard-reverse oddball paradigm and to identify electrophysiological markers specific to each subject group.

2. Methods

2.1. Participants

This study was performed in accordance with the relevant guidelines and regulations approved by the Ethics Committee of the Harbin Medical University. All subjects provided written and informed consent before participating in this study.

Sixty participants (30 patients with cognitive impairment and 30 controls) were recruited between July and December 2015 from outpatient or inpatient clinics of the neurology department at the Second Affiliated Hospital of Harbin Medical University. Before being enrolled in the study, all participants underwent an initial assessment that included a neurological, a neuropsychological and a magnetic resonance imaging (MRI) evaluation. Individuals were excluded if they presented with diseases that could affect cognitive function, such as alcohol addiction, depression, normal pressure hydrocephalus, encephalitis, schizophrenia, and deafness or major hypoacusis. None of the participants were taking drugs that could affect central nervous system (CNS) functions in the month prior to their enrollment in the study.

The thirty patients were divided into two subgroups (P-AD and P-VD) based on the diagnosis criteria listed in the DSM-V (2013). P-AD subjects were diagnosed following the criteria set by Petersen [24]: (1) memory complaints persisting for at least 6 months, (2) abnormal memory for age, (3) normal daily living activities, (4) normal general cognitive function, (5) Hachinski ischemia score (HIS) <4 and (6) not demented. P-VD subjects were diagnosed based on the criteria established by Rockwood [25] and Jianping Jia [26]: (1) cerebral vascular disease, (2) cognitive impairment assessed by neuropsychological testing, (3) cognitive impairment occurring within 3 months after cerebral vascular disease onset, (4) causal relationship between cerebral vascular disease and cognitive impairment, (5) lack of dementia, and (6) cerebral MRI showing multiple lacunar infarctions and leukoaraiosis, which consists of the appearance of multiple small infarcts located in the subcortical white matter of the corona radiata. Thirty age-matched controls without cognitive complaints were recruited.

2.2. Neuropsychological evaluation

All participants were assessed with a standardized neuropsychological test battery. The Mini-Mental State Examination (MMSE) and the Montreal cognitive assessment (MoCA) were used to assess global cognitive functioning, including measures of attention, executive functioning, memory, language, and spatial orientation. The Hamilton Rating Scale for Depression (HRSD) was used to exclude depression (HRSD < 8) as a confounding factor. HIS was used to investigate vascular factors, whereas the Ability of Daily Living (ADL) scale was used to assess normal activities of daily living (ADL = 14).