Perceptual and response interference in Alzheimer's disease and mild cognitive impairment

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H I G H L I G H T S

- Patients with cognitive impairment, such as Alzheimer’s disease (AD) and mild cognitive impairment (MCI), are more distracted than normal controls (NC) by irrelevant information.
- Interference process subjected to conflicts happens not only at the response level but also at the perceptual level as demonstrated in the work, and subjects of MCI and AD present interference at distinct stages.
- The alterations of N2 are larger than those of P300 in the task and N2 demonstrates more sensitive to the deterioration of cognitive impairment than P300.

A B S T R A C T

Objectives: The ability to resolve conflicts is indispensable to the function of daily life and decreases with cognitive decline. We hypothesized that subjects with different levels of cognitive impairment exhibit different conflict resolution performances and may be susceptible to interference effects at different stages.

Methods: Sixteen normal controls (NC), 15 mild cognitive impairment (MCI) and seven Alzheimer’s disease (AD) patients were recruited to perform in a modified Eriksen flanker task.

Results: We observed that the AD and MCI patients exhibited smaller accuracy rate and longer response time compared to NC subjects. Longer N2 and P300 latencies were observed in the AD group. Furthermore, the MCI group showed a longer latency than the NC group in the P300 latency. The magnitude of the perceptual and response interference effects was larger in the AD group than the other groups, and the MCI group significantly differed from the NC group at the perceptual level.

Conclusion: The ability to resolve conflict decreased with impaired cognition and the perceptual and response interference effects may be useful in distinguishing MCI and AD.

Significance: The perceptual or response interference effect may potentially be employed as a useful non-invasive probe for the clinical diagnosis of MCI and AD.

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1. Introduction

In cognitive psychology, information processing occurs at several distinct levels, including stimulus encoding, target detection, response selection, and response execution (Koch et al., 2010). Theoretically, conflicts may initiate processes at any or all of these levels (Eriksen and Schultz, 1979; van Veen et al., 2001). Kornblum and colleagues showed that interference tasks involved conflicts not only at the response level but also at the perceptual level.
Perceptual conflict occurs when the presence of task-irrelevant perceptual information has a negative impact on the processing of task-relevant perceptual information, and response conflict occurs when simultaneous neural signals support competing response alternatives (Kornblum et al., 1990; Kornblum, 1994). Alzheimer's disease (AD), an age-related neurological degenerative disorder characterized by early cognitive and behavioral problems, is of great interest for researchers. Mild cognitive impairment (MCI) is the transitional stage from normal aging to AD and do not yet encompass the definition of dementia (Morris et al., 2001; Petersen, 2004). Amnestic MCI (aMCI) is a subtype of MCI and is characterized by the main complaint of memory deterioration. It is considered a transitional stage between normal aging and AD, and patients show a high rate of progression from this state to the fully fledged disease (Petersen et al., 2001; Scheltens et al., 2002). The participants in our study all received a diagnosis of aMCI.

Studies investigating the neuropsychology of AD have typically been primarily focused on cognitive impairments as they relate to memory function. Recently, a growing number of studies have analyzed impairments in conflict resolution and have found that conflict resolution ability is reduced in patients with AD (Casey et al., 2000; Castel et al., 2007; Fernandez-Duque and Black, 2006; Gamboz et al., 2010; Mahoney et al., 2010). However, few studies have explored conflict resolution ability in multiple impaired groups, nor have they studied differences in perceptual and response conflict resolution among AD, MCI patients and normal controls (NC). To clarify the difference, we used the event-related potential (ERP) to measure brain response. ERP reveals potential functional brain abnormalities that are not detectable during clinical or behavioral examinations (Zhang et al., 2002). It shows promising applications for the evaluation of cognitive processes and consists of a series of positive and negative voltage deflections, which are referred to as components. ERP components have been associated with sensory, cognitive, executive, and motor events. The N2 and the P300 are the most frequently recorded potentials and are also the most prominent potentials indicating changes related to cognitive impairment and conflict resolution (Bennys et al., 2007). The N2 reflects the level of conflict presented by a stimulus. The more negative the N2 was, the higher the level of conflict became (Danielmeier et al., 2009; Forster et al., 2011). The P300 is elicited by a response to deviant stimuli. Its amplitude is considered to be a manifestation of the brain activity that regulates attention to an incoming stimulus when its representation is updated (Polich, 2007). This study used N2 and P300 amplitude differences to indicate differences in cognitive functioning among the three groups in their ability to confront and handle conflicts.

In this study, a modified flanker task (Eriksen and Eriksen, 1974) was employed and it required participants to make judgments about the central target stimulus while ignoring distracters. In this task, there were four conditions: target-alone (none), congruent, neutral and incongruent. By comparing the target-alone with the neutral condition, “perceptual” interference can be studied because these stimuli differ only in the presence of flankers. By comparing the incongruent stimuli with the neutral stimuli, “response” interference can be studied because these two stimuli are not perceptually different but differ in that incongruent flankers prime a particular response, whereas neutral flankers do not.

We hypothesized that subjects with different levels of cognitive impairment display different conflict resolution performances and may be susceptible to interferences at different stages. To address it, 16 NC, 15 MCI and seven AD patients were recruited to conduct the task. Next, we investigated the perceptual interference by evaluating the difference between the neutral and target-alone stimulus and response interference by assessing the difference between the neutral and incongruent stimuli.

### 2. Methods

#### 2.1. Subjects

This study was approved by the Medical Ethics Committee of the PLA general hospital. All of the participants were recruited by an advertisement (http://www.301ad.com.cn, Chinese version), and written consent forms were obtained from the subjects or their legal guardians. Moreover, all subjects were not treated with any medication that might influence their cognition during the task. They were right-handed and performed a battery of neuropsychological tests that included the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR) (Morris, 1993) and Activities of Daily Living scale (ADL). The demographic and neuropsychological details for the participants are listed in Table 1.

The recruited AD patients fulfilled the following inclusion criteria: (1) diagnosed with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria for probable AD; (2) CDR = 1; (3) were not receiving nootropic drugs such as anticholinesterase inhibitors; (4) were able to perform the neuropsychological test. The diagnostic criteria for MCI was as stated in Petersen et al. (1999) including: (1) memory complaints, lasting at least 6 months; (2) CDR = 0.5; (3) intact functional status and ADL > 26; and (4) lack of dementia. Meanwhile, the AD and MCI patients also met the core clinical criteria for probable AD dementia and MCI as described in the recently published recommendation of the new diagnostic criteria (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). The criteria for the NC subjects comprised the following: (1) normal general physical status; (2) CDR = 0; and (3) no memory complaints. Structural MRI images were recorded and analyzed with voxel-based morphometry (VBM) to quantify the differences between subjects’ brains that correspond to the groups. There were no significant differences in the parietal and frontal lobes among the three groups.

Excluding conditions for this study were as follows: (1) metabolic conditions such as hypothyroidism or vitamin B12 or folic acid deficiencies; (2) psychiatric disorders such as schizophrenia or depression; (3) infarction or brain hemorrhaging as indicated by MRI/CT imaging; or (4) Parkinsonian syndrome, epilepsy and other nervous system diseases. In addition, patients with a metallic foreign body were excluded from the study.

#### 2.2. Task

The stimulus display was administered by EEvoke (Advanced Neuro Technology (ANT) software BV, 2004). Participants were positioned roughly parallel to a CRT monitor and responded to a stimulus using their thumbs to click on a control pad held with two hands. The left hand was used to respond to a centered arrow facing to the left, and the right hand was used to respond to a centered arrow facing to the right. They were instructed to focus on the task and to respond to a stimulus quickly and correctly. The response window was set to be the same as the inter-stimulus interval.

Before the actual task, a practice test of 15 events was performed. The task was separated into three blocks of the same length, with 100 stimuli for each block, as depicted in Fig. 1A. The task was composed of four conditions, with each condition consisting of 25 events that were placed in a random order. As shown in Fig. 1B, the stimulus of the target-alone consisted of none of the flankers, the neutral stimulus with “+” flanker, the congru-
respectively.

val varied randomly from 1.7 s to 2.4 s. An inter-stimulus inter-
incongruent stimulus indicated by opposite arrows. Each event
with each condition comprising 25 events.

separated into three blocks of the same length, each with 100 stimuli. In each
block, the task relevant stimuli were presented. (B) The stimuli consisted of four

The stimulus display is illustrated in Fig. 1. The focused arrow
and the flankers are centered horizontally on a CRT monitor. The

component displayed the peaks at the same time as those in the

Electroencephalograms (EEGs) were recorded (WaveGuard™,
Advanced Neuro Technology, Enschede, Netherlands) with 30 Ag/
AgCl electrodes placed on the FPz, Afz, Fz, Cz, Fp, O2, Fp1, FC1,
CP1, O1, F3, C3, P3, FC5, CP5, F7, T7, P7, FP2, CP2, O2, F4, C4,
P4, FC6, CP6, F8, T8, and P8. Their positions were consistent with
the 10–20 international system. Two electrodes, A1 and A2, were
linked on the ear lobe as a reference. A ground electrode was at-
tached to the middle of the forehead. Two bipolar electrodes were
used to monitor the vertical EOG. All of the signals were stored

2.3. Data acquisition

2.4. Data preprocessing

The offline EEG data analysis was conducted by EEGLab (Delor-
me and Makeig, 2004) and Matlab. The data were initially band-
pass filtered between 2 and 20 Hz. Next, the epochs were extracted
in −0.5 s to 1 s and locked to the stimuli, re-referenced to the grand
average and corrected by the baseline using the time window from
−0.5 s to 0 s. To remove the ocular artifacts, an independent com-
ponent analysis (ICA) was implemented. The components of the
eye movements were rejected in two ways. The first rejection
criteria involved components that were temporally correlated with
the data recorded by the EOG channel. Subsequently, the component displayed the peaks at the same time as those in the

ent stimulus with flankers indicated by the same arrow and the
incongruent stimulus indicated by opposite arrows. Each event
was displayed on the monitor for 300 ms. An inter-stimulus inter-
val varied randomly from 1.7 s to 2.4 s.

The stimulus display is illustrated in Fig. 1. The focused arrow and the flankers are centered horizontally on a CRT monitor. The
total width of the five symbols is 4.2 cm (2.4° visual angle [VA]), measured from the first arrow to the last arrow, and they are

separated by a space of 0.05 cm. The five symbols have the same
height of 2.2 cm (1.0°VA). The central arrow constitutes the target,
and the flanking arrows constitute the distractors. Target and dis-
tractors could point in the same direction (congruent trials) or in
different directions (incongruent trials).

Table 1
The demographic and performance information of the subjects. The F test and t test were used to investigate the group difference and the difference with respect to the NC group, respectively.

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>MCI</th>
<th>AD</th>
<th>F test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F (n)</td>
<td>9/7</td>
<td>9/6</td>
<td>3/4</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>69.3(1.8)</td>
<td>72.9(1.9)</td>
<td>68.5(2.9)</td>
<td>1.5(p=0.23)</td>
</tr>
<tr>
<td>Education (y)</td>
<td>14.0(0.9)</td>
<td>12.8(0.9)</td>
<td>11.2(1.4)</td>
<td>2.51(p=0.09)</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.3(5.3)</td>
<td>27.0(5.3)</td>
<td>21.5(0.8)</td>
<td>30.1(p&lt;0.001)</td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%-Non</td>
<td>98.7(3.3)</td>
<td>87.0(3.4)</td>
<td>84.2(5.0)</td>
<td>3.3(p&lt;0.05)</td>
</tr>
<tr>
<td>%-Neu</td>
<td>98.5(3.5)</td>
<td>86.7(3.6)</td>
<td>78.0(3.3)</td>
<td>4.5(p&lt;0.02)</td>
</tr>
<tr>
<td>%-Con</td>
<td>97.8(3.5)</td>
<td>86.4(3.6)</td>
<td>82.2(5.2)</td>
<td>3.0(p=0.06)</td>
</tr>
<tr>
<td>%-Incon</td>
<td>89.8(3.9)</td>
<td>77.9(4.0)</td>
<td>47.9(5.9)</td>
<td>10.1(p&lt;0.001)</td>
</tr>
<tr>
<td>Reaction time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ms-Non</td>
<td>558(29)</td>
<td>603(30)</td>
<td>654(45)</td>
<td></td>
</tr>
<tr>
<td>ms-Neu</td>
<td>584(29)</td>
<td>652(30)</td>
<td>735(45)</td>
<td>4.8(p=0.01)</td>
</tr>
<tr>
<td>ms-Con</td>
<td>580(32)</td>
<td>644(33)</td>
<td>696(48)</td>
<td>2.7(p=0.08)</td>
</tr>
<tr>
<td>ms-Incon</td>
<td>673(32)</td>
<td>765(34)</td>
<td>764(45)</td>
<td>3.2(p=0.05)</td>
</tr>
<tr>
<td>N2 Latency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ms-Non</td>
<td>296(10.4)</td>
<td>295(9.6)</td>
<td>300(15.2)</td>
<td>0.1(p=0.95)</td>
</tr>
<tr>
<td>ms-Neu</td>
<td>271(10.6)</td>
<td>300(9.9)</td>
<td>283(15.6)</td>
<td>2.1(p=0.13)</td>
</tr>
<tr>
<td>ms-Con</td>
<td>261(11.4)</td>
<td>286(10.6)</td>
<td>290(16.8)</td>
<td>1.8(p=0.19)</td>
</tr>
<tr>
<td>ms-Incon</td>
<td>266(10.4)</td>
<td>279(9.7)</td>
<td>296(15.3)</td>
<td>0.6(p=0.54)</td>
</tr>
<tr>
<td>N2 Amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μV-Non</td>
<td>−3.25(0.2)</td>
<td>−1.91(0.2)</td>
<td>−1.96(0.3)</td>
<td>3.28(p=0.05)</td>
</tr>
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<td>μV-Neu</td>
<td>−3.61(0.3)</td>
<td>−2.67(0.3)</td>
<td>−2.34(0.4)</td>
<td>2.16(p=0.13)</td>
</tr>
<tr>
<td>μV-Con</td>
<td>−3.46(0.3)</td>
<td>−2.56(0.2)</td>
<td>−2.76(0.4)</td>
<td>1.41(p=0.26)</td>
</tr>
<tr>
<td>μV-Incon</td>
<td>−3.71(0.2)</td>
<td>−2.42(0.2)</td>
<td>−2.44(0.4)</td>
<td>4.32(p=0.02)</td>
</tr>
<tr>
<td>P300 Latency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ms-Non</td>
<td>435(14.4)</td>
<td>436(13.4)</td>
<td>467(21.2)</td>
<td>1.00(p=0.38)</td>
</tr>
<tr>
<td>ms-Neu</td>
<td>423(11.59)</td>
<td>448(10.8)</td>
<td>467(17.0)</td>
<td>2.15(p=0.13)</td>
</tr>
<tr>
<td>ms-Con</td>
<td>432(12.9)</td>
<td>432(12.0)</td>
<td>438(19.0)</td>
<td>0.15(p=0.89)</td>
</tr>
<tr>
<td>ms-Incon</td>
<td>414(13.6)</td>
<td>450(12.7)</td>
<td>426(20.1)</td>
<td>1.48(p=0.24)</td>
</tr>
<tr>
<td>P300 Amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μV-Non</td>
<td>2.40(0.2)</td>
<td>1.30(0.2)</td>
<td>1.37(0.3)</td>
<td>3.45(p=0.04)</td>
</tr>
<tr>
<td>μV-Neu</td>
<td>2.54(0.2)</td>
<td>1.75(0.2)</td>
<td>1.47(0.3)</td>
<td>3.36(p=0.05)</td>
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<tr>
<td>μV-Con</td>
<td>2.09(0.2)</td>
<td>1.56(0.2)</td>
<td>2.25(0.3)</td>
<td>2.59(p=0.09)</td>
</tr>
<tr>
<td>μV-Incon</td>
<td>2.37(0.2)</td>
<td>1.52(0.2)</td>
<td>1.66(0.3)</td>
<td>2.98(p=0.06)</td>
</tr>
</tbody>
</table>

Standard error in parentheses.

*p Differs from controls at p<0.05.

*p Differs from controls at p<0.01.

*p Differs from controls at p<0.001.

Fig. 1. The experimental design. (A) The modified Eriksen flanker task was separated into three blocks of the same length, each with 100 stimuli. In each block, the task relevant stimuli were presented. (B) The stimuli consisted of four separate conditions; the target alone, neutral, congruent and incongruent events, with each condition comprising 25 events.
EOG were removed. The second criteria relied on the topography. The component of the eye movements demonstrated a spatial weight located at the frontal channels. After its removal, the remaining components were then back-projected onto the EEG channels. We then designated N2 as the negative peak from 200 ms to 350 ms on the electrodes at F3, Fz and F4 (Folstein and Van Petten, 2008), and P300 as the positive peak from 300 ms to 550 ms on the electrodes at P3, Pz and P4 (Polich, 2007). The latencies of the N2 and P300, respectively, corresponded to the latencies of the maximum peaks of the N2 and P300 measured from stimulus onset.

2.5. Statistical analysis

The statistics were performed by the R software (R Development Core Team, 2011). Two-sample two-tailed t tests were conducted to evaluate the group differences between two of the three groups. As the median of the population was more robust, it was more appropriate to use the median rather than the mean to determine an “average”; thus, the median response time and response accuracy were analyzed using a multivariate analysis of covariance (MANCOVA). For this analysis, the diagnosis (AD, MCI, and NC) was the between-subject factor and the conditions (target-alone, neutral, congruent and incongruent) were within-subject factor, with age and the Mini-Mental State Examination (MMSE) being included as covariates (Krueger et al., 2009).

When a significant multivariate main effect was detected with MANCOVA, additional univariate ANCOVAs were performed to elucidate differences in either the response times or accuracy with a between-subject factor group with any two of three possible levels and a within-subject factor with any two of four levels. If there was a significant multivariate Group × Condition interaction effect, further ANCOVAs were conducted to investigate the interaction with a two-level group factor and a two-level condition factor. For all tests, the alpha level was set at 5%. By the same principle, the ERP components were also analyzed by MANCOVA (p < 0.05). In this study, the accuracy and response time were replaced with either the amplitude or latency of N2 and P300.

3. Results

3.1. Subjects and statistical results

The mean values for each of the cognitive and flanker measures were completed by the AD, MCI and NC subjects and are displayed in Table 1. The AD, MCI and NC group did not statistically differ in age (F2,35 = 1.49, p = 0.23); however, the number of years of education in the AD group was slightly smaller than that of the NC group (p = 0.09). For the clinical measures, in particular, the scores of the MMSE, the MCI patients performed better than the AD patients (p < 0.001) but performed poorer than the NC (p = 0.01).

3.2. Performance

In terms of accuracy, a group effect (F2,29 = 6.4, p = 0.005) indicated that there were significant differences among the three groups. The accuracy of the MCI group was higher than that of the AD group and lower than that of the NC group. A significant condition effect (F2,24 = 21.9, p < 0.001) was also observed. Compared with other stimuli, more errors were made in response to the incongruent stimuli by all of the groups. Because a Group × Condition interaction (F6,24 = 9, p < 0.001) was found in the multivariate analysis (Fig. 2A), two comparisons were used to test the Group × Perceptual and Group × Response conflict interaction. Although no significant Group × Perceptual conflict interaction was found (F2,108 = 0.6, p = 0.5), a Group × Response conflict interaction was observed (F2,108 = 7.2, p = 0.002). Further testing showed that the response interference effect was larger in the AD group than in the MCI and NC groups (F1,19 = 7.2, p = 0.009 and F1,65 = 19.8, p < 0.001, respectively), while the effect was not significantly different between the MCI and NC groups.

For the response time, a group effect (F2,32 = 2.8, p = 0.07) indicated that there were no significant differences among the groups, while the condition effect (F3,60 = 24.2, p < 0.001) indicated that the responses were slower in the incongruent stimuli compared with the other stimulus types. The Group × Condition interaction (F3,60 = 2.5, p = 0.02) plot of the response time is shown in Fig. 2B. Moreover, we found no significant Group × Response conflict interaction (F2,32 = 3.3, p = 0.06) and the Group × Perceptual conflict interaction (F2,32 = 8.6, p = 0.001) showed that the perceptual interference effect was larger in the AD group than in the MCI (F1,19 = 4.4, p = 0.05) nearly and NC groups (F1,19 = 19.7, p < 0.001) significantly.

3.3. ERPs

The averaged ERPs of every condition are shown in Fig. 2C–F. Representative waveforms only at the Cz electrode are shown for brevity. After conducting an MANCOVA analysis, the N2 latency showed a significant condition effect (F3,60 = 5.4, p = 0.002). Furthermore, the latencies of the MCI group were longer than those of the NC group, and although the latencies of the AD group were also longer than those of the NC group, they were not significant (Fig. 3A). In Fig. 3C, the Group × Condition interaction effects were significant (F3,60 = 2.4, p = 0.03). Further analysis showed that the effect was significant between the MCI and NC groups as compared with the target-alone and the neutral conditions (F1,28 = 5.7, p = 0.02) and between the MCI and AD compared to the neutral and the incongruent effect (F1,18 = 6.7, p = 0.02).

For the N2 amplitude, there was a condition effect (F3,60 = 6.4, p < 0.001). Further testing showed that the amplitudes evoked by the neutral stimuli were higher than the target-alone stimuli (F1,13 = 10.4, p = 0.003). A group main effect also existed in the N2 amplitude (F2,32 = 3.8, p = 0.03). As depicted in Fig. 3B, the effect appeared between the NC and MCI groups (p < 0.001) and between NC and AD groups (p < 0.05); however, no Group × Condition effects were found (Fig. 3D).

The multivariate P300 latency analysis demonstrated a nearly significant Group × Condition effect (F3,60 = 2.1, p = 0.06), as shown in Fig. 3E. Further testing showed that the effect showed nearly significant differences between the AD and MCI subjects from the neutral to the incongruent condition (F1,18 = 3.1, p = 0.09).

For the P300 amplitude, a group effect (F2,32 = 3.9, p = 0.03) was found in all of the conditions. Further t testing showed that the group effect showed differences between the NC and MCI patients (p < 0.001) and between the NC and AD patients (p < 0.05); however, no Group × Condition effects were observed (Fig. 3F).

4. Discussion

This study explored the ability to resolve conflicts among persons with different levels of cognition impairment using a flanker task and investigated whether these groups demonstrated any interference effects. The two levels, perceptual and response, were examined here. Perceptual and response are two necessary processes that occur during conflict resolution. The behavioral and ERP data were recorded to study the interference effect. Perceptual conflict occurs when the presence of task-irrelevant perceptual information has a negative impact upon the processing of task-relevant perceptual information, and response conflict occurs when
simultaneous neural signals support competing response alternatives (Kornblum, 1994).

The behavioral data of the subjects showed that the MCI patients had a more accurate and faster response than the AD patients, but a lower accurate and slower response than the NC. A Group × Condition interaction for both RT and accuracy was found. This interaction demonstrated that the level of cognition interacted with conflict resolution. As the level of conflict rose, the accuracy decreased and RT increased in all groups. Furthermore, this significant interaction effect suggested that conflict resolution in AD is significantly decreased compared to MCI and NC, as the interaction effect was only significant between the AD group and either the
Therefore, we concluded that cognition was more impaired in patients with AD than in patients in the MCI and NC groups. These findings were consistent with Wylie's group (2007), who found that both MCI and healthy control groups showed a significant response time cost to an incongruent stimulus and the cost was larger in the MCI group. Moreover, the AD and
MCI patients encountered greater difficulty in resolving conflict than the healthy elder controls (van Deursen et al., 2009; Wylie et al., 2007).

The N2 component was typically evoked prior to the motor response, suggesting a link to the cognitive processes of stimulus evaluation, selective attention and conscious discrimination (Hill et al., 2002). Comparison of the N2 latency and amplitude revealed that the AD group significantly elicited smaller N2 amplitudes and slower N2 responses than both the NC and MCI groups. These observations are consistent with several previous studies (Bennys et al., 2007; Papaliagkas et al., 2011; Tachibana et al., 1996). The differences in the amplitude and response time might reflect the reduced speed and efficiency of conflict detection in AD and MCI patients. The ERP results indicated that the MCI and AD groups’ worse conflict resolving performances could be attributed to either an impairment of neural processing or inefficient frontal neural functioning during conflict resolution. Based on the behavioral and ERP data, we conclude that the conflict resolving performance is correlated with cognitive levels and that the ability of resolving conflict is partially impaired in AD and MCI patients compared with NC subjects.

Previous studies have proposed that the P300 component is sufficiently sensitive to detect early stages of cognitive impairment (Ashford et al., 2011; Bennys et al., 2007; Polich and Corey-Bloom, 2005). In contrast, our study found changes in N2 that were larger than those of P300. One reason for this discrepancy may be that most previous studies employed an auditory oddball task, whereas we used a flanker task in this study. The flanker task covers strategic monitoring and the immediate control of motor response with a larger N2, while the oddball task reflects neural reactions to unpredictable, but recognizable, events with a larger P300. Because the flanker task is related to executive function, we conclude that N2 is more sensitive than P300 in evaluating the interference effect due to the impairment of cognitive function.

In addition, N2 activation in the frontal brain regions is related to conflict monitoring (Botvinick et al., 2004; Kerns et al., 2004); however, P300 activation in the central-parietal regions is correlated with attention control processing (Liotti et al., 2000). A number of studies have implicated early and significant changes in executive function and early neurobiological changes in the frontal lobes of AD or MCI patients (Baddeley et al., 2001; Duke and Kasznik, 2000; Perry and Hodges, 1999; Royall et al., 2002). Neuroimaging studies of early AD and MCI have found increased prefrontal activity during cognitive tasks compared with normal elder control subjects (Agosta et al., 2012; Pariente et al., 2005). Thus, the N2 component of ERP could be of high diagnostic value for the early diagnosis of AD and MCI.

In a cognitive task, there will be several perceptual or cognitive processes where conflict interference effects may occur. A number of independent mental systems in the brain are involved in the cognition of a human being. If the outputs of the systems are incongruent, an interference effect occurs and additional resources are required to resolve the conflict, which may have a negative effect on the subject’s performance (De Houwer, 2003; Kim et al., 2011; Nassauer and Halperin, 2003; Sugg and McDonald, 1994).

We hypothesized that, if response deficiency presented itself, then AD patients would show a larger response interference effect than either patients with MCI or the NC group. The accuracy in incongruent trials declined dramatically in AD patients when compared to the neutral condition or to the MCI or the NC group; thus, the response interference effect was larger in the AD group. As the time spent making correct responses was a more meaningful measure for depicting subjects’ speed, only response times in correct trials were analyzed in this study. However, there was no significant group difference in RT in response conflict trials between the groups. However, subjects’ RTs depended upon their accuracy.

Fig. 2A showed that the accuracy of the AD in incongruent trials was only 50%. This lower accuracy, which was nearly equal to random chance, might imply that the AD patients did not have sufficient cognitive capabilities to successfully resolve the conflict. Thus, we propose that the AD patients pressed either the right or the left button randomly without identifying the targeting accurately. Combining their much lower accuracy and their RTs, which were only equal to those of the MCI group, we could infer that response conflict was impaired more seriously in AD. There were no significant differences between the MCI and NC groups. The ERP results showed that the difference in the N2 latency between the neutral and target-alone stimuli was more significant in the MCI than in the NC group. In addition, the difference in the N2 and P300 latencies between the neutral and incongruent stimuli was more significant in the AD group than in the MCI group. Thus, the MCI subjects demonstrated a stronger perceptual interference during conflict resolution than the NC subjects, and the AD patients exhibited the strongest perceptual interference. The AD patients revealed a significantly higher level of interference in the response than both the MCI and NC; however, the MCI patients did not differ from the NC.

Flanker-induced interference may attribute to perceptual processing (Duncan and Humphreys, 1989; Eriksen and Schultz, 1979; Smid et al., 1991). The interference results in slow performance under neutral flankers due to the additional time required to recognize the central target. Compared with the NC subjects, patients with AD or MCI were more distracted by the irrelevant information at the perceptual level, as demonstrated by their increased response time and N2 latency. In addition to effects on the perceptual level, the interference effect may result from the response level. When a greater number of flankers appear compared with the target, the response activation is initially due to the flankers and, subsequently, from the target. The reaction times will be delayed by the incongruent flankers due to a conflict between the flanker and target-based response. At this level, the AD patients are more distracted. Thus, compared with the NC, we speculate that patients at the early stage of cognitive impairment are susceptible to the interference mainly from the perception level and patients at the later stage are susceptible to both the perception and the response level.

Although our reported results demonstrate a legitimate study, we recognize the limitations. First, we included a relatively small number, particularly in the AD group. However, our results were significant overall, indicating that the group differences were sufficiently large. In addition, the ocular movements recorded during the ERP were unavoidable in the elder patients with cognitive impairment. Thus, we introduced an additional step to remove the noise. Although the method of removing the noise in this study has been employed in previous studies, the results should still be carefully interpreted.

We conclude that subjects with AD and MCI are more distracted than NC by irrelevant information. In addition, subjects with AD have conflict interference on both levels (perceptual and response), and MCI demonstrate at the perceptual level. Thus, the different levels of interference may be a predictor in distinguishing AD and MCI.

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