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Electrophysiological activity underlying inhibitory control processes in late-life depression: A Go/Nogo study

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Abstract

Late-life depression is characterized by the coexistence of affective disorder and executive impairment. We investigated the neural correlates of inhibitory control processing in people with late-life depression using event-related potentials (ERPs). A visual Go/Nogo task was employed. A larger Nogo-N2 and Nogo-P3 was found in the depressed group compared to the control group. This reflects the non-physiological process of conflict monitoring and inhibitory control in depressed patients. The results also showed that the difference wave between Go and Nogo conditions (Pd3) over the frontal electrode sites was more robust and earlier in the control group compared to the depressed group, which reflects frontal dysfunction in the depressed group. Also in the depressed subject a significant correlation between the 17-item Hamilton rating scale for depression (HRSD-17) and the amplitudes of Nogo-N2 and Pd3 was found. Our results imply that the Nogo-N2, Nogo-P3 and Pd3 features can be considered as endophenotypic markers of the late-life depression.
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Keywords: Late-life depression; Inhibitory control; Event-related potentials; N2; P3

Late-life depression is characterized by the coexistence of affective disorder and executive dysfunction. The clinical signs include psychomotor retardation, apathy, poor insight, and severe behavioral disability. Executive dysfunction is associated with poor antidepressant response, recurrence and relapse [1], and often persists after improvement of affective symptoms [22].

It has been proposed that executive control is engaged in decision-making, conflict resolution, error correction, and response inhibition [2]. Inhibitory control, which involves initiation, active switching, and inhibition of overlearned responses, is known as a central component of executive function essential for normal mental processes [24]. A recent behavioral study revealed that geriatric depressed patients have poor inhibitory control, in addition to selective attention, sustained attention and focused effort deficit [19]. However, the neural basis of inhibitory control deficit in late-life depressed patient is still unclear.

Neuroimage studies have reported the involvement of the prefrontal cortex (PFC), Anterior cingulated cortex (ACC) and frontal limbic area in the inhibition mechanism [13]. These areas are reliably activated when subjects must overcome interference from incorrect but prepotent response tendencies [5,7]. Conflict-monitoring hypothesis suggests that the ACC is active during the cognitive task requiring the decision between conflict responses in order to strategically allocate additional attention resources [6,20]. In neuroimaging studies, there is evidence for PFC and ACC dysfunction in depressive patients when functional activation is studied during executive task performance [10].

While the functional neuroimaging provides good spatial resolution, the event-related potentials (ERPs) yield high temporal resolution. Two major ERPs components in Go/Nogo task have been consistently linked with the process of inhibitory control. First, the Nogo-N2, a negative deflection over frontocentral electrodes at approximately 200–300 ms post-stimulus onset, was increased in the Nogo compared to the Go task [9]. The Nogo-N2 has been located exactly within the ACC and is considered to be a monitor of conflict between competing responses [12,8]. Second, an enhanced positive peak at anterior electrodes in Nogo

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relative to Go ERPs in 300–500 ms range, known as Nogo-P3 [3], was thought to be related to response inhibition and to index a later stage of the inhibitory process.

In an Eriksen flanker task, major depression patients showed smaller error related negativity [26]. A reduction of an early fronto-temporal positivity in the N2 time window in an auditory Go/Nogo task has been reported in younger adult depressed patients [14]. These results suggest impaired response monitoring processes in major depression. However, no electrophysiological studies of response monitoring processes have been conducted on late-life depression while the pathogenesis and clinical manifestation in elderly people are different compared to younger adults. The aim of our study was to investigate whether late-life depressed patients show a brain processing impairment in inhibitory control which can be reflected by N2 and P3 abnormalities in a visual Go/Nogo task.

Twenty patients aged at least 60 years, mean 68.7 ± 4.1, with a major depressive disorder according to the American Psychiatric Association were recruited from the first affiliated hospital of Dalian Medical University. The patient group consisted of six subjects with recurrent major depressive disorder (296.3x) and 14 subjects with major depressive disorder, single episode (296.2x). Nine subjects were taking selective serotonin reuptake inhibitors and three patients serotonin and noradrenalin reuptake inhibitors, while seven subjects were naive to antidepressant before the study. Nineteen elderly subjects with no signs of late life depression served as the control group, and were age and gender matched. All subjects participated voluntarily in the study and were normal or corrected-to-normal vision and right-handed. They did not have any history of neurological or other mental diseases. Depression severity was evaluated using a Chinese version of HRSD-17. The Mini-Mental State Examination (MMSE) was administered to screen for dementia. Frontal executive function was evaluated using the Wisconsin card sorting test (WCST). Two patients and one control were excluded because an insufficient number of correct artifact-free trials were available.

The study protocol conformed to the 1964 Declaration of Helsinki. All the subjects signed informed consent.

An uncued visual Go/Nogo task was presented by STIM-2 software (Neuroscan, Inc.) in a dimly lit room. The experiment consisted of 200 stimuli. Single or double triangular figures were used as the stimuli, which were white on a black background, presented pseudorandomly with equal probability on the screen, and with a viewing distance of 150 cm. The stimulus size was 2.8° horizontal by 3.8° vertical. Participants were instructed to press the left mouse button with the left or right thumb as fast as possible for each single triangle (Go), but withhold their response when shown double triangles (Nogo). The duration of the stimulus was 50 ms and the inter-trial-interval was set at 950 ms. The thumb used was counterbalanced among the subjects. All subjects performed a short training session containing 20 stimuli to ensure that they understood the task correctly. The reaction times and response accuracy to Go stimuli were measured.

The electroencephalography (EEG) was recorded from 32-channel array (10/20 system) with linked earlobe reference electrodes using Ag/AgCl electrodes mounted in an elastic cap. The electrooculogram (EOG) was recorded with two pairs of electrodes, one placed above and below the right eye, and another 10 mm from the lateral canthi. The electrode impedances were kept below 5 kΩ throughout the experiment. The EEG was amplified by a Neuroscan NuAmps amplifier with a band pass of 0.1–100 Hz and sampled at a rate of 1000 Hz.

The EOG artifacts were corrected using the method proposed by Semlitsch et al. [27]. The EEG was segmented into the epoch from 200 ms pre-stimulus to 800 ms post-stimulus and the baseline corrected to the mean amplitude 200 ms before the stimulus. The trials contaminated with artifacts greater than $\pm 100\ \mu V$ were rejected before averaging. We removed the trials with response times shorter than 100 ms, as they were assumed to reflect non-deliberate behavior. The artifact-free EEG epochs with correct response for Go and Nogo conditions were averaged respectively and at least 50 trials were available for each subject and condition. For further analysis, the ERPs data were digitally low-pass filtered at 16 Hz (24 dB/octave).

The peak amplitude and peak latency of N2, as well as P3 at midline electrodes (FZ, FCZ, CZ, CPZ, PZ) were measured in Go and Nogo conditions in controls to show Go/Nogo effect, as both components are affected by the Go/Nogo task. Frontocentral (F3, FZ, F4, FC3, FCZ, FC4, C3, CZ, C4) N2 and P3 were measured for between-group comparisons, which reflected the group difference of frontal inhibitory control processing. The time windows of their peaks were 180–300 ms for N2 and 300–500 ms for P3 in both Go and Nogo trials, which were derived from inspecting grand-average and individual subject data. Furthermore, we measured the difference wave of N2 (Nd2) and P3 (Pd3) components by subtracting the Go trials from the Nogo trials (Fig. 3). The peak value of 200–300 ms for Nd2 and 330–430 ms for Pd3 were measured, respectively. The neuropsychological and behavioral data (i.e., HRSD, MMSE and WCST scores, reaction time, and error rate) was analyzed using a one-way analyses of variance (one-way ANOVA). The repeated measure analyses of variance (RMANOVA) were conducted on ERPs data. Three-way RMANOVA of N2 and P3, Nd2 and Pd3 were calculated for between-group comparisons with factors of the Group (Patients and Controls), Brain region (left, middle and right) and Electrode site (F3/FZ/F4, FC3/FCZ/FC4, C3/CZ/C4). The Greenhouse-Geisser corrections were adopted where appropriate. Mean variations were further evaluated using the Fisher LSD Post hoc test. The correlation between the ERPs and neuropsychological data was assessed by calculating Spearman's rank correlation coefficient. The P-value was from two-sided statistical tests, and $P < 0.05$ was regarded as statistically significant.

The neuropsychological and behavioral performance scores in control and depressed subjects are shown in Table 1. The patient group showed poor performance for WCST compared to the controls. The patients also had significantly longer reaction time and greater incidence of commission error than that of the control group.

As illustrated in Figs. 1 and 2, the Go/Nogo paradigm applied in the present study elicited robust N2 and P3 components and yielded reliable Go/Nogo effect between conditions,

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