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Originals

Cognitive Responses Control in Normal Ageing : Evidence from a Go/NoGo Task of Event-related Potentials

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SUMMARY

The Go and NoGo conditions of the Continuous Performance Test (CPT) of event-related brain potentials (ERPs) represent the execution and inhibition of a participating motor control. The present study examined this cognitive response control in 20 healthy normal ageings when the subjects perform a visual CPT paradigm. A conventional 2-tones auditory paradigm was also used to elicit P3. The Global Field Power (GFP) was employed for an ERP component analysis. The new modified Wisconsin Card Sorting Test (WCST) was used to evaluate frontal lobe function, and Mini-Mental State Examination (MMSE) was used to exclude subjects with clinical intellective decline. P3 amplitude elicited by the NoGo condition significantly increased and the scalp location of its centroids was more anteriory distributed than in the Go condition. There was no difference in P3 latency to be found between Go and NoGo conditions. These results suggest that NoGo P3 may be a potential neurophysiological marker of cognitive response control. It is suitable to evaluate the capability of execution or inhibition in a prepared motor response.

Key Words : Go/NoGo P3, motor inhibition, CPT, response control, GFP

INTRODUCTION

The ability of voluntary response control to an already prepared action plays an important role in the organization of human behavior, which requires the brain not only to execute but also to inhibit. This voluntary movement control is an important manifestation of the functional integrity of the higher executive control system. P3 of ERP is considered a sensitive electro-physiological tool for evaluating a wide spectrum of processing in human brain function. A cued continuous performance test (CPT) paradigm has been developed to quantify sustained attention and to validate frontal function [1]. The cued CPT requires attention to a preparing stimulus (cue) and to the immediately following target or non-target stimulus. The cue directs the subject to anticipate a motor reaction that is executed after the target (Go condition), and suppressed after the non-target stimuli (NoGo conditions) [2～4]. The CPT paradigm is particularly suitable for investigating the very basic processes of a prepared response control on a motor level [4]. Source localization with low resolution electromagnetic tomography (LORETA) of the P3 components identified significant electrical hyperactivity in the prefrontal brain area during the NoGo condition of the CPT paradigm [3]. Metabolic studies with near infrared spectroscopy (NIRS), PET and fMRI showed activation of the right frontal regions in healthy subjects during the performance of a CPT [5～7]. Recent investigations of ERP have revealed that the positive centre of the brain electrical field of P3 is localized more anteriorly during the inhibition of preparing motor response

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(i. e. NoGo condition) compared to its executive (Go condition)[4,8].

The prefrontal lobe has been said to have executive function such as planning, set-shifting/inhibition and habit learning[9,10]. It plays a pivotal role in the physiological mechanism of response control. Various anatomical, neuropathological, and electrophysiological studies have located the response control in the prefrontal area[11,12]. Functional neuroimaging studies suggest that the lateral inferior prefrontal and the anterior cingulated cortex subserve executive function[13]. Garavan et al.[14] reported that inhibition-related activity was predominantly right-lateralized in the middle and inferior frontal gyri. Prefrontal damage resulted in inability of response control to inhibit irrelevant input and sustain attention[15]. Moreover, lesion studies in animals and humans showed activity of the anterior frontal area during the inhibition of motor response[16,17].

The CPT paradigm has been applied to investigate the effects of response control on ERPs[4,18,19]. Several neurophysiological studies with the CPT paradigm in healthy subjects have shown that the P3 amplitudes are higher and their scalp locations are anteriorly distributed during the NoGo condition compared with the Go condition[2,20,21,22]. The latency of the P3 is generally found to be more prolonged on the NoGo condition than in the Go condition[3,20,21]. But most investigations of the CPT task in healthy subjects are focused on young subjects. There are no data on the P3 in Go/NoGo tasks from normal elderly healthy subjects.

The purpose of the present study is to investigate the inhibition of response control when performing a CPT paradigm in normal elderly healthy subjects. We want to know if our elderly subjects would prepare their response on the basis of the preliminary information as given by cue in order to respond to the inhibitory requirements of NoGo as it has already been proven by previous studies in young subjects.

METHODS

Subjects

Twenty normal healthy elderly subjects participated in the present study (11 male and 9 female). The mean age of the subjects was 61.4 ± 12.0 years (range : 40 − 78). The mean duration of education was 11.3 ± 2.3 years (range : 9-16 years). All subjects were volunteers and were free of brain damage, psychiatric diseases, disturbances of eyesight or hearing or other conditions that might compromise neuropsychological functioning, and had no history of using any drugs that affect the central nervous system (CNS). We excluded subjects with clinical dementia based on DSM-IV and a Mini Mental State Examination (MMSE)[23] score less than 25. All subjects were fully informed as to the nature and purpose of the study and gave their consent to it. The backgrounds of all subjects are shown in Table 1.

Neuropsychological examination

In order to exclude subjects whose frontal lobe function had been impaired, the new modified WCST[24] was applied. The difficulty in the change of category or "set" (perseveration at a higher level) can be evaluated by mean of this test. Since the original WSCT is too difficult and distressing for elderly subjects, we applied the new modified version that has been used successfully in Japan. The modified test includes the order of the reaction cards and the process of giving instructions. The maximum classification score and the perseverative errors reported by Nelson[25] were used to evaluate the results of this test. The examination was conducted again after detailed explanation of the test, if the subject did not achieve on all categories 4 in the first test. We excluded subjects whose perseverative errors were over 10 in the first test, and categories did not achieve 4 and had more than 6 perseverative errors 6 in the second test. Only one of 20 subjects' achieved categories was 3 and her perseverative errors were 12 in the first test. Her achieved categories were 5 and perseverative errors were 3 after the second test (Table 1).

Procedure

The conventional 2-tones auditory oddball task and CPT task are applied for event-related potential (ERP) recordings. Stimuli were presented with a sequence of binaural stimuli via earphones for the auditory oddball paradigm : 100 ms tone bursts (10 ms rise/fall time) of 80 dB at 1.5 s intervals ; in random sequence, 20% of the tones with a pitch of 2000 Hz were rare 'target' tones, and 80% of the tones with a pitch of 1000 Hz were frequent 'non-targe' tones.

The CPT paradigm was followed by the 2-tones para-

Table 1 Subject information.

No. of subjects (N)	20
Gender M/F (N)	11/9
Age (years, Mean ± SD/range)	61.4 ± 12.0/40-78
Education (years, Mean ± SD/range)	11.3 ± 2.3/9-16
MMSE (Mean ± SD)	29.20/1.47
Score of 30 (N)	13
Score of 29 (N)	4
Score of 27 (N)	1
Score of 26 (N)	1
Score of 25 (N)	1
Achieved WCST categories (median, range)	4 (3-6)
WCST perseverative errors (median, range)	2 (0-12)
Task performance (%, range)	
2-tone paradigm	99.20 ± 0.01 (90-100)
CPT paradigm	99.13 ± 1.93 (93-100)

digm. Stimuli which consisted of 5 Japanese vowels [a], [i], [u], [e], [o] were administrated in hiragana (syllabograms) letters, i. e. [あ], [い], [う], [え], [お]. The letters on the screen were 5 cm × 5cm in size. Stimuli were presented sequentially in random order on the LCD screen. Each letter was shown for 200 ms in the center of the LCD screen, and the inter-trial interval was random at 1610～2490 ms. The letter [お] was presented as a signal to prepare a motor response. In each session 200 letters, were used, in the Go condition 15 letters (7.5%), and in the NoGo condition 32 letters (16%).

Protocol

ERP recordings were performed at 2：00 pm to exclude the effects of circadian changes. The tests were conducted in the order of the auditory oddball paradigm, the CPT paradigm. During the 2-tone paradigm, the subject lay on a bed in a sound-attenuated and dimly lit Faraday room, The subjects were instructed to close their eyes and silently count the target tones without using their fingers for counting. At the end of the session, they were asked to report the count ("counting performance value"), and this was acknowledged without providing information about errors. The subjects were given a brief practice session to ensure that they understood the instructions and could discriminate the tones. Stimuli were presented until 20 artifact-free targets were collected. After a short break, the session was repeated.

During the CPT paradigm, subjects were seated on a comfortable chair beside the bed in the same electromagnetically shielded recording chamber and were required to place their head on a board in order to maintain fixation on the central point of the LCD. The distance between the LCD screen and the subjects was 60 cm. The subjects were instructed to press a button with their right thumb as fast as possible whenever the letter [お] was followed by another [お] (Go condition), whereas if other letters [あ]・[い]・[う]・[え] followed the letter [お], they were asked not to press the button on the required response inhibition (NoGo condition) (Fig. 1).

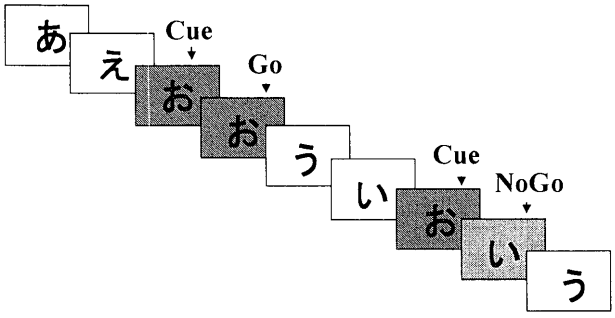

Fig. 1 The five Japanese vowels [あ] (a), [い] (i), [う] (u), [え] (e), [お] (o) were used for a continuous performance task paradigm with hiragana letters. The letter [お] was used as a signal to prepare a motor response. The subject was instructed to press a button whenever the letter [お] was followed by an [お] (Go condition). When other letters ([あ], [い], [う], or [え]) followed an [お], the subject was instructed not to press the button for required response inhibition (NoGo condition).

The subjects were given a brief practice session to ensure that they understood the instructions and could

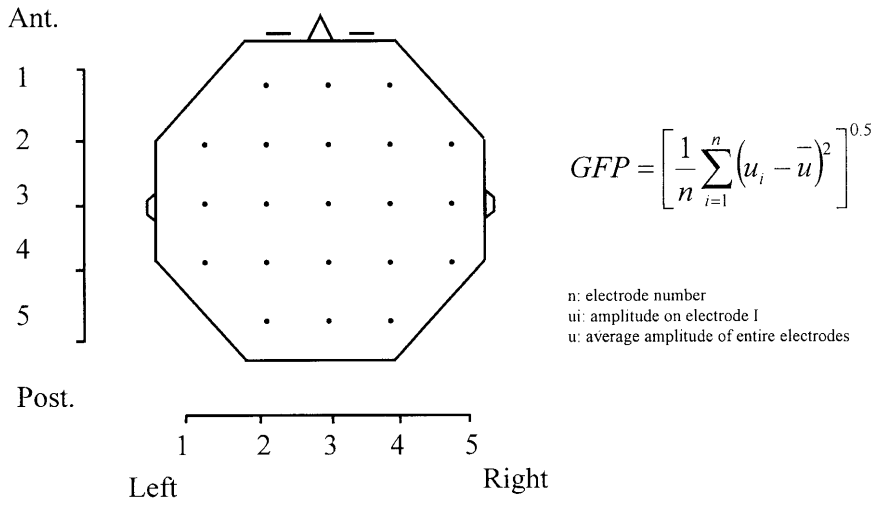

Fig. 2 1. Diagram of electrode array. The head seen from above ; nose up, left ear left. Numbers identify the location of electrodes (dots) along the anterior-posterior and left-right dimensions. The formula shows where GFP come from.

discriminate the target. The rate of acceptable performance was calculated in a series of preliminary tests. Subjects with a task performance ratio of $< 85\%$ were excluded from the ERP analysis. The mean rate of task performance was 99.20 +/− 0.01 in the 2-tone oddball paradigm, and 99.13 +/− 1.93 % in the CPT paradigm.

After a short break, each task was repeated. ERP during the 1,024 ms post-stimulus were averaged on-line at a frequency of 250 samples/sec, with automatic artifact rejection for signals bigger than 136 microvolts. The results of two sessions of ERP were averaged.

EEG recordings

Scalp potentials were recorded (BioLogic Brain Atlas, 0.53-30 Hz bandpass filtered) with Ag/AgCl surface electrodes attached with paste at 20 electrode locations according to the international 10/20 system (Fz, Cz, Pz, Oz, Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6) referenced to linked earlobes. Another electrode attached to the forehead was used as a ground. The impedance of each electrode was always < 5K Ohm.

Data analysis

The Global Field Power (GFP)[26] was computed for each time point in the multichannel data, resulting in a signal GFP curve for each 20-channel ERP average. The momentary electric strength or "hilliness" of the ERP landscape was identified by GFP[26, 27] and conventionally computed as the square root of the mean of the squared voltages as the average reference. The P3 component was identified as the time point of maximal GFP within a time window of 250-600 milliseconds after each stimulus, yielding the GFP strength (amplitude) and time of post-stimulus occurrence (latency) of the P3 components. The hardware band-pass filter was set to 0.3 to 15 Hz. The reference-independent measures of the location of centroids[26, 27] were determined and analyzed. In order to numerically assess differences between the landscapes of the mapped ERP fields, spatial data reduction was employed. The location of the centroids (points of gravity) of each map's positive and negative area vs. the average reference were computed, invoking a planar dipole source model for the description of the map's landscape. Locations of the centroids (+ C and − C) corresponding to the center of gravity of the positive and negative scalp potentials were projected onto the right-left and anterior-posterior axes of the head and plotted as a function of time. The international 10/20 system was used to number electrode positions in order from anterior to posterior (A-P) and from left to right (L-R) (Fig. 2). For example, three indicates the midline electrode, and 1 the anterior-most electrode on the A-P axis and the furthest left electrode on the L-R axes. The space program (Michel C, Zurich, Switzerland) was used for all computations.

Statistical Evaluation

Student's t-test was used to analyze differences in the

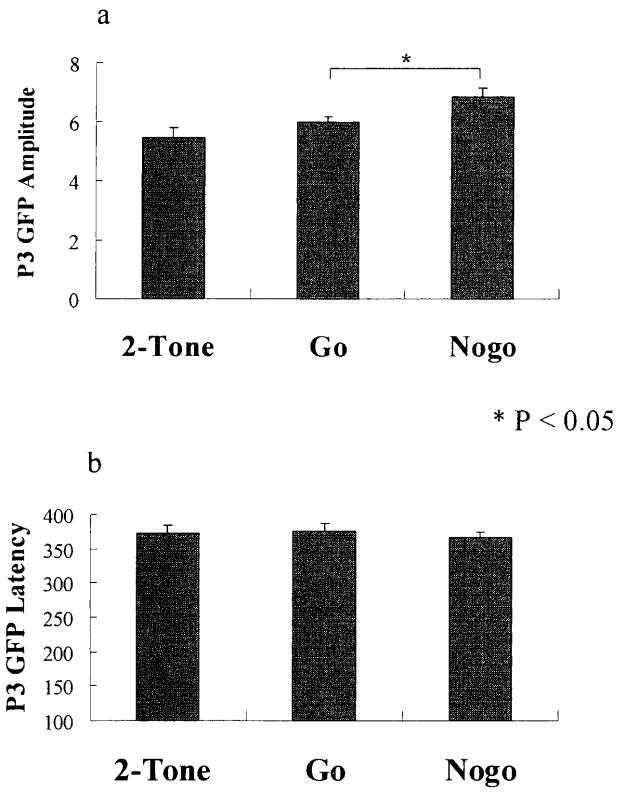

Fig. 3 Differences in P3 GFP amplitudes and latencies between Go and NoGo conditions in the CPT paradigm and auditory oddball paradigm. a. shows P3 GFP amplitudes increased during the NoGo condition compared with the Go condition ($p < 0.05$). The Go P3 GFP amplitude did not show a difference compared with the P3b elicited in the oddball auditory paradigm. b. shows that P3 GFP latencies did not show differences between the Go and NoGo conditions in the CPT paradigm. Go P3 GFP latency also did not show any differences compared with the P3b elicited in the oddball auditory paradigm.

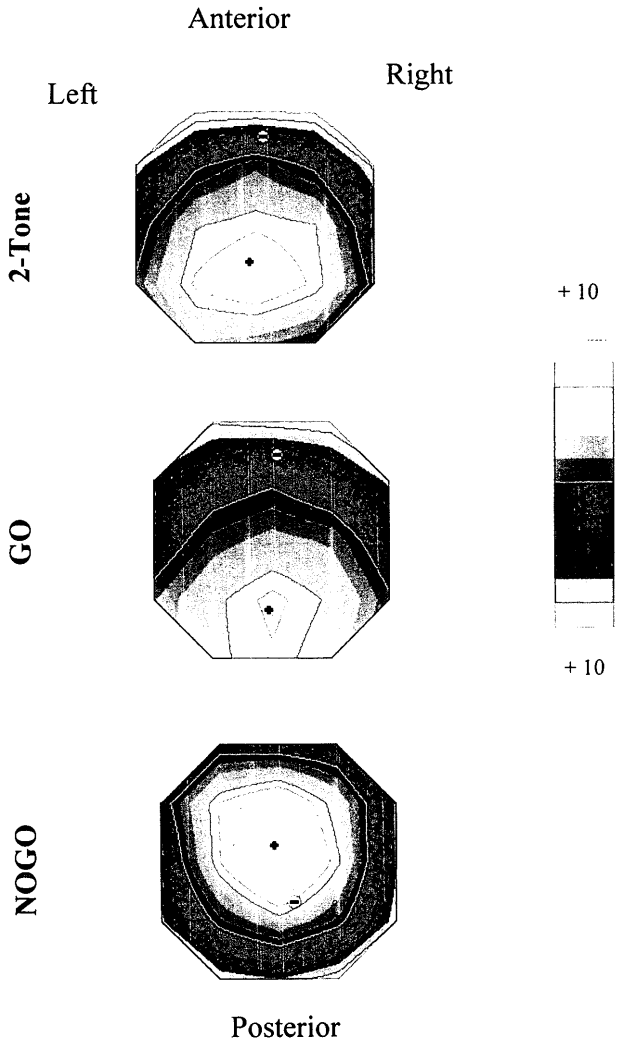

Fig. 4 P3 GFP scalp distribution of centroids. The centroids on P3 peak latency in the NoGo condition significantly anterioly distributed in comparison with the Go condition ($p < 0.0000005$) in the CPT paradigm. The centroids on P3 peak latency in the Go condition show the same distribution as seen in the oddball auditory paradigm.

P3 GFP amplitude, latency and its scalp location of centroids between Go and NoGo conditions in the CPT task, and the task relevant to P3b between the 2-tone paradigm and the CPT paradigm. A p value less than 0.05 denoted the presence of a statistically significant difference.

RESULTS

P3 GFP amplitudes increased during the NoGo condition more than during the Go condition ($p < 0.05$). The Go P3 GFP amplitude did not show a difference compared with the P3b elicited in the oddball auditory paradigm. P3 GFP latencies did not show differences between the Go and NoGo conditions in the CPT paradigm. The Go P3 GFP latency also did not show a difference compared with the P3b elicited in the oddball auditory paradigm (Fig. 3).

The positive location of centroids (+C) on Anterior-Posterior (A-P) axes on the P3 GFP peak latency was significant anterior distributed for the NoGo condition in the control group ($p < 0.0000005$) compared with Go condition. The P3 GFP + C on A-P axis was distributed in the posterior area for the Go condition as well as to be seen in the auditory oddball paradigm. The P3 GFP + C on A-P axis for the Go condition in the CPT task did not differ from that in the auditory oddball paradigm (Fig. 4).

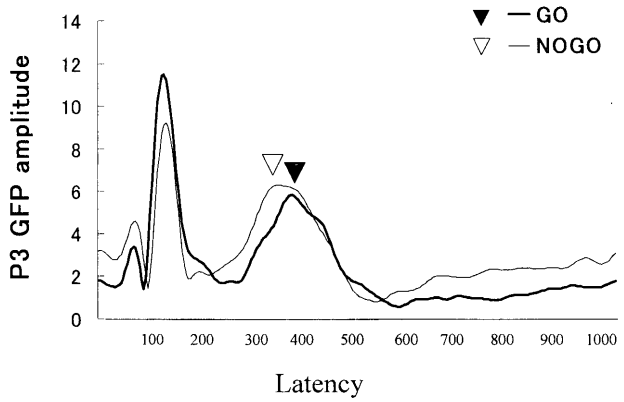

Fig. 5 The grand mean waveform of Go and NoGo conditions in the CPT paradigm. The P3 elicited by NoGo stimuli is larger than the P3 elicited by Go stimuli. The thin line and the empty triangle show the wave elicited by the NoGo stimulus, and the thick line and solid triangle show the wave elicited by the Go stimulus.

Fig. 5 shows the grand average waveform of the Go and NoGo condition in the CPT paradigm. The amplitude of NoGo P3 is increased and its latency looks shorter than that of Go P3.

DISCUSSION

The present study investigated inhibition processing of response control in a CPT paradigm in the normal health ageing subjects. Our results replicated the traditional P3 Go/NoGo differences, which have been reported by earlier studies in the young subjects [2, 21, 22, 28] : the P3 amplitude elicited in the NoGo condition significantly increased and its scalp locations of centroids were more anteriorly distributed than with the P3 elicited in the Go condition. But, our results did not show any difference in between Go and NoGo P3 latency.

Inhibition is described as an important contributory process in successful selective attention. Selective attention has been proved to be disrupted by frontal lobe disfunction. Studies in humans and animals have demonstrated that prefrontal damage disrupts inhibitory modulation [29, 30]. The prefrontal lobe has been proposed to play a critical role in the process of inhibitory control [15, 31]. CPT of ERP is considered a suitable electrophysiological method for evaluating the response control of the frontal lobe.

The CPT is a well-established neuropsychological task for investigating sustained attention [1]. In particular, the CPT emphasizes the different effects of executive (e. g. Go-condition) and inhibition of the anticipated motor response (e. g. NoGo-condition). The P3 elicited in the Go/NoGo task has been investigated in healthy control subjects in which the P3 had higher amplitudes with the fronto-central electrode side distribution after NoGo stimuli when prepared for the Go condition [2~4, 32]. Robert et al.[21] investigated whether the NoGo P3 augmented by an inhibitory generator dampens the impending motor response. Their results showed that the NoGo P3 was larger and more frontally dominant than the P3 elicited in the Go condition which required perceptual execution without suppression of an explicitly prepared motor response. They then suggested that the distinctive topography of this wave points to a P3 source manifested at the position of the topographic distribution of this wave, and to a possible involvement of this source in response suppression. The magnitude of the amplitudes is a parameter which reflects the amount of active neurons [33]. The higher NoGo P3 amplitude is in line with the interpretation that inhibitory processes are more demanding than executive ones [34].

Strik et al.[3] investigated P3 microstates by means of Low Resolution Electromagnetic Tomography (LORETA) in 10 healthy subjects while performing CPT. Their results disclosed a significant hyperactivity located in the right frontal lobe during the NoGo in the P3 microstate. These results suggest that the NoGo-anteriorization would be due to increased activity of sources in the frontal lobe during the inhibitory motor control. Consistent results were obtained in a STOP task that was completed by Brandeis et al.[35]. This study showed that phasic frontal activation was associated with successful inhibition of the motor response. Van't Ent and Apkarian [19] investigated the cortical potentials associated with suppression of intended motoric actions in 10 right-handed healthy subjects. They found the latency was shorter and the amplitude was bigger on the NoGo condition than in the Go condition. P3 was bigger over the fronto-central scalp electric side in the NoGo condition and over the pareito-posterior electric side in the Go condition. They suggest that these findings reflect a general, non-effector specific processing mechanism associated with detection and/or suppression of an inappropriate tendency to respond.

The present results are consistent with those of previous studies even though our subjects are elderly. Our results showed that P3 elicited in the NoGo condition was

quite large and its topographic distribution of centroids was more anteriorly located than with P3 elicited in the Go condition. Moreover, the aspects of P3 in the Go condition did not show any difference from the P3 elicited in the auditory oddball paradigm, but our results were obtained from elderly healthy subjects.

Houghton and Tipper[36] recently proposed a neural network model of selective attention. The model assumes that target selection requires excitation to facilitate target processing and inhibition to suppress distractor processing. In the cued CPT, subjects need excitation to execute the target processing (the Go condition) and inhibition to suppress distractor processing (the NoGo condition). A three dimensional source analysis of CPT conducted by Strik et al. [14] demonstrated that both Go and NoGo P3 components were explained by two main sources, which are occipito-temporal for the Go condition and frontal for the NoGo condition. Consistent with previous studies, the increased P3 GFP amplitude with anterior distribution for the NoGo condition shown in our elderly subjects may indicate relative contribution of inhibitory frontal lobe activity.

CONCLUSION

Inhibitory motor control is a measurable brain function related to the frontal lobe, which demands more processing load than the executive motor function. The inhibitory response control is most important in the level for evaluation of the cognitive decline with neurological disorders such as Parkinson's disease, Huntington's disease, etc. The results seen in our elderly subjects in the present study replicated the differences between the Go and NoGo conditions in P3, which were previously investigated in the young subjects in the CPT paradigm. These results indicate that the NoGo P3 probably is a potential neurological index for the evaluation of the capacities of inhibitory processing of cognitive response control, which have been shown to be related to frontal function even in elderly subjects. The employment of CPT is a non-invasive and powerful method for the neurophysiological distinction of different response controls of cognitive processing. The Go/NoGo differences shown in the present study suggest that our elderly subjects can be a valuable comparable matched control to investigate cognitive decline related to frontal lobe dysfunction, especially inhibitory control with neurological disorders.

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