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The NoGo P300 'anteriorization' effect and response inhibition

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Abstract

Objective—The P300 event-related potential shows anterior P300 increases on NoGo tasks (target stimulus = withhold response) relative to Go tasks (target stimulus = commit response). This 'NoGo anteriorization' has been hypothesized to reflect response inhibition. However, silent-count tasks show similar P300 anteriorization. The P300 anteriorization on silent-count tasks relative to Go tasks cannot reflect inhibition-related processes, and questions the degree to which anteriorization observed on NoGo trials can be ascribed to response inhibition. Comparison of anteriorization between the silent-count and NoGo tasks is thus essential. P300 topography on NoGo and silent-count tasks has not been previously compared.

Methods—P300 on Go, NoGo, and silent-count auditory oddball tasks were compared. If the NoGo P300 anteriorization reflects response inhibitory processes, the NoGo P300 should be larger anteriorly than the Go P300 (overt responses) and the silent-count P300s (covert responses). If anteriorization primarily reflects negative voltage Go task motor activity that reduces the normal frontal P300 amplitude, then the Go task P300 should be smaller than both the NoGo and silent-count P300s, which should not differ from one another.

Results—The Go task elicited a bilaterally reduced frontal P300 and asymmetrical frontal P300 relative to both the NoGo and silent-count tasks. The NoGo task P300 and silent-count task P300 showed similar amplitude and topography. P300 and slow wave on the NoGo task were not asymmetrical.

Conclusions—The increased frontal P300 in NoGo tasks cannot be attributed solely to a positive-going inhibitory process, but likely reflects negative voltage response execution processes on Go trials. However, the alternative explanation that memory-related processes increase the silent-count P300 anteriorly to the same degree as NoGo inhibitory processes cannot be ruled out.

Keywords

Button-press; Event-related potentials; Motor-related potentials; P3(00); Scalp topography

1. Introduction

During the widely used oddball task, P300 is elicited while subjects actively monitor trains of stimuli for the occurrence of an infrequent target stimulus. Subjects indicate the detection of low-probability targets by either verbal report (silent-counting task) or overtly indicating the presence of the target typically by button-pressing (a Go task). To avoid motor contamination

coincident with P300 from button pressing, subjects might also indicate target detection by making an overt response to the standard, non-target stimuli and withhold responses to the target stimuli (a NoGo task). NoGo P300 on auditory oddball tasks has been little studied.

Yet, Go-NoGo paradigms have been widely used in behavioral studies of response selection and inhibition, and several studies have compared P300 between the active response of Go trials and the withholding of a response on the NoGo trials. Most of these studies have used visual stimuli, either equiprobable Go and NoGo stimuli (e.g. Kiehl et al., 2000; Pfefferbaum et al., 1985; Yong-Liang et al., 2000) or visual Continuous Performance Tests (e.g. Fallgatter et al., 1999; Tekok-Kilic et al., 2001). For auditory stimuli, Simson et al. (1977) reported P300s elicited in an S1-S2 CNV-type task with equiprobable Go and NoGo tones. Regardless of stimulus modality, one effect on P300 has been consistently reported across tasks. The NoGo P300 shows a more anterior distribution relative to the Go P300, the so-called NoGo P300 'anteriorization'. This ERP effect has been hypothesized to reflect response inhibition on NoGo trials.

In an effort to describe topographic differences in P300 between silently counting and pressing a button to the target stimuli in auditory oddball tasks, Salisbury et al. (2001) compared the Go P300 and silent-count P300. P300 amplitude on the Go task was smaller frontally relative to silent-counting due to a broad bilateral negative field and also unilaterally reduced in close proximity to the motor cortex contralateral to the responding hand. The silent-count P300 thus showed an anteriorization effect, as had been reported for the NoGo P300: broadly increased P300 amplitude bilaterally and even greater increases contralateral to the responding hand. This pattern matches that described for the putative NoGo inhibition effect. Overall P300 reduction on a button-pressing task relative to the silent-count had been reported earlier on oddball tasks for analyses of the traditional midline sites (Fz, Cz, Pz) by Barrett et al. (1987) and Polich (1987a), but was not observed in two other studies by Starr et al. (1995, 1997) nor by Polich in subsequent studies (personal communication). Salisbury et al. (2001) argued that the act of button-pressing elicited motor-related potentials (MRPs) that arise in close temporal proximity with P300 and distort the 'true' P300 field (see Kok, 1988). Since it is unlikely that the silent-counting of targets involves the inhibition of some not-to-count prepotent response, it is likely that the frontal reduction on the Go task relative to the silent-counting task is directly due to response execution activity. Hence, it becomes unclear whether the similar P300 anteriorization seen on NoGo tasks reflects the additive effect of a response inhibition process on the NoGo task, or rather reflects a reduction of the P300 on the Go task due to response production activity in premotor and motor areas coincident with P300.

Several studies have attempted to separate response production processes from response inhibition processes in an effort to determine what underlies the NoGo anteriorization. Strik et al. (1998) suggested that the NoGo P300 anteriorization was due to greater activity in the right frontal cortex, concluding that the relatively greater positive activity on NoGo trials versus Go trials reflected response inhibition and summed with the P300. Since the observed greater positivity seen on the NoGo task was relative to the Go trial, however, the alternative hypothesis that such increased activity reflects standard P300 activity in any task that is cancelled on Go trials through the additive effects of a negative-going motor process cannot be ruled out.

By contrast with Strik et al. (1998), two studies argued for a left-sided positive-going inhibitory processes. Roberts et al. (1994) used a visual imperative stimulus type Go/NoGo task to evoke P300. They found that the NoGo P300 was larger frontally relative to the Go P300, and also that the NoGo P300 was more positive over the left hemisphere (contralateral to the responding hand). This effect was interpreted as reflecting a lateralized positivity on NoGo trials that reflected response inhibition. Importantly, Roberts et al. also showed that the P300 was larger on the left for control trials, where there was no inhibition needed. Thus, it may be that the task

used by Roberts et al. elicited a P300 with a left-greater-than-right asymmetry, as has been seen for more central sites in standard auditory oddball experiments. Hence, the Roberts' data can be understood to reflect a distortion of the normal P300 field on Go trials with a contralateral negativity, since both NoGo and control trials were larger on the left.

Salisbury et al. (2001) assessed laterality effects on Go and silent-count trials, and found that the difference between silent-count P300 and Go P300 was relatively larger on the left for frontal sites. Again, however, a silent-count P300 cannot be understood to have any type of inhibitory component. Hence, a left-greater-than-right P300 on NoGo trials relative to Go trials cannot be taken as evidence of an inhibitory NoGo positive component. Similarly, Kiefer et al. (1998) used the same left-greater-than-right P300 asymmetry on NoGo trials relative to Go trials to suggest that a left-sided positive component was active on NoGo trials. However, simply comparing the two conditions without some neutral condition not involving an overt motor response, or inhibition of such a response, does not allow for an accurate assessment of the directionality of the effect.

Roberts et al. (1994) also used principal components analysis of control trials (those not requiring an overt response, containing a subset of stimuli (i.e. O-X on an A-X CPT) to which a prepotent response had to be inhibited) to isolate a positive component putatively related to inhibition. A positivity was seen to target stimuli not preceded by the imperative cue, but preceded P300, with a peak at 240 ms. Hence, this positivity cannot underlie the NoGo P300 enhancement. The crux of Roberts et al.'s (and Kiefer et al.'s, 1998) explanation of their laterality shift was that the P300 was not smaller contralateral to the responding hand on Go trials, and the NoGo P300 was more positive on the left. However, this is not *prima facie* evidence of a left-hemisphere inhibitory process on NoGo trials, since P300 topography was not assessed on tasks not requiring a covert response or response inhibition, like a silent-count.

On the other hand, P300 on a silent-count task is essentially symmetrical over lateral frontal sites (e.g. Salisbury et al., 2001). Thus, lateral frontal topographic differences between the silent-count and NoGo P300, with greater NoGo positivity contralateral to the inhibited response hand, would suggest that inhibitory processes were present. Additionally, it is unclear the extent to which Go P300 is reduced contralateral to the responding hand. Thus the present experiment aimed to compare the topography of P300 on NoGo and silent-count tasks, and to replicate the report of Go task frontal P300 asymmetry.

In a Go oddball task, subjects must make an overt response to indicate the detection of a target stimulus. They are required to inhibit such a response to the frequently presented standard stimuli. For the silent-count task, subjects must make a covert response to indicate the detection of a target stimulus and inhibit such a response to the frequently presented standard stimuli. Both the Go task and the silent-count task require the commission of a response to a rarely presented target stimulus. Hence, if the anterior P300 increase observed on NoGo tasks relative to Go tasks reflects the addition of a positive-going response inhibition process that is not present in silent-count tasks, then the silent-count P300 should likewise be smaller than the NoGo P300.

As counter-argument, the silent-count task might elicit a positive voltage memory-related process that exactly matches the positive voltage NoGo inhibitory component. If such was the case, one might expect topographic differences between the tasks, as the neural substrate for memory and inhibition in the frontal lobe are likely superior and inferior, respectively (e.g. D'Esposito et al., 2000). In the absence of any significant topographic or overall amplitude difference between the silent-count and NoGo P300 anteriorization, the most parsimonious explanation would be that the anteriorization had similar neural substrate between the two tasks, and thus that much of the cause of the anteriorization could be ascribed to the Go task.

However, it might be possible that the response inhibition processes on the NoGo trial and the memory processes on the silent-count trials were similar enough that differences in topography might be missed in this study.

Remarkably, the Go, NoGo, and silent-count P300 on an auditory oddball task have never been directly compared. Only Kiefer et al. (1998) and Weisbrod et al. (2000), examining different subsets of the same subjects, reported P300 to low-probability (oddball) auditory tones when the targets were Go or NoGo stimuli, and replicated the P300 anteriorization on the NoGo task. Consistent with the additive positive inhibitory activity model, this anteriorization was interpreted as the activity of a positive voltage inhibitory process coincident with P300. If the P300 anteriorization on NoGo trials relative to Go trials is solely due to the additive effect of a separate inhibitory positivity that is not P300, then such an increase in positivity should not be apparent for silent-count P300s. Such a model cannot account for the P300 anteriorization observed on silent-count tasks relative to Go tasks.

The present study compared the P300 to identical auditory stimuli under Go, NoGo, and silent-counting conditions. The aims of the study were to replicate the frontal P300 reduction and asymmetry in the Go condition relative to the silent-count condition, and to determine if the absolute amplitude and topography of P300 differed between the silent-count and NoGo tasks. It was predicted that if the NoGo P300 anteriorization was due to response inhibition, the NoGo P300 would be larger and more asymmetrical (i.e. left > right) than the Go and the silent-count P300. By contrast, if the NoGo anteriorization was mainly due to reduced P300 on the Go trials from overlapping MRPs, then the NoGo P300 would be larger than the Go P300, but identical to the silent-count P300.

2. Methods

2.1. Subjects

Procedures were approved by the local IRB and all subjects gave informed consent. Thirty-four healthy subjects were recruited with newspaper advertisements from the local population. All subjects were screened for a negative history of drug use, neurological disease or trauma, and psychopathology (SCID-NP; Spitzer et al., 1990) as well as any family history of psychopathology, all factors known to affect P300 amplitude and topography.

Two of the subjects were unable to perform the Go task, with 151 and 153 out of a possible 170 false alarms, and two subjects were unable to perform the NoGo task, with 170 and 113 out of a possible 170 false alarms. These subjects were dropped from further analyses. Two more subjects were dropped from the remaining pool due to a peak P300 amplitude at Pz on at least one of the experimental conditions that was negative. The final 28 subjects analyzed averaged 24.0 years of age (SD 6.0, range 18-47), and included 22 men and 6 women. Subjects performed the Information and Vocabulary subscales of the WAIS-R (Wechsler, 1981) to test remote memory and fund of information, and the Digits forward and backward subscales of the WAIS-R to test short-term immediate and working memory. All demographics and tests results are presented in Table 1.

2.2. Oddball paradigms

Three distinct oddball paradigms were presented to subjects in a counter-balanced fashion. The order of presentation, and potential subsequent establishment of different prepotent response tendencies, had no effect on P300 amplitudes or distributions. All tasks were variants of a two-tone oddball task. In all cases, the standard pure tone was 1 kHz at 97 dB SPL, 50 ms duration (10 ms rise/fall) presented on 85% of trials. The target pure tone was 1.5 kHz at 97 dB SPL, 50 ms duration (10 ms rise/fall) presented on 15% of trials. All tones were presented with a

variable inter-stimulus interval of 1.3 ± 0.2 s. Each paradigm contained 200 stimuli and was presented once.

For the silent-count task, subjects were required to keep a mental count of the number of target stimuli, to be reported at the end of the run. For the Go task, subjects were required to press a button with their right thumb upon detection of each target tone. For the NoGo task, subjects were required to press a button with their right thumb to every standard tone, and *to refrain from pressing* upon detection of a target. For all 3 tasks the infrequent tone was the target. For all analyses, the correct detection of a target was defined as a hit, regardless of the specific response required. A miss was defined as the failure to detect a target tone, a false alarm as responding to a standard tone as if it was a target, and a correct rejection as the correct detection of a standard tone.

2.3. Recording system

EEG activity was recorded from the scalp through 28 tin electrodes in pre-configured caps (ElectroCap International). Linked-earlobes were used as the reference, the forehead as ground. Two electrodes located medially to the right eye, one above and one below, were used to monitor vertical eye movements. Electrodes placed at the outer canthi of the eyes were used to monitor horizontal eye movements. All electrode impedances were below 3 k Ω , and the ears were matched within 1 k Ω . The EEG amplifier bandpass was 0.15 (6 dB/octave rolloff) to 40 Hz (36 dB/octave rolloff). Single trial epochs were digitized at 3.5 ms/sample. Each epoch was of 900 ms duration, including a 100 ms pre-stimulus baseline.

Averaging and artifact rejection were done off-line automatically. ERP responses were digitally low-pass filtered at 8.5 Hz with a 24 dB/octave rolloff to remove ambient electrical noise, muscle artifact, and alpha contamination. Within each 200 trial block, epochs from each electrode site were baseline corrected by subtraction of the average pre-stimulus voltage, and corrected for eye movement artifact using regression-based weighting coefficients (Semlitsch et al., 1986). Subsequently, epochs which contained voltage exceeding ± 50 μ V at F7, F8, Fp1, or Fp2 were rejected. Averages were constructed for target tones (including only hits for the Go and NoGo tasks). There were no significant differences in the mean number of trials used to construct averages for each condition (Go 24.4; NoGo 24.0; silent-count 24.8, $P > 0.78$).

2.4. Analyses

P300 was measured on all average waveforms by recording peak P300 amplitude and latency at the most positive point from 250 to 450 ms at each recording site. In the case of double peaks, the later (P3b) peak was selected. Each site was manually inspected and adjusted if necessary so that the same potential was measured from each site. To test for broad inhibitory potentials that might overlap with P300 differentially on the tasks, slow wave was measured as the mean amplitude from 450 to 600 ms over the frontal region.

Repeated measures Analysis of Variance (ANOVA) was used to test for effects between the different paradigms. Two analyses of P300 amplitude were conducted. For midline effects, two within-group factors were used: Task (Go, NoGo, silent-count) and Site (Fz, Cz, Pz). For anterior hemispheric effects, 3 within-group factors were used: Task (Go, NoGo, silent-count), Hemisphere (left, right) and Site. Frontal regions were defined as F3, C3, and FTC1, and their right-side homologues F4, C4, and FTC2, which overlie motor and premotor cortices. Follow-up tests included repeated-measures ANOVA between pairs of tasks, and t tests between specific sites between and within tasks. To assess the degree to which P300 amplitude was affected by slow wave activity, which putatively might reflect an inhibitory process, Pearson's correlations between P300 amplitude and slow wave were performed for each task. Results

were considered significant at $P \leq 0.05$, corrected where factors had more than two levels with the Huynh-Feldt epsilon.

3. Results

3.1. Task performance

Response outcomes for the Go and NoGo tasks and the number of targets reported on the silent-count task for each subject are presented in Table 2. There was no statistically significant difference between the number of targets detected among the 3 paradigms ($P > 0.4$), assessed by comparing percentage of hits for the operant tasks (hits/total targets $\times 100$) with the percentage of correct targets in the silent-count task $\{[(30 - \text{ABS}(30 - \text{count}))/30] \times 100\}$. The silent-counting condition does not allow for separating hits from false alarms, although any number greater than 30 (the total number of targets) must be a false alarm; hence, accuracy was adjusted in this case.

3.2. P300

Grand averaged ERP responses for each condition are presented in Fig. 1. The primary differences between the silent-counting task and the Go task are a broad bilateral fronto-central reduction and a unilateral reduction contralateral to the responding hand in the Go P300. The same topographic differences are present between the Go task and the NoGo task. The P300 amplitude and topography appear virtually identical between the silent-count and NoGo tasks.

Analysis of P300 along the traditional sagittal midline revealed only trend-level differences in P300 amplitude between the 3 tasks ($F_{2,54} = 2.54$, $P = 0.09$, $\epsilon = 1.0$). Of primary importance, however, was a significant task by site interaction ($F_{4,108} = 6.78$, $P < 0.001$, $\epsilon = 0.86$), revealing topographic differences in the midline distribution of P300. Although all 3 tasks showed the expected posteriorly maximal P300 ($F_{2,54} = 60.94$, $P > 0.001$, $\epsilon = 0.80$), P300 at Fz on the Go task was smaller than in the silent-counting task (6.0 vs. 8.2 μV , $t_{27} = 2.4$, $P < 0.03$) and the NoGo task (6.0 vs. 9.4 μV , $t_{27} = 4.0$, $P < 0.001$). The NoGo P300 and silent-count P300 were not significantly different at the frontal site ($t_{27} = 1.38$, $P > 0.17$). That t value would never achieve significance, even using a one-tailed probability and an infinite number of subjects (critical value of $t > 1.7$). The NoGo P300 was larger than the silent-count task at Fz by 1.2 μV , a small effect size of $d = 0.18$ SD. Assuming a new task with moderate power (0.67, 2 to 1 odds that d will be detected), a sample size of well over 300 would be needed to detect significant differences that might be ascribed to an inhibitory process on the NoGo task. Thus, although there is some evidence that the NoGo P300 is larger frontally than the silent-count P300, the magnitude of this effect is small relative to the difference between these two tasks and the Go task.

The 3 conditions did not differ at Pz, with the largest effect size (between the Go and NoGo tasks) only 0.02 SD (Go 14.47 μV ; NoGo 14.53 μV ; silent-count 14.41 μV). Because of the virtual identity among tasks at Pz, there is no need to normalize the amplitude data and any topographic differences cannot be attributed to the confound of overall voltage differences.

Color-coded voltage maps of P300 topography in each condition are presented in Fig. 2. The broad frontal reduction and asymmetry in the Go task relative to the other two conditions is apparent. Analysis of P300 over the left and right hemisphere sites for frontal lobe revealed a significant effect of task on P300 amplitude ($F_{2,54} = 4.8$, $P < 0.02$, $\epsilon = 1.0$). In addition, a task by hemisphere effect was present ($F_{2,54} = 5.22$, $P < 0.01$, $\epsilon = 1.0$). Comparisons between each pairing of tasks revealed that the Go task was bilaterally reduced relative to the silent-count task ($F_{1,27} = 5.12$, $P = 0.03$) and the NoGo task ($F_{1,27} = 7.76$, $P = 0.01$), which did not differ from each other ($P > 0.45$). Analysis of hemispheric P300 amplitude revealed that the Go task

displayed a unilateral reduction of P300 contralateral to the response hand relative to the silent-count task (task $\times$ hemisphere interaction $F_{1,27} = 4.1$, $P = 0.05$) and the NoGo task ($F_{1,27} = 12.4$, $P < 0.01$). Importantly for assessment of inhibitory activity on the NoGo task, the silent-count and NoGo tasks were not different in frontal hemispheric distributions ($P > 0.27$). Comparing each homologous site between hemispheres within each task revealed that the Go task was significantly asymmetrical at F3 and F4 ($t_{27} = 4.55$, $P < 0.001$) and at C3 and C4 ($t_{27} = 3.60$, $P = 0.001$). The silent-count and NoGo tasks were essentially symmetrical, with no significant differences between hemispheric homologous sites within conditions. Specific comparisons between the silent-count and NoGo task for left hemisphere frontal sites, where the NoGo should be larger if inhibition were present, revealed no significant differences (all amplitudes differed by less than 1 mV, but the NoGo trials were larger).

Slow wave was compared between tasks at the frontal midline site (Fz). Slow wave differed between tasks ($F_{2,54} = 91.7$, $P < 0.001$, $\epsilon = 1.0$). Slow wave was marginally more negative on Go trials ($-4.9 \mu\text{V}$) than on silent-count trials ($-3.7 \mu\text{V}$, $t_{27} = 1.93$, $P = 0.064$) and on NoGo trials ($-1.4 \mu\text{V}$, $t_{27} = 5.42$, $P < 0.001$). Slow wave was significantly more negative on silent-count trials than on NoGo trials ($t_{27} = 3.23$, $P < 0.01$). These data are consistent with a positivity in the slow wave range that is sensitive to response mode and might reflect an inhibition-related positivity. If this positivity overlapped P300, then one might expect correlations between activity in slow wave and P300: If the positive activity observed to vary with response mode in the slow wave interval also caused increases in P300 on the NoGo trials, then the NoGo P300 amplitudes should correlate with slow wave amplitudes. Such was not the case. Slow wave on the NoGo task was not associated with NoGo P300 amplitude ($r < 0.16$, $P > 0.4$, explaining only 2.6% of the variance in P300). Slow wave amplitudes correlated strongly with between tasks (all r 's > 0.7 , $P < 0.001$), but not with P300 amplitudes (all r 's < 0.16 , $P > 0.4$). P300 amplitudes were strongly correlated between tasks (all r 's > 0.5 , $P < 0.01$).

Comparing slow wave at lateral sites between silent-count and NoGo tasks revealed no evidence for different topography between tasks ($F_{1,27} = 0.06$, $P > 0.9$). Thus, although slow wave appeared to be sensitive to response mode, it was neither asymmetrical, nor relatively more asymmetrical on the NoGo task than on the silent-count task, and thus was unlikely to reflect prepotent response hand inhibition in contralateral motor cortices.

P300 latency along the midline was significantly different among tasks ($F_{2,54} = 5.42$, $P = 0.007$, $\epsilon = 0.99$), albeit the magnitudes of the differences were small. Comparing each pair of conditions revealed that P300 latency on the Go task was significantly shorter than the silent-counting task ($F_{1,27} = 4.94$, $P < 0.04$, 8.3 ms) with a trend for longer latencies more posteriorly for both conditions ($F_{2,54} = 3.17$, $P < 0.08$). Likewise, the Go task was significantly shorter in P300 latency than the NoGo task ($F_{1,27} = 10.1$, $P = 0.001$, 14.3 ms). Finally, comparisons between the NoGo task and the silent-count task revealed that P300 latency was not significantly different between tasks ($P > 0.2$).

4. Discussion

P300 amplitude on a Go task was frontally asymmetrical. This replicates Salisbury et al. (2001), and suggests that response production MRPs contralateral to the responding hand do influence P300 topography on Go tasks. In addition, the Go P300 was reduced frontally over both hemispheres relative to the P300 recorded on a NoGo task. These results comprise the NoGo P300 anteriorization effect previously reported, with larger NoGo P300 frontally, and an additional relative left-sided increase (since subjects responded with their right hands). Of primary importance, however, was the finding that the Go task P300 was also reduced and asymmetrical relative to the P300 on a silent-count task (where the infrequent target stimulus did not require response inhibition). Thus, current models that suggest the NoGo P300

anteriorization is due to a left-sided inhibitory mechanism cannot account for the same finding in the silent-count task. Rather, it is likely that the frontal reduction and asymmetry selectively present on the Go task can be attributed directly to motor fields.

The NoGo P300 was slightly but non-significantly larger than the silent-count P300 at left-sided and central sites. This might indicate the presence of left-sided inhibitory processes on the NoGo task, but the magnitude of this difference was small, less than 1 μ V. If there was a positive frontal voltage shift related to response inhibition processes on NoGo trials in the P300 range (e.g. Roberts et al., 1994), then this activity must necessarily be greater on NoGo trials than on silent-count trials. Although the NoGo P300 was larger at Fz than the silent-count P300, the effect size (0.18 SD) indicates that this difference is small. Most importantly, there was no evidence of significantly lateralized positivity on the NoGo task relative to the silent-count. Since the silent-count cannot be reasonably construed as reflecting any response inhibition on the target trial, the increased P300 on the NoGo and the silent-count tasks relative to the Go task (P300 anteriorization) may reflect to a large degree negative shifts on the Go trial. Although there may be some effect of response inhibition on P300 in NoGo tasks, the magnitude of this effect is much too small to account for the robust difference between Go and NoGo P300 at frontal sites. Likewise, the Go P300 and silent-count P300 should be the same, which was not the case. The silent-count P300 showed anteriorization of virtually identical magnitude and the same scalp topography as did the NoGo P300.

Slow wave, subsequent to P300, did appear to be differentially sensitive to response mode. However, slow wave did not show any asymmetry, and was not markedly asymmetrical on NoGo trials (i.e. did not track the active inhibition of a prepotent responding hand), and did not correlate with P300 amplitude on the NoGo trials. Thus, it does not appear that the process reflected in slow wave can be identified with inhibition of a specific response in the contralateral motor cortices, or overlaps temporally with P300. It is unclear the degree to which the slow wave activity measured here corresponds to the P507 reported by Falkenstein et al. (1995), who suggested that the P507 was not related to response inhibition but rather reflected a second P300 process (following their earlier P400 on visual and auditory Go/NoGo tasks). Like Falkenstein et al. we did not see clear evidence that suggested this activity after P300 was directly related to response inhibition. Although Falkenstein argued that the reduced Go P300 was likely not related to MRPs because the overt reaction time overlapped to a greater degree with P300 on auditory than visual tasks, but the P300 was not more reduced on the auditory task, there might be several other factors that cause a priori differences in P300 between those auditory and visual tasks (i.e. psychophysical perceptual differences). In the current auditory oddball Go/NoGo comparisons, it is clear that the reaction time (430 ms) occurs at such a length that MRPs related to response preparation and execution would occur coincident with P300 (350 ms), assuming 50-100 ms pre-response would contain the largest MRP activity. However, Roberts et al. (1994) examined B-X trials on an A-X CPT and suggested that the X on B-X trials elicited a component with a frontal distribution similar to the NoGo P300. Because the X stimulus in that case are not supposed to elicit a response, the authors argued that this reflected inhibition. One might suppose then that there may be some inhibitory activity coincident with P300, though one might also argue that such activity reflects a stimulus evaluation-based P300 for a salient stimulus, and that inhibitory activity in the P300 range should have been observed on A-Y trials, where the response was primed by the S1 cue, which was not the case. Hence, it seems most likely the NoGo task does not introduce a large magnitude positive-voltage inhibitory process in the P300 range, but rather the Go task introduces negative MRPs that reduce P300.

One alternative explanation would be that the silent-count P300 is a NoGo trial and contains the same amount of inhibitory activity as a NoGo trial. In relation to inhibitory processes, it remains difficult to see how the subject counts by inhibiting the prepotent response not-to-

count. In fact, the same argument would apply to the button-press itself, namely the inhibition of the prepotent response not-to-press. In terms of response competition, it is clear that in oddball tasks the target response, no matter what it is, is not the prepotent response. For example, in a recent fMRI study of anterior cingulate activity in oddball-type tasks, Braver et al. (2001) argued that the silent-count task was equivalent with a NoGo trial, since it required the inhibition of the prepotent response established by the high-probability standard stimuli. It is important to note that Braver et al. were not examining P300 or putative inhibitory responses, but rather examined cingulate activity related to a low-probability response in the context of response competition and cognitive control. They demonstrated anterior cingulate activity to each target on Go, NoGo, and silent-count tasks. Kiefer et al. (1998), reporting on a subset of controls in the Weisbrod et al. (2000) report, suggested that NoGo anteriorization could be attributed to source activity in anterior cingulate and inferior frontal lobes, but given that Braver et al. showed similar anterior cingulate fMRI activity on low-probability Go, NoGo, and silent-count trials, it is unclear to what extent cingulate activity can explain the anteriorization. Furthermore, as discussed in the Introduction, because relative differences between Go and NoGo tasks were assessed in the Kiefer et al. (1998) study, one cannot ascribe such differences directly to one specific task.

A second possible alternative is that the additional working memory load on the silent-count task (where the current target count has to be maintained) relative to the Go task (where the count is not maintained) may elicit a new frontal component that mimics the response inhibition component on NoGo trials. Although we cannot rule this alternative explanation out of the realm of possibilities, several data suggest such is not the case. Firstly, inhibitory processes likely reflect activity in inferior frontal regions whereas P300 activity related to working memory load likely involves dorsolateral cortical areas (see D'Esposito et al., 2000). Hence, activity in these anatomically distinct areas should lead to different scalp topographies. Topographies did not differ between the NoGo and silent-count tasks. Secondly, P300 tends to be lower with greater working memory demand, though this is for increasing load rather than a small load versus no load. For example, Mecklinger and colleagues (Mecklinger and Pfeifer, 1996; Mecklinger et al., 1992) reported smaller P300 and larger negative slow wave activity with increasing memory loads on working memory tasks. Lastly, working memory load is equated for Go and NoGo stimuli on n-back continuous performance tasks (a variant of the imperative stimulus task), but the same NoGo anteriorization is observed (Abara et al., 2001). We conclude that it is unlikely that a positive-going working memory potential on the silent-count task mimics a positive-going response inhibition potential on the NoGo task, but cannot reject such a contention. Further research should address this issue.

It is doubtful that a scalp-recorded positive shift due to response inhibition can be hypothesized to completely explain the NoGo P300 anteriorization. The most parsimonious explanation is that motor response execution fields on Go trials directly cause anterior reductions of P300. Unless the silent-count task can be understood to contain a strong inhibitory process, the data of this experiment indicate that inhibitory processes play only a small role in the NoGo anteriorization, as reflected in the small magnitude of the greater NoGo P300 relative to the silent-count P300 (1.2 μ V). The frontal reduction on the Go trial relative to both NoGo and silent-count P300s (2.2-3.4 μ V) is more likely attributable to response execution fields.

In comparing the NoGo P300 with the silent-count P300, it appears that the NoGo P300 may be a viable alternative for eliciting P300 while acquiring task performance. The NoGo task cannot be understood as simply an oddball paradigm where the target stimulus has been made frequent. The overt behavior of the subject on this NoGo task is identical to the overt behavior of a Go task where the probability of the target is 85%. However, the P300 evoked on these two tasks is not the same. Early on in P300 research Tueting et al. (1971) demonstrated that increasing the target probability reduced P300 amplitude. This effect has been replicated by

many others (e.g. Katayama and Polich, 1996; Polich, 1987b; Squires et al., 1977). The work of Sasaki et al. (1996) bears particularly on this issue. Sasaki et al. showed that P300 to target stimuli was smaller with increasing probability, but also measured the P300 to the standard (increasingly infrequent) non-target stimuli. Although the response to the standard showed a greater P300 with decreasing probability, it was not as large as the response to the infrequent target, particularly at Pz. This effect of target designation exemplifies the importance of task relevance to the generation of P300 above and beyond the effects of stimulus probability. In Johnson's Triarchic model of P300 amplitude task relevance is described as a factor additive with the effects of probability (Johnson, 1986). The NoGo task described herein, because of the definition of the NoGo trial as the target, retains the combination of probability and task relevance necessary to elicit a P300 as large as that of the silent-count. Because it elicits a P300 with similar amplitude and topography as the silent-count P300, the NoGo P300 may be advantageous as a paradigm in that it provides accurate measures of task performance, which the silent-count task does not.

The latency of P300 in this experiment was shorter on the Go task than the silent-count and the NoGo tasks. Ford et al. (1982) argued that P300 latency reflected the depth of processing, and thus one might suggest that the differences in P300 latency in this experiment reflect less extensive processing of target stimuli in the Go task. It is possible that response selection processes played a role in these latency differences, as it can be argued that because tasks used the exact same stimuli, stimulus selection processes should be roughly equated between the two tasks. Low and Miller (1999) reported similar lateralized readiness potential (LRP) activity on a NoGo trial and the Go trial, and Endo et al. (1999) reported that an early phase motor preparatory response arose in motor cortex on NoGo and Go trials in a MEG experiment. Those data suggest that response preparation processes are the same on Go and NoGo trials. We cannot rule out the possibility that the latency differences reflect late response selection processes. Yet, because P300 is typically less coupled to response selection than to stimulus evaluation, it is most likely that this latency prolongation reflects the increased cognitive resources needed to inhibit the prepotent response or to increment the silent-count relative to button-press. It remains unclear at what stage of response selection the NoGo and silent-count tasks might require longer processing times.

Finally, unlike Strik et al. (1998), we found no evidence of a right-sided asymmetry in the NoGo P300. Unlike Kiefer et al. (1998) and Roberts et al. (1994), we found no evidence of a left-sided asymmetry in the NoGo P300. Rather, we found a P300 generally symmetrical over frontal regions for both the NoGo task and the silent-count task, and an asymmetrical P300 on the Go task. This can be modeled by motor potential overlap on the Go trial. It is unclear why other studies found asymmetry on NoGo tasks. Stimulus modality and study design likely play a role.

P300 amplitude, topography and latency are largely the same between the silent-count and the NoGo tasks. Because the P300 elicited on the NoGo task was virtually identical to the P300 elicited on the silent-count task, and both were larger anteriorly than the Go task P300, the P300 anteriorization effect on NoGo trials may in fact reflect less of a contribution from response inhibitory processes directly on NoGo trials, but rather reflect response production MRPs on the Go task coincident with P300.

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References

- Abara JP, McCabe DC, Shucard JL, Parrish JB, Shucard DW. Event-related potential components as indices of working memory during verbal and spatial N-back tasks. *Psychophysiology* 2001;38:S19.
- Barrett G, Neshige R, Shibasaki H. Human auditory and somatosensory event-related potentials: effects of response condition and age. *Electroencephalogr Clin Neurophysiol* 1987;66:409–19. [PubMed: 2435521]
- Braver TS, Barch DM, Gray JR, Molfese DM, Snyder A. Anterior cingulate cortex and response conflict: effects of frequency, inhibition, and errors. *Cereb Cortex* 2001;11:825–36. [PubMed: 11532888]
- D'Esposito M, Postle BR, Rypma B. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Exp Brain Res* 2000;133:3–11. [PubMed: 10933205]
- Endo H, Kizuka T, Masuda T, Takeda T. Automatic activation in the human primary motor cortex synchronized with movement preparation. *Cogn Brain Res* 1999;3:229–39.
- Falkenstein M, Koshlykova NA, Kiroj VN, Hoorman J, Hohsbein J. Late ERP components in visual and auditory Go/NoGo tasks. *Electroencephalogr Clin Neurophysiol* 1995;96:36–43. [PubMed: 7530187]
- Fallgatter AJ, Mueller ThJ, Strik WK. Age-related changes in brain electrical correlates of response control. *Clin Neurophysiol* 1999;110:833–8. [PubMed: 10400196]
- Ford J, Pfefferbaum A, Tinklenberg J, Kopell B. Effects of perceptual and cognitive difficulty on P3 and RT in young and old adults. *Electroencephalogr Clin Neurophysiol* 1982;54:311–21. [PubMed: 6179758]
- Hollingshead, AB. Two-factor index of social position. Yale Station; New Haven, CT: 1965.
- Johnson R. A triarchic model of P300 amplitude. *Psychophysiology* 1986;23:367–84. [PubMed: 3774922]
- Katayama J, Polich J. P300, probability, and the three-tone paradigm. *Electroencephalogr Clin Neurophysiol* 1996;100:555–62. [PubMed: 8980420]
- Kiefer M, Marzinek F, Weisbrod M, Scherg M, Spitzer M. The time course of brain activations during response inhibition: evidence from event-related potentials in a Go/No-go task. *NeuroReport* 1998;9:765–70. [PubMed: 9559953]
- Kiehl KA, Smith AM, Hare RD, Liddle PF. An event-related potential investigation of response inhibition in schizophrenia and psychopathy. *Biol Psychiatry* 2000;48:210–21. [PubMed: 10924664]
- Kok A. Overlap between P300 and movement related potentials: a response to Verleger. *Biol Psychol* 1988;27:51–8. [PubMed: 3251560]
- Low KA, Miller J. The usefulness of partial information: effects of go probability in the choice/nogo task. *Psychophysiology* 1999;36:288–97. [PubMed: 10352552]
- Mecklinger A, Pfeifer E. Event-related potentials reveal topographical and temporal distinct neuronal activation patterns for spatial and object working memory. *Cognitive Brain Research* 1996:211–24. [PubMed: 8924049]
- Mecklinger A, Kramer AF, Strayer DL. Event related potentials and EEG components in a semantic memory search task. *Psychophysiology* 1992;29:104–19. [PubMed: 1609022]
- Oldfield RC. The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia* 1971;9:97–113. [PubMed: 5146491]
- Pfefferbaum A, Ford JM, Weller BJ, Kopell BS. ERPs to response production and inhibition. *Electroencephalogr Clin Neurophysiol* 1985;60:423–34. [PubMed: 2580694]
- Polich J. Response mode and P300 from auditory stimuli. *Biol Psychol* 1987a;25:61–71. [PubMed: 3447637]
- Polich J. Task difficulty, probability, and inter-stimulus interval as determinants of P300 from auditory stimuli. *Electroencephalogr Clin Neurophysiol* 1987b;8:311–20.
- Roberts LE, Rau H, Lutzenberger W, Birbaumer N. Mapping P300 waves onto inhibition: Go/No-Go discrimination. *Electroencephalogr Clin Neurophysiol* 1994;92:44–55. [PubMed: 7508852]
- Salisbury DF, Rutherford B, Shenton ME, McCarley RW. Button-pressing affects P300 amplitude and scalp topography. *Clin Neurophysiol* 2001;112:1676–84. [PubMed: 11514251]

- Sasaki, T.; Yabe, H.; Saito, F.; Sato, Y.; Fukushima, Y. P300 to nontarget stimuli in a two-tone discrimination paradigm. In: Ogura, C.; Koga, Y.; Shimokochi, M., editors. Recent advances in event-related brain potential research. Elsevier; Amsterdam: 1996. p. 133-8.
- Semlitsch HV, Anderer P, Schuster P, Presslich O. A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology* 1986;23:695–703. [PubMed: 3823345]
- Simson R, Vaughan HG, Ritter W. The scalp topography of potentials in auditory and visual go/nogo tasks. *Electroencephalogr Clin Neurophysiol* 1977;43:864–75. [PubMed: 73454]
- Spitzer, R.; Williams, J.; Gibbon, M.; First, M. The Structured Clinical Interview for DSM-III-R (SCID-NP). Vol. non-patient edition. American Psychiatric Press; Washington, DC: 1990.
- Squires KC, Donchin E, Herning RI, McCarthy G. On the influence of task relevance and stimulus probability on event-related potential components. *Electroencephalogr Clin Neurophysiol* 1977;42:1–14. [PubMed: 64341]
- Starr A, Sandroni P, Michalewski HJ. Readiness to respond in a target detection task: pre- and post-stimulus event-related potentials in normal subjects. *Electroencephalogr Clin Neurophysiol* 1995;96:76–92. [PubMed: 7530191]
- Starr A, Aguinaldo T, Roe M, Michalewski HJ. Sequential changes of auditory processing during target detection: motor responding versus mental counting. *Electroencephalogr Clin Neurophysiol* 1997;105:201–12. [PubMed: 9216489]
- Strik WK, Fallgatter AJ, Brandeis D, Pascual-Marqui RD. Three-dimensional tomography of event-related potentials during response inhibition: evidence for phasic frontal lobe activation. *Electroencephalogr Clin Neurophysiol* 1998;108:406–13. [PubMed: 9714383]
- Tekok-Kilic A, Shucard JL, Shucard DW. Stimulus modality and the Go/NoGo effects on P3 during parallel visual and auditory continuous performance tasks. *Psychophysiology* 2001;38:578–89. [PubMed: 11352146]
- Tueting P, Sutton S, Zubin J. Quantitative evoked potential correlates of the probability of events. *Psychophysiology* 1971;7:385–94. [PubMed: 5510812]
- Wechsler, D. Manual for the Wechsler Adult Intelligence Scale—revised. The Psychological Corp; Cleveland, OH: 1981.
- Weisbrod M, Kiefer M, Marzinzik F, Spitzer M. Executive control is disturbed in schizophrenia: evidence from event-related potentials in a Go/NoGo task. *Biol Psychiatry* 2000;47:51–60. [PubMed: 10650449]
- Yong-Liang G, Robaey P, Karayanidis F, Bourassa M, Pelletier G, Geoffroy G. ERPs and behavioral inhibition in a Go/No-go task in children with attention-deficit hyperactivity disorder. *Brain Cogn* 2000;43:215–20. [PubMed: 10857697]

Fig. 1.
Grand averaged waveforms for each task. Note the bilateral fronto-central reduction and left-less-than right asymmetry of P300 in the Go task, and the equivalence of all 3 tasks at Pz.

Fig. 2.

Integrated scalp topographies of P300 over a 50 ms interval (Cz peak latency $\times 25$ ms) for each condition. Note that the P300 maximum is shifted posteriorly in the Go task relative to the other conditions. The topographies of the NoGo and silent-count tasks are virtually identical. There is little indication of greater frontal activity in the NoGo task than in the silent-count task.

Table 1

Basic demographic, cognitive, and clinical measures

Age	24.0 ± 6.0
Handedness ^a	0.79 ± 0.2
SES ^b	2.3 ± 1.2
Parental SES	1.6 ± 0.9
WAIS-R information ^c	13.6 ± 1.9
WAIS-R digits ^c	12.7 ± 2.5

Values are mean ± SD.

^a Oldfield (1971). -1, left-handed; 1, right-handed.

^b Socio-economic status, Hollingshead (1965). 5, lowest; 1, highest.

^c Scaled scores Wechsler (1981) Adult Intelligence Scales.

Table 2

Performance measures

Accuracy (%)		
Go	96.1 ± 9.9	
NoGo	93.1 ± 7.4	
Silent-count	95.6 ± 9.1	
	Hits	False alarms
Go	28.8 ± 3.0	1.9 ± 8.3
NoGo	27.9 ± 2.2	11.2 ± 20.6

A total of 30 targets and 170 standards were presented in each condition. Misses and correct rejections are calculable from these totals.