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Title: Response priming in the Go/NoGo task: The N2 reflects neither inhibition nor conflict

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ABSTRACT

Objectives: In the Go/NoGo task, the N2 and P3 components are often thought to index response inhibition, or conflict between competing responses. If so, they should be affected by response preparation when the prediction of an informative cue is incorrect.

Methods: Twenty-six adult participants completed a cued-Go/NoGo task. Targets required a left or right button press, or no response, while cues predicted the probable identity of the target. Analyses examined (a) effects of cues on response preparation, and “inhibitory” components to NoGo targets, (b) typical Go/NoGo differences, and (c) the impact of cue (in)validity.

Results: A reaction time benefit was associated with valid cueing, and a cost with invalid cueing. Late CNV results indicated that participants used cue information to prepare responses, and the P3, but not the N2, showed an increase with prior preparation. Typical frontal N2 and P3 NoGo > Go effects were observed, and the P3 but not the N2 showed an Invalid > Valid effect.

Conclusions: The P3, rather than the N2, reflects the inhibition of a planned response and/or the conflict between competing responses.

Significance: The findings suggest the need for a major review of current interpretations of the N2 and P3 in inhibitory tasks.

Response priming in the Go/NoGo task: The N2 reflects neither inhibition nor conflict

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****Note to type-setter: “Brain & Behaviour Research Institute” is a registered name
and should not be changed in any way.****

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1. Introduction

Several robust differences in the event-related potential (ERP) are observed when responses must be executed or inhibited in the Go/NoGo task. The N2 component is increased in the frontal region, and the P3 is increased in the frontocentral region, on NoGo compared to Go trials (e.g., Pfefferbaum et al., 1985; Kok, 1986; Jodo & Inoue, 1990; Jodo & Kayama, 1992; Roberts et al., 1994; Fallgatter et al., 1997; Fallgatter & Strik, 1999; Van 't Ent & Apkarian, 1999; Bruin & Wijers, 2002; Nieuwenhuis et al., 2003; Bekker et al., 2004; Smith et al., 2006). Debate is ongoing in the literature as to which component best reflects inhibitory processing, since results from other inhibitory tasks show both similarities and differences relative to results from the Go/NoGo task. For example, in the stop-signal task, the N2 is larger on trials where inhibition is unsuccessful, while the P3 is larger on successful trials (De Jong et al., 1990; Brandeis et al., 1998; van Boxtel et al., 2001; Dimoska et al., 2003; Kok et al., 2004; Ramautar et al., 2004; Bekker et al., 2005). Researchers using the stop-signal task generally agree that the N2 may represent an overlap with error-related processing (Kok et al., 2004), while the P3 may reflect evaluation of the outcome of inhibition (Dimoska et al., 2003), or the inhibitory process itself (Kok et al., 2004; Ramautar et al., 2004; Bekker et al., 2005). In the Eriksen flanker task, the N2 is interpreted as reflecting an inhibitory process, since the N2 shows robust effects of target-flanker incompatibility, while the P3 shows almost none (Gehring et al., 1992; Kopp et al., 1996a, 1996b; Heil et al., 2000; van Veen & Carter, 2002; Bartholow et al., 2005). In the Posner task (Posner et al., 1978), where cues validly or invalidly predict the identity of a target (and thus the required response), N2 and P3 are both larger on invalidly- than validly-cued trials (e.g., Gehring et al., 1992; Band et al., 2003). Importantly, an overt response is still executed on invalidly-cued trials in the Posner task, and incongruent-flanker trials in the Eriksen task, suggesting that the N2 and P3 “inhibition” effects in other tasks may reflect conflict between competing responses, rather than total inhibition of any response. Indeed, many of the results cited above could be reinterpreted in light of the conflict hypothesis (e.g., Nieuwenhuis et al., 2003): the observed N2 and P3 effects could be due to a signal to change the planned response to a different one. Conflict between the Go and NoGo

response can occur, as well as conflict between the Go and Stop responses, the responses demanded by the target and by flanker stimuli, and between validly and invalidly cued responses. The functional significance of the N2 and P3 'inhibitory' effects is thus unclear.

A potential confound with many of these experimental paradigms is the comparison of trials where movement-related potentials do or do not occur (e.g., Go vs. NoGo, unsuccessful vs. successful stop). Pfefferbaum et al. (1985) showed that the N2 NoGo > Go effect was greater, but the P3 effect was unchanged, when participants counted Go stimuli, compared to when they pressed a button in response. A study by Bruin and Wijers (2002) is often cited as showing similar effects (a NoGo > Go N2 effect for counting comparable to that for pressing, and a more anterior P3 focus for NoGo than Go in both tasks), yet the usual effect of larger P3 amplitudes for NoGo than Go trials was not found in the counting task. The NoGo P3 in the count condition was never larger than the Go P3, even at frontocentral sites. Thus the contribution of movement-related potentials to the observed Go/NoGo effects remains a question (Salisbury et al., 2001, 2004).

The problem of movement-related potential overlap can be avoided, however, by comparing the outcomes when responses are differentially primed (Bruin et al., 2001). The use of cues or primes results in response preparation in both Posner-type tasks (e.g., Gehring et al., 1992; Band et al., 2003; Leuthold, 2003) and the Eriksen task, where analyses of the lateralised readiness potential (LRP) shows response processing according to the flankers (Gratton et al., 1988; Smid et al., 1990; Kopp et al., 1996a, 1996b; Heil et al., 2000). Where this response preparation is inappropriate, inhibition is necessary, and presumably greater inhibition is required following greater response preparation.

Bruin et al. (2001) utilised differences in response preparation to examine response inhibition processes, by presenting participants with three different targets, requiring a left button press, a right button press, or a NoGo response. On each trial, the target was preceded by one of four different equiprobable cues which predicted either (a) a NoGo target on 100% of those trials (the Specific NoGo cue), (b) a Go Left or Go Right target on 25% of trials each, or a NoGo on 50% of trials (the Non-specific Go

cue), (c) a Go Left or NoGo target on 50% of trials each (the Specific Go Left cue), or (d) a Go Right or NoGo target on 50% of trials each (the Specific Go Right cue). The authors reasoned that response preparation should be elicited according to the cue (and thus, according to what targets could be presented), and that the strength of inhibition required should increase over these varying levels of response preparation. Despite finding an N2 NoGo effect following Non-Specific and Specific cues, the critical test of ERPs to NoGo stimuli following each of the cues revealed no difference in amplitude in the N2 time range (200-280 ms post-target). However, the NoGo P3 did show an increase in amplitude according to the prediction of the cue. Analyses of the LRP timelocked to targets revealed a slightly earlier onset of significant lateralisation to Go targets following Specific than Non-specific cues, but no LRP activity was present to NoGo targets following Specific cues. In addition, no lateralisation according to the expected responding side was found in the cue-target interval. The authors interpreted their lack of an N2 difference to NoGo targets following different cues as evidence against an inhibitory interpretation of this component, and concluded instead that the P3 may reflect the inhibitory process.

Although the conclusions of Bruin et al. (2001) are compelling, there are some problems with their methodology and interpretations. For instance, whether the NoGo N2 amplitude is affected by the cue may depend on whether response preparation according to the cue is actually elicited: Bruin et al. did not find LRP activity signalling this response preparation in the cue-target interval. The lack of response preparation according to the cue may in turn be caused by the low global response probability (37.5% overall) and/or by the percentage of validly-cued trials (although participants could trust the cue information on 100% of NoGo cue trials, Non-specific and Specific cues predicted the correct target on only half the trials). If the cue predicts the target correctly only at chance levels, and if NoGo targets are presented on a large proportion of trials (62.5%), then high levels of cue-related preparation for a Go response are unlikely.

The current study modifies the task of Bruin et al. (2001) in several ways, with the aim of gaining further understanding of the functional correlates of the N2 and P3. The global response probability was raised to 66%, in order to ensure that response inhibition was difficult whenever a NoGo stimulus was presented. With respect to

cue validity, the overall percentage of validly-cued trials was similar to that of Bruin et al., but for individual cue types, the percentage was slightly higher (60% compared to 50%). In order to further examine the response conflict interpretations of N2 and P3, invalid cues were introduced, such that specific cues could be followed by not only the expected valid target (e.g., a Specific Left cue followed by a Go Left target) or a NoGo stimulus, but also by an invalidly-cued target (Go Right), so that conflict between the planned and required response could be induced.

By increasing both cue validity and response probability, participants would be expected to increase their use of the information given by the cue to prepare fast responses. This would be revealed by differences in amplitude and topography of the late CNV to Specific, Non-specific and NoGo cues. It was also expected that the usual N2 and P3 NoGo effects would be seen in comparisons of Go and NoGo targets after Non-specific and Specific cues, but the primary tests of interest were comparisons of NoGo targets after different cues, and of Invalidly- vs. Validly-cued Go targets following Specific cues. If a component reflects motoric inhibition, then its amplitude should increase as a function of prior levels of preparation; if it reflects response conflict, then it should be larger for Invalid than Valid targets.

2. Methods

Subjects

Participants were 26 adults (11 male) with a mean age of 22.6 years (SD 7.2 years) who participated to fulfil an undergraduate course requirement. All participants were right-handed and had not consumed caffeine in the two hours prior to testing, alcohol or illicit drugs in the previous 24 hours, or illicit drugs more than once a month for the past six months. No participants reported any neurological disorders or problems with vision or hearing. The research protocol was approved by the joint University of Wollongong and Illawarra Area Health Service Human Research Ethics Committee before data collection began.

Apparatus and stimuli

Participants completed six blocks of a cued auditory Go/NoGo task with 67 trials per block. Each trial consisted of a cue (S1) followed by a target (S2), both 200 ms in duration with 40 ms rise and fall times. The S1-S2 stimulus onset asynchrony was fixed at 1500 ms, while the S2-S1 interval varied randomly between 3000 and 4000 ms (mean 3500 ms). All stimuli were delivered through stereo headphones, and were either 1000 Hz or 2000 Hz.

Three different stimuli were presented as targets (S2; see Table 1): a 70 dB tone presented to the left ear (requiring a left button press response, ‘Go Left’), a 70 dB tone of the same frequency presented to the right ear (requiring a right button press response, ‘Go Right’), or a 70 dB tone of a different frequency presented binaurally (requiring no response, ‘NoGo’). Thus, the participant was required to discriminate targets on both pitch (Go/NoGo) and side of presentation (Go Left vs. Go Right).

Four different cue stimuli (S1) preceded these targets: a 60 dB tone, of the same frequency as Go targets, presented to the left ear (Specific Left cue), the right ear (Specific Right cue), or binaurally (Non-specific cue), and a 60 dB tone of the same frequency as the NoGo target (NoGo cue). Thus, participants could distinguish cues from targets by both the loudness of the tone and the timing of stimuli (short fixed S1-S2 interval, longer variable S2-S1 interval). The Go/NoGo assignment of high- and low-pitched cues and targets was counterbalanced between participants.

There were ten cue-target alternatives, presented in Table 1. The NoGo cue was presented on 10% of trials, while the Non-specific, Specific Left, and Specific Right cues were each presented on 30% of trials. The probability of each target varied according to the cue presented: the NoGo cue was always followed by the NoGo target (100% correct information given by the cue). The Non-specific cue was followed on 40% of trials by the NoGo target, and on 30% of trials by each of the Go Left or Go Right targets. That is, the Non-specific cue predicted a Go response on 60% of trials, but gave no information about the side of response (60% correct information). Given a Specific Left and Specific Right cue, valid targets (Go Left and Go Right, respectively) constituted 60% of trials, invalid (Go Right and Go Left)

20%, and NoGo the remaining 20%. Thus, validly-cued targets were three times more likely than either invalidly-cued or NoGo targets, and as likely as correctly cued Go targets following Non-specific cues.

Participants were instructed that the cue gave information about the likely identity of the target, namely, that left cues predicted left targets, right cues predicted right targets, and binaural cues predicted an unspecified Go response on the majority of trials, and that NoGo cues always predicted NoGo targets. Thus, participants were informed that the prediction of a cue was usually correct, but, in the case of Non-specific and Specific Go primes, they were not informed of the exact probability of each cue-target pair. Participants were given substantial training in order to respond correctly to each of the cue-target pairs (see below).

Procedure

Participants were familiarised with the testing procedure and laboratory before written informed consent was obtained. It was stressed that consent to participate could be withdrawn at any time with no unfavourable consequences. Participants then filled out a brief questionnaire assessing neurological disorders, drug use, etc.

Once recording electrodes were fitted, subjects were seated in a dimly-lit, sound-attenuated, electrically-shielded chamber where testing took place. Prior to the experimental task, participants completed three short (< 3 min) tasks which became increasingly more complex, and served as training/practice for the experimental task. Participants practised these tasks until 80% correct performance was achieved, then progressed to the experimental blocks.

Task instructions appeared on a computer screen for the subject to read, stressing speed and accuracy equally, with participants instructed not to guess what target would be presented, nor to respond to the cues. Subjects were encouraged to keep as still as possible throughout the task and to keep eye movements to a minimum using a central fixation cross on the computer monitor. Short breaks were given between blocks of the experimental task if necessary.

Recording

An electrode cap containing tin electrodes was fitted, with continuous EEG recorded from 17 sites (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, and T6) of the International 10-20 system. Cap electrodes were referenced to linked earlobes. Vertical EOG was measured with tin cup electrodes placed 1 cm above and below the left eye, and horizontal EOG from 1 cm lateral to the outer canthi. Impedances for ear and eye electrodes were below 3 k Ω , with scalp electrodes below 5 k Ω . The subject was grounded by a cap electrode located midway between Fpz and Fz. EEG and EOG signals were amplified 5,000 times with a bandpass down 3 dB at 0.01 and 100 Hz, via 24 channels of Grass amplifiers, sampled through a Labmaster A/D card at 512 Hz, and displayed and recorded using Neuroscan software.

Data analysis

The ERP epoch began 100 ms before the cue and lasted until 900 ms after the target stimulus (total 2500 ms). Epochs were baseline-corrected to the pre-cue activity, and digitally low-pass filtered down 48 dB at 15 Hz. Trials were rejected if subjects made any response to the cue, or an incorrect response to the target. Further, trials were rejected if signal amplitude exceeded ± 100 μ V in any EOG channel, or ± 150 μ V at any scalp site. Since the number of trials for each cue-target pair differed, a random sample of 24 correct trials was selected for the higher probability pairs to maintain a relatively equal signal-to-noise ratio (24 trials were chosen as that was the maximum number of epochs for Specific NoGo and Specific Invalid trials, the rarest of the cue-target pairs). Average ERPs for each site, cue-target pair and subject were then calculated.

In order to establish latency ranges over which the late CNV was maximal, and the contribution of other components to the waveforms were minimal, ERPs from all 17 scalp sites were reduced to 552 points via a spline fit and subjected to a principal components analysis (PCA). The PCA used the covariance matrix and varimax rotation (Kayser & Tenke, 2003) and extracted 38 factors, together accounting for 96.9% of the variance (9 factors accounted for 85.9%). The first factor extracted

represented the late CNV (55.0% of the variance), and this was used to define the time range over which mean amplitude late CNV measures were derived (the last 600 ms before the onset of S2). In addition to this, baseline-to-peak amplitudes and latencies were calculated for the S2-N2 and S2-P3. For peak detection, a computer algorithm selected the greatest negativity in the range 180-260 ms post-S2 at Fz as N2, and the greatest positivity in the range 280-400 ms post-S2 at Pz as P3, and then reported amplitudes at all other sites at the same latencies (Picton et al., 2000). These measurements and ERPs were subsequently re-baselined to 100 ms pre-S2, effectively equating these for the late CNV. **Note that the correlation of this baseline measurement (-100 to 0 ms) with late CNV measurement (-600 to 0 ms) exceeded $r = .810$ at every site (all $p < .001$).** Oddy et al. (2005) have shown that a PCA-based factor representing the late CNV can be subtracted from ERP waveforms without alteration of the N2 and P3 effects in a Go/NoGo task. The warning ERPs and measurements **of the late CNV** were averaged across target types, since participants could not know which target would be presented following Go cues. Responses to targets following Specific Left and Specific Right cues were collapsed to create NoGo, Valid and Invalid ERPs and measurements.

Statistical analysis

A 2 x 3 factorial ANOVA on RT examined the effects of response side (left/right) and cue (Non-specific/Specific Valid/Specific Invalid), with planned contrasts comparing RT for validly- vs. non-specifically-cued targets, and also invalidly- vs. non-specifically cued targets. Commission errors to NoGo stimuli were analysed for effects of response side and cue type.

The main analyses of ERP data were restricted to the sites Fz, Cz and Pz. The analysis approach was similar to that of Bruin et al. (2001), with four separate analyses performed: effects of priming on ERP components in the foreperiod; effects of priming on inhibition; effects of target given a Non-specific prime; and effects of target given a Specific prime. Where there were main effects of cue or target type, ERP data were also submitted to vector scaling (McCarthy & Wood, 1985) and only

condition x topography interactions that remained significant after this procedure are reported. All effects have (1, 25) degrees of freedom.

To check that the cues differentially affected response preparation, late CNV amplitude measures were entered into a *Sagittal* (Fz/Cz/Pz) x *Cue* (NoGo/Non-specific/Specific Left/Specific Right) ANOVA. Planned contrasts on the *Cue* factor compared activation to NoGo primes with the mean to Go primes (Non-specific, Specific Left and Specific Right), activation to Non-specific with Specific (the mean of Specific Left and Specific Right), and activation following Specific Left vs. Specific Right cues. Planned contrasts for the *Sagittal* factor compared frontal with parietal activation, and the mean of these with central activation. Such sagittal contrasts are optimal for deriving information about the topographic distributions of each component. As the contrasts were planned and there were no more of them than the degrees of freedom for effect, no Bonferroni-type adjustment to alpha was necessary (Tabachnick & Fidell, 1996). Also, the single degree of freedom contrasts are not affected by violations of symmetry assumptions common in repeated measures analyses, and thus do not require Greenhouse-Geisser-type corrections. It should be noted that analyses are carried out over a substantial number of variables, each of which may be considered to constitute a separate experiment. This increases the frequency of type I errors, but as this is an increase in *frequency*, rather than probability, it cannot be 'controlled' by adjustment of α levels (Howell, 1997). The late CNV at sites in the left and right central region following Specific Left and Specific Right cues was also subjected to a *Cue* x *Lateral* (C3/C4) repeated measures ANOVA, to assess whether significant response lateralisation occurred to Specific cues.

N2 and P3 amplitude and latency to NoGo stimuli were subjected to *Sagittal* x *Cue* analyses as described above, but with data from a virtual frontal pole site used in addition to the Fz, Cz and Pz sites. This was because examination of the ERP waveforms revealed that in situations where N2 was of relatively small amplitude, it was accompanied by a large P3. This has implications for the interpretation of results: perhaps the small N2 in some situations is due simply to overlap of a large P3. However, the P3 component was barely visible at prefrontal sites Fp1 and Fp2, and thus could be assumed to not affect the waveform at these sites. Furthermore, the N2

is generated in the frontal cortex (e.g., Mathalon et al., 2003). Therefore, ERP waveforms and amplitude measurements were averaged across Fp1 and Fp2 to create a virtual midline site Fp for target stimuli only. Sagittal contrasts for all targets included the comparisons described above (Fz vs. Pz, and their mean vs. Cz), with an extra contrast comparing Fp and Fz. This extra contrast allowed us to determine whether the N2 effects were significantly different at a site where overlap with the P3 was minimal. N2 and P3 to targets following a Non-specific cue were subjected to a *Sagittal x Target* (NoGo/Go Left/Go Right) analysis. Contrasts for the Target factor compared the mean of Go Left and Go Right (Go) with NoGo. For targets following Specific cues (collapsed across Specific Left and Specific Right), a *Sagittal x Target* (Valid/Invalid/NoGo) analysis was used. Planned contrasts on the Target factor compared Valid with Invalid, and the mean of these (Go) with NoGo. Note that comparisons of NoGo targets across different levels of preparation avoid the problem of movement-related potential overlap since no overt responses are given, while for comparisons of Invalidly- and Validly-cued targets, overt responses are given in both cases.

3. Results

Behavioural performance

Responses to targets were faster following Valid than Non-Specific cues (345 vs. 360 ms, $F = 9.9$, $p < .01$), but there was no difference in RT following Invalid and Non-Specific cues (360 vs. 365 ms, $F = 1.7$, $p > .05$). In addition, there was an effect of response side which approached significance ($F = 4.1$, $p = .055$), with faster responses for the right than left hand (352 vs. 362 ms).

Regarding inhibitory accuracy following the four cues, participants made more errors following Go than NoGo cues (0.83 vs. 0.32 % errors; $F = 6.0$, $p < .05$), and a significant Cue x Response Side interaction showed that to NoGo targets following Specific cues, participants made more commission errors with the uncued than cued side. That is, following a Specific Left cue, subjects made more commission errors to

NoGo targets with the right than left hand (2.1 vs. 0.0%), and following a Specific Right cue, more errors with the left than right hand (1.3 vs. 0.2%; $F = 10.4$, $p < .01$).

Effect of cue type on late CNV

The ERPs to cue stimuli are shown in Figure 1. An N1-P2 complex is clearly seen, with P2 appearing larger at Cz for the Specific primes. This is followed by the early CNV, observed as a frontal-negative/parietal-positive slow wave from 400-600 ms post-stimulus, which appears much larger following NoGo cues. The late CNV arises from approximately 1000 ms post-stimulus, and increases to the end of the epoch. The late CNV shows a clear separation at most sites between the different cues, with smallest amplitude for the NoGo cues, larger for the Non-specific cues, and largest with Specific cues. The late CNV also appears to be somewhat lateralised, being larger contralateral to the expected responding hand for the Specific primes (i.e., larger at C3 than C4 for the Specific Right cues, and larger at C4 than C3 for the Specific Left cues).

Statistical analysis confirmed these observations on the late CNV. It displayed a frontocentral maximum (see Table 2 for effect summaries and means, and Figure 2 for topographic maps of this and other components). The late CNV was globally smaller following NoGo than Go primes. In addition, while the late CNV to NoGo primes showed an even $Fz > Cz > Pz$ gradient, that to Go primes showed a $Cz > Fz > Pz$ gradient. The late CNV was larger following Specific than Non-specific primes, and the $Cz > Fz/Pz$ effect was slightly larger for Specific Right than Specific Left.

Further analyses of the late CNV at C3 and C4 revealed that a right > left effect (-5.3 vs. -6.1 μV) was observed following Specific Left cues, while a left > right effect (-5.8 vs. -5.1 μV) was observed for Specific Right cues ($F = 22.6$, $p = .000$).

Effect of cue type on ERPs to NoGo stimuli

ERPs to NoGo stimuli following each of the four cues can be seen in Figure 3. A clear N1 component is seen, followed by the N2 peak. The N2 appears most negative following NoGo cues, slightly less with Non-specific cues, and smallest with Specific

cues. A distinct difference is seen in the waveforms in the 250-500 ms period: while a large amplitude P3 component is seen following Go cues, the P3 is of low amplitude or with no clear peak at most sites following NoGo cues. The NoGo P3 also appears to be larger following Specific than Non-specific cues.

N2 was largest at Fp, slightly reduced at Fz, and was positive and equipotential at Cz and Pz (see Table 3). N2 was more negative following a NoGo than Go cue, and the Fz/Pz > Cz effect was larger following Go than NoGo cues. N2 to NoGo stimuli peaked earlier after a Specific than Non-specific cue (209 vs. 225 ms; $F = 6.5$, $p < .05$).

P3 to NoGo stimuli was almost nonexistent at the frontal pole site, and showed a centroparietal maximum (see Table 3). It was much larger following a Go than NoGo cue. This Go > NoGo effect was larger at Fz than Fp, and larger still at Pz. The NoGo P3 was larger across the scalp following a Specific than Non-specific cue, and peaked earlier following Non-specific than Specific cues (328 vs. 347 ms; $F = 4.2$, $p = .050$).

Effect of target type following Non-specific cues

ERP waveforms to targets following Non-specific cues can be seen in Figure 3. There appears to be little difference between trial types in the N1 time range, although an augmented N2 can be seen for NoGo relative to Go Left and Go Right targets at most sites. The frontocentral increase in P3 for NoGo relative to Go targets can also be seen clearly.

The N2 component was largest at Fp, and showed a strong frontal maximum (see Table 4). N2 was more negative globally following NoGo than Go stimuli, but response topography did not differ between target types.

P3 was almost nonexistent at site Fp, and showed a parietocentral maximum (see Table 4). P3 was larger for NoGo than Go trials, particularly in the frontocentral region. That is, the effect was very small at Fp and Pz, and much larger at Fz and Cz. There were no significant Go/NoGo effects on peak latency for any component.

Effect of target type following Specific cues

ERPs to target stimuli following Specific cues (collapsed across Specific Left and Specific Right) can be seen in Figure 3. No large difference in the N1 component is apparent, but the N2 component appears more negative when validly- than invalidly-cued targets are presented, with the NoGo N2 peak being of intermediate amplitude, and perhaps with a shorter latency. The P3 appears larger for Invalidly- than Validly-cued targets, and an increase for NoGo targets is also apparent frontocentrally but not parietally.

N2 to targets following Specific cues was larger at Fp than Fz and showed a strong frontal maximum (see Table 5). N2 was globally more negative following Validly- than Invalidly-cued targets. This Valid > Invalid cue difference was larger at Fz than Fp, and larger at Cz than Fz/Pz. N2 peak latency was shorter for Invalidly- than Validly-cued targets (219 vs. 234 ms, $F = 5.3$, $p < .05$). The NoGo > Go effect was larger at Pz than Fz, and almost non-existent at Cz. N2 peak latency was shorter for NoGo than Go targets (209 vs. 227 ms, $F = 10.7$, $p < .01$).

P3 was almost non-existent at Fp, and showed a parietocentral maximum. P3 was globally larger for Invalidly- than Validly-cued targets, but no topographic differences remained after normalisation. P3 peaked marginally earlier for Invalidly- than Validly-cued targets (297 vs. 325 ms; $F = 3.4$, $p = .079$). The P3 was larger across the scalp following NoGo than Go targets. This target-type difference was very small at Fp, and was larger at Fz than Pz. The P3 peak was later for NoGo than Go stimuli (347 vs. 311 ms; $F = 8.2$, $p < .01$).

4. Discussion

This study was designed to examine response competition processes via the use of informative cues. Cue stimuli were used to induce varying levels of response preparation, with the aim of examining variations in response inhibition and response conflict when the planned response was inappropriate. The major comparisons of

interest were the late CNV following the cue, indexing preparation of the expected response, increased inhibitory activity to NoGo targets according to the preparation for a Go response, and differential activation for Invalidly- vs. Validly-cued trials, indicative of response conflict/competition.

Reaction time was faster with the right than left hand, an unsurprising result given that only right-handed participants were included in the study. The result is consistent with the literature on response speed for the dominant vs. non-dominant hand. Reaction time showed the expected benefit of valid cueing relative to non-specific cueing, and a small cost of invalid cueing. These effects are compatible with the literature (e.g., Posner et al., 1978), and are usually interpreted as the outcome of prior preparation for the expected response. It should be noted, however, that these RT differences were very small, with a benefit for valid relative to non-specific cueing of 15 ms, and a cost of invalid relative to non-specific cueing of only 5 ms, in contrast to Posner et al.'s (1978) original valid benefit of approximately 40 ms, and invalid cost of approximately 60 ms. The small effect in this study may be due to the lower proportion of valid cueing (60%) compared to Posner et al.'s 80%; indeed, work by Riggio and Kirsner (1997) has shown that the validity effect (defined as the difference in RT between invalidly- and validly-cued trials) decreases with the proportion of valid cues. Their validity effect was significant with 90% and 75% valid cues (33 and 27 ms, respectively) but not with 60% valid cues (only 10 ms). Thus, in comparison with Riggio and Kirsner's results, the validity effect in this study (20 ms) appears rather strong in relation to the proportion of valid cues.

Commission errors to NoGo targets following Specific cues were more likely to occur with the uncued than the cued hand. This result seems counterintuitive, as one would expect inhibition errors with the prepared hand, rather than the unprepared hand. Too few errors were made overall to perform analyses of the LRP or commission error reaction times, but the result is worth further investigation in future studies.

Analyses of activity to cue stimuli examined differences in response preparation (late CNV) following the NoGo, Non-specific, Specific Left and Specific Right cues. Late CNV amplitude increased with the likelihood of making a specific/definite overt response, with the smallest amplitude following NoGo cues, when participants knew

no response would be required. Slightly larger amplitude was observed following Non-specific cues, when a response was likely but the response side was not known, and the largest late CNV amplitude was observed with Specific cues. Although of relatively small amplitude, the late CNV following NoGo primes is worthy of note. Across the scalp, the late CNV reached an amplitude of $-3 \mu\text{V}$, despite explicit instructions to participants that, given a NoGo cue, no response to the following target would ever be needed. **Participants may not have trusted these instructions, or** it may be that the CNV elicited by Go cues, occurring on the majority of trials, is also automatically elicited by the rare NoGo cue, although with a lesser amplitude. **The different topographic distributions of the CNV following Go and NoGo cues (central and frontal maxima, respectively), suggest that different processes underlie these components. The central maximum for Go cues can be clearly linked to the motor preparation for a Go response, and stimulus anticipation processes could be active when subjects expect a NoGo stimulus. Although the stimulus-preceding negativity (SPN) typically has a parietal focus (Damen & Brunia, 1987; van Boxtel & Bocker, 2004), this is in situations where the anticipated stimulus is a probe or affective stimulus, or provides information about past or future performance (van Boxtel & Bocker, 2004). Clearly, one would not expect that any of these types of anticipation would be elicited prior to NoGo targets when the target identity is known. Thus, while a low amplitude late CNV may be automatically elicited by the ongoing relationship between an informative S1 and S2, it is unclear what type of process (anticipatory or otherwise) underlies this late CNV when it is known that no task is required by the target, and when S2 gives no information about past or future task performance.**

Analyses of the late CNV following Non-specific and Specific cues were of utmost importance to the interpretation of results from this study. The understanding of variations in activity to NoGo targets as a reflection of response inhibition is dependent on whether different levels of prior response preparation occurred. The amplitude increase in late CNV for Specific compared to Non-specific cues, particularly in the central region, was expected, since a prediction about the responding hand was made with Specific but not Non-specific cues. Similar results were observed by Leuthold et al. (1996), who found that the late CNV increased with the number of known movement parameters signalled by S1, with low CNV

amplitude when no information about the required response was given, intermediate amplitude when either hand information or direction information were given, and greatest amplitude when the cue gave both hand and direction information. In addition, the lateralisation in the central region for Specific Left and Specific Right cues, with greater amplitude on the side contralateral to the expected responding side, is further evidence that participants prepared responses according to the information imparted by the cue, in line with results from Gehring et al. (1992) and Band et al. (2003).

Analyses of ERPs to target stimuli focused on the N2 and P3 components. The N2 to NoGo targets was increased relative to Go targets following both Non-specific and Specific cues, showing that a significant N2 NoGo effect can be obtained with auditory stimuli. Previously, it was thought that a significant N2 NoGo effect could be obtained only with visual stimuli (e.g., Falkenstein et al., 1995, 1999, 2002), but Nieuwenhuis et al. (2004) have shown that this is likely due to the perceptual overlap between Go and NoGo stimuli. That is, there is a strong overlap of visual but not auditory features for the letters F and J, or M and W, the usual stimuli used by Falkenstein's group. Similar visual features are likely to elicit some response activation on NoGo trials, thus requiring greater inhibition to withhold the response, while dissimilar auditory features would not. Nieuwenhuis et al. showed that a strong auditory, but not visual, N2 NoGo effect could be obtained when auditory but not visual features of the stimulus were similar (stimuli S and F). **In contrast, the perceptual overlap of pitch stimuli appears to be sufficient to produce a significant N2 NoGo effect in adults (Karlin et al., 1970; Banquet et al., 1981; Kiefer et al., 1998; Burle et al., 2004; Kaiser et al., 2006) as well as children (Smith et al., 2004; Johnstone et al., 2005). Indeed, a significant effect can be observed even when the pitch of Go and NoGo tones are quite different (this study, and our previous work using identical stimuli, Smith et al., 2006).**

Although the N2 NoGo effect is usually interpreted as an indication of inhibitory processing (e.g., Kok, 1986; Jodo & Kayama, 1992; Nativ et al., 1992; Bokura et al., 2001), results from the present study do not support this interpretation. Given that participants prepared responses according to the prediction of the cue, one would expect an increase in the N2 to NoGo targets dependent on these prior levels of

response preparation. In contrast, results showed that the NoGo N2 was of a greater amplitude following NoGo than Go cues; that is, the NoGo N2 was largest when participants knew no response was necessary, and when response preparation was at a minimum (indexed by late CNV amplitude). This is in support of Bruin et al. (2001), who, using similar cue-target pairs as this study, found equipotential amplitudes in the N2 time range (200-280 ms post-target) to NoGo targets following these different cues. Bruin et al. therefore proposed that the NoGo N2 did not index the strength of an inhibitory process. However, their conclusion was undermined by the fact that no response preparation according to the cue occurred, as indexed by LRP amplitude, and Bruin et al. themselves noted that the N2 inhibitory process might depend on the occurrence of sufficient response preparation. It was therefore critical in this study that the participants prepared responses according to the prediction of the cue, which was supported in the late CNV analyses. Despite this, however, there was no inhibitory increase in the N2 to NoGo stimuli dependent on the cue/prior level of preparation. It appears, then, that the N2 to NoGo targets does not reflect the strength of motoric inhibition.

An additional aim of this study was to test the response conflict/competition interpretation of the N2 component. Some researchers have suggested that the increased N2 on NoGo trials represents the detection/correction of an incorrect tendency to respond (e.g., van Veen & Carter, 2002; Nieuwenhuis et al., 2003; Donkers & Van Boxtel, 2004; Yeung et al., 2004). That proposal argues that N2 amplitude is increased when response conflict is high, for example, when, in the context of a high frequency response, a low frequency response must be given instead (Nieuwenhuis et al., 2003), or when activation of an incorrect response must be suppressed in order to give the correct response, as is commonly the case in the Eriksen flanker task (van Veen & Carter, 2002). In the current study, the use of Invalid trials should have elicited response conflict, since participants prepare their responses according to the Specific cues, and that prepared response is inappropriate when an invalidly-cued target is presented. Thus, if the response conflict interpretation of N2 is correct, higher N2 amplitudes on Invalidly- than Validly-cued trials are expected. This was not the case, however: larger N2 amplitudes were associated with Validly- than Invalidly-cued trials, particularly in the frontocentral region. Thus, the current results contradict the response conflict account of the N2.

However, the result requires replication before a strong conclusion can be made: only one other study has found a similar Valid > Invalid result (Schröger, 1993), while a multitude of studies, especially those using the Eriksen flanker task, have found the opposite effect (e.g., Kopp et al., 1996a, 1996b; Band et al., 2003; Bartholow et al., 2005).

It is important to note that none of the N2 results appear to be affected by overlap with the P3. Examination of Figure 3 revealed that in some situations, a small N2 was followed by a large P3, suggesting the possibility that N2 appeared small due to overlap with the P3. However, the analyses of the N2 and P3 at the frontal and virtual frontal pole sites indicate that this was not the case. Firstly, as the P3 was small or absent at the Fp site, its contribution to the average waveform at this site, and particularly to amplitudes measured in the N2 time range, was minimal. Secondly, although the N2 peak is not as well-defined, but is generally larger at Fp than Fz, the same general pattern of results was observed. The lack of any N2 interaction between the sites for NoGo targets indicates that the same effect (larger following NoGo than Go cues) was observed. Similarly, the lack of an interaction between the sites for targets following Nonspecific cues suggests the same NoGo > Go effect held. After Specific cues, a significant interaction was observed, but the effect was a difference in magnitude of the Valid > Invalid effect, *not* its direction. It would appear, therefore, that the major conclusions and suggestions from the current data are not open to criticism based on overlap with a large P3.

For the P3 component itself, the usual frontocentral increase for NoGo relative to Go trials was observed following both Non-specific and Specific cues. Such an effect is typical of Go/NoGo tasks (e.g., Podlesny et al., 1984; Jodo & Inoue, 1990; Filipović et al., 1999; Tekok-Kilic et al., 2001; Bekker et al., 2004; Oddy et al., 2005; Smith et al., 2006), and similar effects are observed in the stop-signal task where successful inhibition is compared to unsuccessful (e.g., De Jong et al., 1990; Brandeis et al., 1998; Kok et al., 2004; Bekker et al., 2005). These robust P3 effects led to the interpretation of the NoGo/successful-stop P3 as an inhibitory component (e.g., Fallgatter & Strik, 1999; Bokura et al., 2001; Bruin et al., 2001; Bruin & Wijers, 2002; Donkers & Van Boxtel, 2004; Kok et al., 2004; Ramautar et al., 2004; Bekker et al., 2005; Smith et al., 2006). Confidently drawing such a conclusion is difficult in

these tasks because of overlap of movement-related potentials occurring on Go but not NoGo trials, and on unsuccessful but not successful stop trials. However, that problem was avoided in this study and that of Bruin et al. (2001) by the comparison of ERPs to NoGo targets following different cues, without overt responses, but with inhibition presumably more difficult following higher levels of preparation. In these comparisons, the NoGo P3 was almost nonexistent after NoGo cues, was larger following Non-specific cues (particularly at Cz), and largest and later following Specific cues. It should be noted that Bruin et al. (2001) presented remarkably similar waveforms and virtually the same results from their paradigm using visual stimuli. Their conclusion was that the NoGo P3 was an index of response inhibition, and results here support that conclusion.

The current study extended the focus on response inhibition and conflict by considering the effects of invalid cueing. The P3 component was increased for Invalidly- relative to Validly-cued targets, particularly at Cz, in support of consistent findings in the literature (Gehring et al., 1992; Schröger, 1993; Band et al., 2003; Bennett et al., 2004; Ofek & Pratt, 2004). This effect is sometimes interpreted as a reflection of target expectancy; that is, the P3 is larger when a target is unexpected than expected, and that expectancy can be experimentally manipulated, for example, by varying instructions, stimulus probability, or informative cues. However, an alternative interpretation might also be put forward for the P3 effects. If the NoGo P3 represents an inhibitory mechanism, then the larger P3 on Invalidly- than Validly-cued trials may be interpreted also as evidence of response conflict or competition between the prepared and required response. **That is, in this study the P3, not the N2, appears consistent with an inhibition and/or competition interpretation.**

The current paradigm is unable to distinguish between the inhibition and competition explanations of the NoGo P3. This is partly because inhibition of all responses, as occurs when a NoGo target is presented, could be considered a subset of response competition, when there is conflict between the prepared/expected response and that which is required. A different approach would be required to assess whether P3 represented response inhibition or competition, when a Go response is required in the context of frequent NoGo responses. On those Go trials, competition with the prepotent NoGo response would exist, but no response inhibition would be required.

Such a paradigm has been examined by Nieuwenhuis et al. (2003), but no analysis of the P3 was undertaken. It is also difficult with the current data to suggest what the N2 component might reflect, but we are able to say that it is neither response inhibition nor competition.

One limitation of this study is that the RT validity effect was rather small, although nonetheless significant. As discussed earlier, this is likely due to the relative proportions of valid and invalid trials following Specific cues (60% and 20%, respectively). In future work, if valid cues were used more often (say, 80% of trials), and NoGo and Invalid trials less often (say, 10% each), this may result in not only stronger behavioural effects, but also greater preparation according to the cue, and stronger inhibitory/conflict processing. In addition, it would also be informative to consider response activation processes when response preparation is low, by including a small number of Go trials after NoGo cues. In this way, one could compare ERPs when the expected or unexpected response is to be executed, whatever that response is. That is, a comparison of NoGo targets following NoGo cues with Validly-cued targets following Specific cues could be informative about the execution of an expected task, while a comparison of Go targets following NoGo cues with Invalid or NoGo targets following Specific cues could be informative about the execution of an unexpected task. The inclusion of Go trials after NoGo cues would also allow examination of response conflict processes in the absence of total response inhibition.

In conclusion, this study used informative cues to elicit varying levels of response preparation, in order to study changes in response inhibition and competition processes when the prepared response is no longer appropriate. Analyses of the late CNV showed that participants did prepare their responses according to the prediction of the informative cues, and relative to Non-specific cueing, small RT benefits and costs were associated with Valid and Invalid cueing, respectively. Despite significant N2 NoGo effects, the amplitude of the N2 component appears unrelated to either the strength of inhibition or to response competition/conflict processes, **although the Valid > Invalid result requires replication before strong conclusions can be made.** The P3, however, was increased for NoGo relative to Go stimuli, increased to NoGo stimuli according to the level of prior preparation, and was larger when the prepared response had to be suppressed in order to execute a different response. **Although a**

different paradigm is required to further discriminate the inhibition and conflict interpretations, the present results suggest the P3, but not the N2, represents an inhibitory and/or conflict process.

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Legends

Figure 1. Grand mean ERPs to cue stimuli. Vertical bars represent warning stimulus onset. Amplitude in μV and time in ms are marked at Fz.

Figure 2. Topographic maps for the late CNV, N2 and P3 components. For the late CNV, maps show grand mean amplitude over the last 600 ms before S2; for N2 and P3, maps show amplitude at the average peak latency. Maps on the left represent responses to the cue for the late CNV, and to NoGo targets following those cues for N2 and P3. Maps on the right represent N2 and P3 responses to Go targets following Non-specific, Valid and Invalid cues (collapsed across response sides). Shaded areas are negative relative to the prestimulus baseline. Spacing between isopotential lines for the Late CNV and N2 is 1 μV ; for the P3 the spacing is 2 μV .

Figure 3. Grand mean ERPs to NoGo targets following different types of cues, targets following Non-specific cues, and targets following Specific cues. Vertical bars represent target stimulus onset. Amplitude in μV and time in ms are marked at Fp.

Tables and Figures

Table 1. Cue-target pairs and their probabilities.

Cue type	p(cue)	Target type	p(target cue)	Number of trials/block
Specific NoGo	0.10	NoGo	1.00	7
Non-specific Go	0.30	NoGo	0.40	8
		Go Left	0.30	6
		Go Right	0.30	6
Specific Left	0.30	NoGo	0.20	4
		Go Left	0.60	12
		Go Right	0.20	4
Specific Right	0.30	NoGo	0.20	4
		Go Left	0.20	4
		Go Right	0.60	12

Table 2. Significant results for the late CNV.

Effect	Contrast	Details	F	p
S	Fz vs. Pz	-5.6 vs. -2.3	33.3	.000
	Cz vs. Fz/Pz	-5.6 vs. -3.9	36.7	.000
C	NoGo vs. Go	-3.1 vs. -4.9	9.1	.006
CxS	Fz vs. Pz	NoGo: -5.8 vs. 0.0	11.2	.003
		Go: -5.5 vs. -3.0		
	Cz vs. Fz/Pz	NoGo: -3.6 vs. -2.9	12.8	.001
		Go: -6.3 vs. -4.3		
C	Non-specific vs. Specific	-4.0 vs. -5.4	10.6	.003
CxS	Cz vs. Fz/Pz	Specific Left: -6.9 vs. -4.9	5.5	.028
		Specific Right: -6.9 vs. -4.5		

Note for this and subsequent tables: Details column represents mean amplitude in μV . C, Cue: NoGo/Non-specific/Specific Left/Specific Right.

Table 3. Significant results for the N2 and P3 to NoGo targets following different types of cues.

Peak	Effect	Contrast	Details	F	p
N2	S	Fp vs. Fz	-3.3 vs. -2.0	10.1	.004
		Fz vs. Pz	-2.0 vs. 3.6	24.7	.000
		Cz vs. Fz/Pz	3.5 vs. 0.8	39.2	.000
	C	NoGo vs. Go	-0.6 vs. 0.8	6.7	.016
	CxS	Cz vs. Fz/Pz	NoGo: 1.1 vs. -0.2	20.7	.000
			Go: 4.3 vs. 1.1		
P3	S	Fp vs. Fz	0.6 vs. 8.3	104.0	.000
		Fz vs. Pz	8.3 vs. 15.0	51.7	.000
		Cz vs. Fz/Pz	12.6 vs. 11.7	95.9	.000
	C	NoGo vs. Go	3.6 vs. 12.2	76.9	.000
	CxS	Fp vs. Fz	NoGo: -0.5 vs. 2.2	115.9	.000
			Go: 1.0 vs. 10.3		
			NoGo: 2.2 vs. 6.5	8.8	.032
			Go: 10.3 vs. 17.8		
	C	Nonspecific vs. Specific	10.5 vs. 13.0	12.8	.001

Table 4. Significant results for responses to targets following Non-specific cues.

Peak	Effect	Contrast	Details	F	p
N2	S	Fp vs. Fz	-3.3 vs. -1.9	6.8	.015
		Fz vs. Pz	-1.9 vs. 6.1	31.2	.000
		Cz vs. Fz/Pz	4.3 vs. 2.1	14.7	.001
	T	NoGo vs. Go	0.1 vs. 1.9	4.6	.042
P3	S	Fp vs. Fz	-1.0 vs. 5.2	118.1	.000
		Fz vs. Pz	5.2 vs. 16.9	69.1	.000
		Cz vs. Fz/Pz	15.0 vs. 11.1	45.4	.000
	T	NoGo vs. Go	10.5 vs. 8.3	5.0	.035
	TxS	Fp vs. Fz	NoGo: -0.1 vs. 8.6	20.1	.000
			Go: -1.5 vs. 3.6		
		Fz vs. Pz	NoGo: 8.6 vs. 16.0	17.8	.000
			Go: 3.6 vs. 17.3		
		Cz vs. Fz/Pz	NoGo: 17.5 vs. 12.3	6.2	.020
			Go: 13.8 vs. 10.4		

T, Target Type: Go/NoGo

Table 5. Significant results for responses to targets following Specific cues.

Peak	Effect	Contrast	Details	F	p
N2	S	Fp vs. Fz	-3.0 vs. -1.6	16.2	.000
		Fz vs. Pz	-1.6 vs. 6.3	36.5	.000
		Cz vs. Fz/Pz	5.0 vs. 2.3	29.4	.000
	T	Valid vs. Invalid	0.9 vs. 2.9	12.0	.002
	TxS	Fp vs. Fz	Valid: -3.7 vs. -2.9	4.8	.038
			Invalid: -2.3 vs. -0.5		
		Cz vs. Fz/Pz	Valid: 3.4 vs. 2.0	15.1	.001
	TxS	Fz vs. Pz	Invalid: 6.7 vs. 3.6		
			NoGo: -1.5 vs. 4.2	14.5	.001
			Go: -1.7 vs. 7.3		
P3	S	Fp vs. Fz	NoGo: 4.9 vs. 1.4	5.4	.029
			Go: 5.0 vs. 2.8		
	S	Fz vs. Pz			
	S	Cz vs. Fz/Pz			
	T	Valid vs. Invalid			
	T	NoGo vs. Go			
	TxS	Fp vs. Fz			
	TxS	Fz vs. Pz			

T, Target Type: Valid/Invalid, Go/NoGo

Response to reviewers

Reviewer #1:

General:

This MS reports a modified and extended replication of the Bruin et al. 2001 study (Clin Neuro 112) which was aimed at elucidating the significance of the well-known N2 and P3 effects in Nogo trials by using priming stimuli. Bruin et al. reported no effects of priming in the N2 range, but a large effect on the P3. Hence they related the P3 rather than the N2 to inhibition. However, as the present authors correctly state, the lack of LRP effects due to specific priming in that study casts doubt on whether the primes have been actually used. This lack of preparation may have been due to the low Go probability and relatively low validity of Go primes. Consequently they modified the Bruin et al. design by enhancing Go probability and prime validity. Moreover they introduced invalid cues to check the conflict hypothesis of the N2 (Nieuwenhuis et al. 2003). Finally they used a longer prime-target interval than Bruin et al. which might enhance cue-induced preparation. The methods are generally sound; the number of participants is high, sufficient practise was administered. A random sample of correct trials equal to the lowest number of trials was selected to equalize S-R ratio across conditions. The CNV measurement is sophisticated.

However, the use of auditory stimuli is unfortunate because auditory stimuli are known to induce a smaller N2 after Nogo stimuli (Kiefer et al. 1998; Tekok-Kilic et al. 2001; Falkenstein et al. 1999; 2002). Even when the criticism of Nieuwenhuis et al. 2004 is accepted that the auditory Nogo-N2 is enhanced with overlapping stimulus features for Go and Nogo stimuli the stimulus overlap should have been high (i.e. similar stimuli should have been taken) instead of low, as in the present study.

The reviewer makes an assumption that the pitch stimuli used in this study have little perceptual overlap, and therefore a strong N2 NoGo effect cannot be obtained. We do not know of any research articles that have specifically addressed the issue of perceptual overlap and the N2 NoGo effect using several different pitches or types of auditory stimuli. However, it appears that the auditory perceptual overlap of most letters is low unless they are specifically selected for perceptual overlap (Nieuwenhuis et al., 2004). In contrast, the perceptual overlap of most pitch stimuli appears to be sufficient to produce a significant N2 NoGo effect (Kiefer et al., 1998; Burle et al., 2004; Kaiser et al., 2006). The results from this study and from our other papers using identical stimuli (e.g. Smith et al., 2006, Int J Psychophysiol; Smith et al., submitted, Int J Psychophysiol) show that a significant N2 NoGo effect can be obtained using 1000 Hz and 2000 Hz stimuli. Although a stronger effect could no doubt be obtained with visual stimuli, or with stimuli closer together in pitch (and therefore with a greater overlap), it nevertheless appears that there is sufficient overlap between the stimuli used in this study to produce a significant Go/NoGo effect. We do not believe the use of auditory stimuli should preclude this paper from publication. We have clarified our discussion of this point in the manuscript.

As expected, no clear and sufficiently large Nogo-N2 is seen after the N1. Hence the risk of overlooking an N2 effect is enhanced. Also, at Fz and more posterior areas the N2 is strongly influenced by the rising flank of the Nogo-P3: the larger the Nogo-P3, the smaller (more positive) the "N2". At FP1 and FP2, which are least influenced by the Nogo P3 the N2 appears to be flatter for validly precued Nogo trials than for the other conditions (Fig. 4, which is similar to the Bruin et al. results). The authors realized this influence (p. 15, 16) and added a Nogo N2 analysis focused on the FP leads. To my opinion this should be used as the only meaningful analysis of the N2. This would also free the results section from the abundance of data.

We consider that analysis of peak data at only one site, as the reviewer suggests, ignores important information about component topography. However, we have reduced the results section substantially. We have averaged ERPs and results from Fp1 and Fp2 to produce a virtual midline site named Fp, and have used this in restructured analyses of midline sites only. Lateral effects were mostly removed from the manuscript, because both reviewers thought the topographical complexity obscured the important results, and indeed we made little reference to lateral effects in the original version of the paper. For the reader interested in lateral effects, we have retained the topographic maps, constructed using data from all 17 recorded sites.

We have reorganised the data analysis such that the N2 frontal pole analyses originally presented in the section titled "Separation of the N2 and P3 components" are now incorporated into the sections titled with each analysis of targets, under the Fp vs. Fz contrast. We have included similar new analyses of the P3, which confirm that the P3 is almost absent at Fp.

Although significant interactions between target types and these sites are observed for N2, these are in every case due to differences in the magnitude, not the direction, of a Go/NoGo or Valid/Invalid effect at Fp and Fz. This supports our original interpretations of the N2 at frontal and frontal pole sites.

We have altered appropriate sections of the Methods and Results to reflect our new analysis structure, and made discussion of the frontal pole data clearer.

The result section is hard to follow; particularly the topography effects are difficult to understand and interpret. In particular the N2 data are certainly influenced by the Nogo-P3, so complex topography effects result. Focussing of the Nogo-N2 at FP1 and FP2 only would help! I would generally suggest to focus all statistical evaluations on the electrode(s) where the Nogo-N2 (FP1, FP2) and Nogo-P3 (Cz) are maximal.

As stated above, we consider that analysis only of the site where the component is maximal excludes valuable information about component topography. However, we have removed the lateral factor from all analyses except the late CNV, where the central lateral effects are important for confirming response preparation following Specific Left and Specific Right cues. The sagittal variation of components is still analysed.

Our new analysis of the P3 at Fp confirms the visual impression that overlap with the N2 is minimal. As mentioned above, the patterns observed at site Fp are the same as those observed at Fz.

To me the overall result pattern appears to be: a) the Nogo P3 (max. at Cz) is largest for Nogo trials after specific cues, smaller after unspecific cues and absent after fully valid Nogo cues. This is the same pattern as in the Bruin et al. study. The Nogo N2 is small and strongly influenced by the Nogo-P3, so only the N2 at FP1 and FP2 can be interpreted. At those electrodes a small but clear phasic N2 is always seen clearly for Nogo targets but not when a Nogo cue preceded the target. This is also similar to the Bruin et al. findings (see their Fig.1).

The discussion of the N2 effects is misleading, and I could not follow the argument on page 20 of no influence of the Nogo P3. The larger Nogo N2 after Nogo cues in the first analysis is most certainly due to the overlap of the Nogo P3. The analysis of the N2 at the frontopolar and frontal leads yielded no cue effect on the N2. However, at FP1 and FP2, no negativity at all is seen for Nogo cues, but a small negativity is well seen for Go cues. This is in line with Fig. 1 of Bruin et al. Hence the present N2 results and particularly the conclusions are doubtful. The Nogo-P3 results and conclusions are o.k. and support the relation of the Nogo-P3 to inhibition.

The reviewer suggests that our results are incorrect because Fp1 and Fp2 (in the original figures, now averaged to produce Fp) show clear N2 peaks following Go but not NoGo cues, and are less affected by overlap from a large NoGo P3 than other analysed sites. Our method of peak detection is to select the component peak at the site of maximum amplitude (in this case, Fz) within a specified latency range (in this case, 180-260ms), and then take amplitude measures at all other sites at the same latency (Picton et al., 2000).

Our statistical analysis confirms the visual impression of the Fp virtual prefrontal site in this latency range, i.e. no increase in N2 dependent on prior preparation. As the reviewer notes, the same result is reported by Bruin et al. at midline sites, with the same conclusion as ours: that the NoGo N2 does not reflect inhibition.

In summary, the present paper confirms and strengthens the Bruin et al. results with improved methodology and design. However, as mentioned above, a considerable problem with the present study is the use of auditory stimuli and the overall small N2 and its overlap with the Nogo-P3. The inclusion of invalid cues is a good idea to extend the old findings and test the conflict hypothesis. However, the N2 data are hard to interpret, and, to my opinion, misinterpreted by the authors: if one tracks the FP data in Fig.6 the valid condition shows almost no N2, while the invalid and Nogo condition does. Hence it seems very dangerous to conclude that the N2 is larger in the valid than in the invalid condition (which would in fact argue against the conflict hypothesis).

As outlined above, our peak detection method uses Fz, where a clear N2 is seen in each condition. Although a clear N2 peak may not be visible for the Valid condition at Fp1 and Fp2 (averaged to produce Fp), the same Valid > NoGo >

Invalid effect is observed as at Fz. Statistically, the same result was supported, that N2 is larger in the Valid than Invalid condition, and the interaction with the sagittal factor revealed that this effect was smaller, but by no means reversed, at Fp. We were just as surprised as the reviewer that the conflict hypothesis is unsupported, but we cannot argue with the ERP plots and statistics. However, the result will require replication before the conflict hypothesis of N2 can be dismissed.

We have added the following phrase to the last paragraph of the Discussion: "the Valid > Invalid result requires replication before strong conclusions can be made."

Also the CNV data should be interpreted with more caution, because of the unexpected CNV after valid Nogo cues.

We believe that our interpretations of the CNV data are reasonable. The CNV following NoGo cues shows a distinctly different topography (frontally maximal) to that following Go cues (centrally maximal), and as such we consider that whatever process underlies the CNV following NoGo cues, it is unlikely to be the same preparation for a motor response observed following Go cues.

We have added consideration of this result to the Discussion section.

LRP data, which would help to support the idea of preactivation, are lacking.

We considered the preparation of motor responses in our analyses of the CNV, but do not feel that further analyses of the LRP would provide any additional information about response preparation.

The text is too long and partly very hard to read (particularly the results section). Again, focussing on the N2 at FP1 and FP2 would greatly improve clarity and readability.

We have substantially reduced the length and complexity of the results section, as described above.

The amount of tables is enormous, and the tables are complex. On the other hand they clear the text from statistical burden. Table 5 could be possibly omitted.

By omission of the lateral factor in almost all analyses, we have substantially reduced the complexity of the tables. The original Tables 5, 6 and 7 have now been integrated into one table.

Fig.1 should be omitted.

We have included the data represented in Figure 1 in the text, and omitted that figure.

The ERP traces (also in the TIF files) have not sufficient quality and it is very difficult to tease apart the different conditions, particularly for more than 3 traces. Traces with large gaps (.._.._) are unfortunate because they obscure subtle differences. For example, in Fig.6, the crucial invalid trace is hard to follow. I suggest to use thin vs. thick, and straight vs. densely dotted lines.

We have redrawn our ERP traces with solid and patterned black lines, and the resolution of those files is now 2500 dpi.

I have also some minor comments, as outlined below.

Details:

Methods: the validity for unspecific go cue is still relatively low, so the good idea to enhance Go probability and cue validity was not optimally pursued.

The Non-specific Go cue predicts a go response but does not provide information about which side to prepare. Go Left and Go Right targets followed the Non-specific Go cue on 30% of trials each, therefore the Non-specific cue validity was 60%. This is the same validity as with Specific Left and Specific Right cues, and above the proportion of NoGo targets following Non-specific cues (40%). We have made this point clearer in the Methods section: "and [validly cued targets were] as likely as correctly cued Go targets following Non-specific cues".

The artifact rejection criterion of 150 microvolts is relatively high.

The 150 microvolt scalp sites criterion was applied after a 100 microvolt horizontal and vertical EOG criterion had been applied. The 150 microvolt criterion was required only for very rare instances where amplifier saturation occurred during the epoch. Each epoch created for averaging was manually reviewed for confirmation of correct artifact rejection.

The number of electrodes is rather low, also the FCz row is not included, which yields maximum amplitude of the Nogo-P3.

Our laboratory equipment only allows for a maximum of 24 channels via standard electrocaps. Our data analysis method allows us to confirm statistically that the NoGo > Go effect is largest frontocentrally.

p.9 line 4 from bottom: The warning ERPs and measurements??

We have clarified this: "the warning ERPs and measurements of the late CNV"

The statistical analysis section is rather complex; it should be made clearer.

We have restructured our statistical analysis, as mentioned above, and trust that this has made the analysis section of the Methods easier to understand.

Results:

The amount of results is overwhelming.

We have restructured these analyses in several ways to make the important results easier to understand.

p.14: Fig.6: at FP1/2 no clear N2 is seen in the valid condition; at the other leads the N2 is overlaid by the Nogo P3.

As mentioned above, the peaks are detected at their traditional site of maximum amplitude (Fz). The Valid > NoGo > Invalid effect observed by visual inspection at Fz is also present at Fp, and statistical analysis confirms this.

Discussion:

p.18: as already stated above, the N2 is rather small, but undoubtedly present in Nogo vs. Go targets after the auditory stimuli used by the authors. The presence of an auditory Nogo N2 has already been shown by others (e.g. Kiefer et al 1998; Tekok-Kilic et al. 2001; Falkenstein et al. 2002). However, the auditory Nogo N2 is usually smaller than the visual one, even when feature overlap is equal for both modalities.

We agree that the N2 NoGo effect is smaller but still present with auditory compared to visual stimuli. Our auditory results add to results from a similar task using visual stimuli published by Bruin et al. Our study aims to replicate and extend these effects. The use of auditory stimuli should not preclude this paper from publication.

p.22. the suggested improvements are very thoughtful!

Reviewer #3:

This is a very commendable study on electrocortical mechanisms of inhibition and conflict monitoring in response to more or less unexpected nogo stimuli, elaborating in a suitable manner on earlier reports like the one by Bruin et al. (2001). Attractive features are the inclusion of CNV analysis, the Validity manipulation, and the attempt to deal with overlap between N2 and P3. The main results are that: 1) Response preparation increases with increasing likelihood of having to respond (CNV); 2) Nogo N2 is largest with presumably minimum levels of conflict or need for inhibition; 3) N2s are larger for validly cued than for invalidly cued targets. These results are justly taken as inconsistent with inhibition or conflict-processing accounts of N2.

A few general and specific remarks:

1) Introduction first par., but also at other locations, e.g., the last 2 sentences of the introduction: A Nogo, as opposed to a go stimulus may be assumed to elicit more

inhibition, but equally likely more conflict processing. The same (however) holds for incongruent Eriksen flankers, and also for the currently used Validity manipulation. Incongruent flankers as well as Invalid cues may activate the incorrect response, which would result in increased inhibition, but equally likely in increased response- conflict processing. It could be made clearer from the outset that the manipulations in the present study do not provide critical evidence for the inhibition versus conflict interpretation (of N2 and P3).

Indeed, the current study is unable to provide critical evidence to distinguish the inhibition vs. conflict hypotheses. Because the results for the N2 are compatible with neither theory, it is difficult to make this clear at the end of the Introduction without foreshadowing the results. However, we have added the following to the end of the first paragraph:

"Indeed, many of the results cited above could be reinterpreted in light of the conflict hypothesis: the observed N2 and P3 effects could be due to a signal to change the planned response to a different one. Conflict between the Go and NoGo response can occur, as well as conflict between the Go and Stop responses, the responses demanded by the target and by flanker stimuli, and between validly and invalidly cued responses. The functional significance of the N2 and P3 'inhibitory' effects is thus unclear."

We had already discussed the problem, along with a possible paradigm to test it, in the third last paragraph of the Discussion. We have kept this part of the manuscript as is, and rephrased the concluding sentence of the manuscript: "Although a different paradigm is required to further discriminate the inhibition and conflict interpretations, the present results suggest the P3, but not the N2, represents an inhibitory and/or conflict process."

- 2) Introduction: reference to Posner may be confusing, as in the original Posner design the cues are generally NOT predictive with respect to the response (hand or side), only with respect to stimulus location.

In the original Posner design (Posner et al., 1978), the cue stimuli were a '+' sign (nonspecific cue, 50% of trials), or an arrow pointing to the left or right side (25% each), presented at central fixation. The target stimulus was an X presented on the left of fixation, demanding a response with the left hand, or an X presented on the right of fixation, demanding a right-handed response. Arrow cues pointed to the same side as the following target on 80% of trials. Thus, the cues in the Posner paradigm are indeed predictive of both stimulus location and its associated response.

We have not changed our text.

- 3) P. 9, l. 26, I do not understand ' $r = .810$ ' .

The correlation between the late CNV measurement (from -600 to 0 ms, relative to S2) and the baseline measurement (from -100 to 0 ms) exceeded .810 at all sites.

We have clarified this in the Method section.

- 4) Results, behavior: The Cue x Response effect on commission errors seems contra-intuitive and deserves some further discussion.

We have added the following to the Discussion:

"Commission errors to NoGo targets following Specific cues were more likely to occur with the uncued than the cued hand. This result seems counterintuitive, as one would expect inhibition errors with the prepared hand, rather than the unprepared hand. Too few errors were made overall to perform analyses of the LRP or commission error reaction times, but the result is worth further investigation in future studies."

- 5) Topographical analysis is presented in very much detail, which distracts from the main questions. For example, Nogo N2 analysis could be limited to Fz.

As stated above, we feel that analysis of components at only one site ignores important information about topographical distributions. We have substantially reduced our statistical analyses, limiting them mostly to the midline sites. We trust that this approach will be more easily understandable.

- 6) Discussion: the expression "motor inhibition/ response competition" is confusing. Please use something like "inhibition and/or conflict" (see also point 1).

We have made the suggested change.

Figure

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