Published in final edited form as:

Psychophysiology. 2015 April ; 52(4): 472–480. doi:10.1111/psyp.12374.

It's not too late: The onset of the fronto-central P3 indexes successful response inhibition in the stop-signal paradigm

Jan R Wessel and Adam R Aron

Psychology Department, University of California, San Diego

Abstract

The fronto-central P3 ERP has been proposed as a neural marker of response inhibition. However, this association is disputed: some argue that P3 latency is too late relative to the timing of action-stopping (stop-signal reaction time; SSRT) to index response inhibition. We tested whether P3 onset latency is a marker of response inhibition, and whether it coincides with the timing predicted by neurocomputational models. We measured EEG in 62 participants during the stop-signal task, and used independent component analysis and permutation statistics to measure the P3 onset in each participant. We show that P3 onset latency is shorter when stopping is successful, that it is highly correlated with SSRT, and that it coincides with the purported timing of the inhibition process (towards the end of SSRT). These results demonstrate the utility of P3 onset latency as a non-invasive, temporally precise neural marker of the response inhibition process.

Keywords

Cognition < Content; Normal Volunteers < Groups Studied; EEG/ERP < Measures Used; Individual Differences < Content

Introduction

The ability to quickly stop action is often investigated with the stop-signal task (SST; Logan, Cowan, & Davis, 1984). On each trial, participants initiate a go-response, which they sometimes have to try to stop when a stop-signal is subsequently presented. From this task, the speed of stopping, stop signal reaction time (SSRT), can be derived for any given participant (Verbruggen & Logan, 2009). SSRT usually ranges from 150 to 300ms in young, healthy participants. At a neural level, whether stopping is successful or not apparently depends on the relative timing of neural activity of the response emission and response inhibition processes (Boucher, Palmeri, Logan, & Schall, 2007; Schmidt, Leventhal, Mallet, Chen, & Berke, 2013). In human research, one way to index and investigate the neural basis of the response inhibition process is via event-related potentials (ERPs) derived from scalp EEG. ERPs are noninvasive and can measure neural processing with millisecond precision. However, there is not yet an unequivocal ERP signature of the response inhibition process.

There are two candidate ERPs for successful response inhibition that are commonly reported: a fronto-central P3 wave and a right fronto-lateral N2 wave. The right fronto-lateral N2 is often reported as a correlate of successful response inhibition that distinguishes children and adolescents with and without ADHD (Liotti, Pliszka, Higgins, Perez, & Semrud-Clikeman, 2010; Pliszka, Liotti, & Woldorff, 2000; Schmajuk, Liotti, Busse, & Woldorff, 2006). However, this ERP is rarely (if ever) observed in adults. In adults, the fronto-central P3 is the most common ERP index of successful response inhibition. Many studies have shown increased P3 amplitudes for successful vs. failed stop-trials in healthy individuals (Bekker, et al., 2005; Dimoska, Johnstone, Barry, & Clarke, 2003; Etchell, Sowman, & Johnson, 2012; Greenhouse & Wessel, 2013; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004; Lansbergen, Bocker, Bekker, & Kenemans, 2007; Ramautar, Kok, & Ridderinkhof, 2004; Senderecka, Grabowska, Szewczyk, Gerc, & Chmylak, 2012; Wessel & Aron, 2013). Furthermore, as for the right fronto-lateral N2, participants with ADHD also show reduced fronto-central P3 amplitudes, with the degree of P3-amplitude reduction being predictive of the degree of stopping impairment that is typical for ADHD (Johnstone, Barry, & Clarke, 2007; Overtoom, et al., 2002). Finally, the P3 is sensitive to whether participants prioritize successful stopping over quick going: when stopping is incentivized by monetary reward, the P3 amplitude increases (Greenhouse & Wessel, 2013). However, despite this body of evidence for the relation between successful response inhibition and the P3 ERP, it is disputed whether the P3 is a direct reflection of the response inhibition process. Several authors have argued that the P3 peaks too late relative to SSRT (Dimoska, Johnstone, Barry, & Clarke, 2003; Huster, Enriquez-Geppert, Lavalley, Falkenstein, & Herrmann, 2013; Naito & Matsumura, 1996). Based on this observation, they suggest that rather than reflecting response inhibition, the P3 instead reflects a different psychological process, such as the post-hoc evaluation of performance (e.g., positive affect at a good outcome; for a review, see Huster, Enriquez-Geppert, Lavalley, Falkenstein, & Herrmann, 2013).

One key to the debate about whether the P3 reflects successful response inhibition is whether the peak amplitude of an ERP is a good indicator for the timing of a neural process. A better indicator of the neural process reflected in an ERP could be the onset of the deflection, rather than its peak (for a similar argument, see Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004). Indeed, studies that employ sample-by-sample testing (i.e., testing each individual sample point in a certain time-range instead of a mean amplitude over that time-range) often show significant ERP differences between two conditions long before the peak of the ERP difference between those conditions. Thus, it is conceivable that the onset of the P3 (instead of its peak) could be a better predictor for the speed and success of the response inhibition process compared to its peak amplitude.

Here, we investigated this issue using an individual differences approach. We pooled data from several SST studies into a large sample of 62 participants. In each participant, we applied independent component analysis (ICA; Jutten & Herault, 1991) to identify an independent component corresponding to the fronto-central P3 ERP. This approach increases the single-trial signal to noise ratio of an ERP (Wessel & Ullsperger, 2011), and furthermore disentangles it from other, potentially superimposed ERPs (Onton, Westerfield, Townsend, & Makeig, 2006). [This increase in signal-to-noise ratio is key in quantifying the onset of an ERP in each individual subject.] We then quantified the onset of the P3 in each participant

using single-trial permutation statistics, and tested whether this P3 onset measurement related to the speed of stopping (measured by SSRT) across the sample. We tested three main hypotheses. 1) Does the latency of the P3 onset in each participant correlate with SSRT across participants? 2) Is the correlation between P3 onset and SSRT higher than the correlation between P3 peak and SSRT? 3) Is the timing of the P3 onset in each participant different depending on whether stopping is successful or not? We were also interested in finding out, with more temporal precision, when the P3 onsets occur relative to SSRT. Neural data and computational simulations suggest that the actual response inhibition process happens within a few milliseconds (~10ms) prior to the end of SSRT (Boucher, Palmeri, Logan, & Schall, 2007), whereas the remaining time before this period is related to other sub-processes of stopping (e.g., the sensory processing of the stop-signal). We thus expected that if the P3 onset relates to successful response inhibition and occurs before SSRT, the time of occurrence should be more precisely in the time-window immediately preceding SSRT.

Methods

Participants

Participants were pooled from three different sources: one previously published study (Wessel & Aron, 2013), one currently submitted study (Wessel & Aron, submitted), and two hereto unpublished studies. All of these studies used slightly different versions of the stop-signal task (see below). Overall, this resulted in a sample of 62 participants (mean age: 21.7y; SEM: .72; 38 female; 2 left-handed). All participants provided written informed consent prior to participation in the studies. All studies were approved by the local ethics committee at UCSD and performed in accordance with the Declaration of Helsinki.

Behavioral task

All tasks were slightly different versions of the standard stop-signal task (Logan, Cowan, & Davis, 1984). In the SST, a go-signal is displayed, which prompts participants to make a quick motor response. On a subset of trials (stop-trials), a stop-signal is displayed with a certain delay (stop-signal delay, SSD) following the onset of the go-signal, which prompts participants to attempt to cancel the go-response. In all versions of the SST used here, SSD was initially set to 200ms, and then dynamically adjusted according to participants' ongoing performance. Specifically, SSD was increased by 50ms in case of a successful stop-trial, and decreased by 50ms in case of a failed stop-trial. This was done in order to achieve a probability of successful stopping [p(stop)] of around .5, which results in a race-like situation between the going and stopping on all stop-trials (Verbruggen & Logan, 2009). Participants were instructed that going quickly and stopping successfully were equally important. All studies followed this general template. Differences between the samples concerned the following parameters: response domain (verbal or manual responses), stop-signal domain (visual or auditory stop-signals), stop-signal probability (25% or 33%), trial numbers, block numbers, and trial timing. The exact details for each group of participants were as follows:

Sample 1 (Verbal responses, visual stop-signals): N = 12—Go-signals consisted of the letter T or the letter K in white print in the middle of the screen. Participants were instructed to respond as quickly as possible by speaking the letter into a Logitech USB microphone, unless a stop-signal occurred. The stop-signal consisted of the respective letter turning from white to red ink. The probability of a stop-signal was 25%. Participants performed 400 trials split across 10 blocks. Trial timing was as follows: 1000ms fixation, 1000ms response deadline, overall trial duration: 2500ms. The onset of verbal responses were detected from the audio recording by a custom online algorithm and checked for accuracy by off-line inspection (This dataset has been published as part of Wessel & Aron, 2013; see therein for details).

Sample 2 (Manual responses, visual stop-signals): N = 10—Go-signals consisted of a rightwards or leftwards pointing white arrow in the middle of the screen. Participants were instructed to respond as quickly as possible by pressing a response button (left or right) with their right hand using a custom keypad, unless a stop-signal occurred. The stop-signal consisted of a red exclamation point appearing above the white arrow. The probability of a stop-signal was 25%. Participants performed 240 trials split across 6 blocks. Trial timing was as follows: 500ms fixation, 1500ms response deadline, overall trial duration: 2500ms (this study is currently submitted as part of Wessel & Aron, in submission).

Sample 3 (Manual responses, auditory stop-signals): N = 14—Go-signals consisted of a rightwards or leftwards pointing white arrow in the middle of the screen. Participants were instructed to respond as quickly as possible by pressing a response button (left or right) with their right hand using a custom keypad, unless a stop-signal occurred. The stop-signal consisted of a 100ms sine-wave tone with a frequency of 900Hz. The probability of a stop-signal was 33%. Participants performed 300 trials split across 6 blocks. Trial timing was as follows: 500ms fixation, 1000ms response deadline, overall trial duration: 2500ms.

Sample 4 (Manual responses, visual stop-signals): N = 26—Go-signals consisted of a rightwards or leftwards pointing white arrow in the middle of the screen. Participants were instructed to respond as quickly as possible by pressing a response button (left or right) with their right hand using a custom keypad, unless a stop-signal occurred. The stop-signal consisted of the arrow turning from white to red ink. The probability of a stop-signal was 33%. Participants performed 300 trials split across 6 blocks. Trial timing was as follows: 500ms fixation, 1000ms response deadline, overall trial duration: 2500ms.

Behavioral analysis

In order to ensure the validity of the race model, all participants' behavioral data were screened for whether mean go-trial reaction time (GoRT) was slower than the mean reaction time on failed stop-trials (FsRT), and whether $p(\text{stop})$ was between .4 and .6 (which tests the efficacy of the SSD staircase algorithm). SSRT was computed according to the mean method (Verbruggen & Logan, 2009).

EEG recording

EEG data was recorded using a BioSemi system (BioSemi Instrumentation, The Netherlands), using 64 scalp electrode sides in samples 1, 3, and 4 (512 Hz sampling rate), and 128 scalp electrode sites in sample 2 (1024 Hz sampling rate). Additional electrodes were placed on the bilateral mastoids (except for sample 2) and canthi, as well as below and above each eye. The data were on-line referenced to the BioSemi CMS-DRL reference. In all samples, the offset from the reference was kept below 25 microvolts.

EEG preprocessing

Data were preprocessed using custom routines in MATLAB 2012a (TheMathWorks, Natick, MA). ICA and dipole fitting (DIPFIT 2.2) were performed using functions from the EEGLAB toolbox (Version 9, Delorme & Makeig, 2004). On import into MATLAB, the data were re-referenced to CP1 (according to the 10–20 system) in the 128-channel montage (sample 2), or a linked mastoid reference in the 64-channel montage (samples 1, 3 and 4; all datasets were later re-referenced to common average before analysis to ensure comparability across samples). The continuous time-series was resampled to 512Hz (in case of the 128-channel montage), and filtered using symmetric two-way least-squares finite-impulse-response (FIR) filters (.5 Hz high-pass, 50 Hz low-pass). Then, the data was epoched with respect to the go-stimulus, beginning at 500ms before stimulus onset and ranging to 1,500ms post stimulus-onset. The time-series were then visually inspected for bad channels and epochs with non-stereotyped artifact activity (e.g., from gross movement or spurious muscle activity). Such data were removed. The remaining data were re-referenced to a common average.

ICA and component selection

Each individual participant's data was subjected to a temporal ICA decomposition using the infomax algorithm (Bell & Sejnowski, 1995; with extension towards sub-gaussian sources, Lee, Girolami, & Sejnowski, 1999). In case of the 128-channel montage, the data were reduced to 64 principal components first (in order to achieve a comparable ICA model order across all samples). The resulting component matrices were screened for ICs representing stereotypic artifacts (blinks, saccades, and electrode artifacts) using outlier statistics (procedure as described in Wessel, Danielmeier, Morton, & Ullsperger, 2012). Such components were removed. On average, 19.6 components remained in the data (sem: 1.6). The remaining components were fitted with individual inverse dipole-solutions using the DIPFIT 2.2 algorithm. Components with non-dipolar equivalent dipole solutions usually represent non-brain signals (as defined by a residual variance of their equivalent dipole solution of greater than 15%, Delorme, Palmer, Onton, Oostenveld, & Makeig, 2012), and were also removed. The automatic classifications based on these criteria were visually screened for inaccurate classifications and manually rectified if necessary (two participants had ICs that had to be manually rejected, and 7 had ICs that were manually retained). The remaining non-artifact components were subjected to further analyses.

From the remaining, non-artifact components, we then selected one IC in each participant that represented the P3 ERP. This was done in order to disentangle the P3 ERP from other ongoing EEG processes that are unrelated to the P3 process, but might be superimposed on

the ERP in channel space. By restricting the focus of investigation on the ERP of interest using this ICA approach, the single-trial signal to noise ratio an ERP significantly increases (Wessel & Ullsperger, 2011). In order to select components that represented the P3, trials were grouped into successful stop-trials, failed stop-trials, and go-trials. Errors (go-trials with wrong response) and misses (go-trials with no response) were removed from all analyses. Additionally, stop-trials with an SSD < 100ms were excluded, to ensure that successful stopping was sufficiently difficult and the result of a 'true' race-process. Furthermore, in order to appropriately match stop- and go-trial numbers, we selected only one go-trial per stop-trial, which was matched by SSD (e.g., for each successful or failed stop-trial with an SSD of 300ms, one go-trial in which a stop-signal would have appeared at 300ms was selected). ERPs for stop-trials were generated from -100 to 500ms relative to stop-signal onset. ERPs for go-trials were generated across the same time period, time-locked to the according time-point in the ERP following the go-signal (i.e., in a trial in which a stop-signal would have occurred at 300ms following the go signal according to the current SSD staircase, the ERP data was extracted around the 300ms time-point following the go-signal). Mean ERP time-courses and topographies can be found in Figure 1. We used a modified version of the COMPASS algorithm (Wessel & Ullsperger, 2011) to select an independent component per participant that represented the P3. Specifically, in order to qualify as the P3 component, an IC had to fulfill three requirements:

1. Topography: The topographical representation of the IC weight matrix had to have a local maximum (or minimum, as IC weight polarities are arbitrary) at fronto-central scalp electrodes (FCz or Cz in the 64-channel montage; A1, C1, D1, and C23 in the BioSemi 128-channel montage).
2. Time course: Out of all ICs that fulfilled the topographical criterion, we selected the one IC whose back-projected time course averaged across the fronto-central electrode sites correlated with the original ERP to the highest degree (the original ERP is the ERP based on the back-projection of all non-artifact ICs). This was measured by a Pearson correlation coefficient.
3. Functional significance: The ERP back-projection of the selected component to the fronto-central channels had to show significant differences between successful *or* failed stop-trials and their respective matched go-trials in a positive direction (i.e., stop-trials had to show more positive voltage compared to the matched go-trials) on at least one sample in the first 500ms following the stop-signal onset. Significance was determined on a sample-by-sample basis, based on monte-carlo truth-label switching permutation testing with a p-value of .05, corrected for multiple comparisons using the false-discovery rate procedure (FDR; Benjamini & Hochberg, 1995).

7 out of the 62 participants had no component that fulfilled criterion 3 (i.e., the selected component did not show a significant stop-trial P3 in at least one sample). In most cases, this was explained by an absence of a visible P3 wave in the original ERP. There was no discernible pattern regarding any particular behavioral abnormalities in these 7 subjects. We suspect that the absence of a fronto-central P3 could be explained by slightly abnormal

anatomy in these subjects. In the following, we focused our investigations on the remaining 55 participants.

EEG Analysis

The onset of the P3 was quantified for successful- and failed stop-trials separately, in order to compare P3 onset latencies depending on the success or failure of stopping (i.e., to test whether the P3 onset latency is shorter when stopping is successful). The P3 onset was defined as the earliest time-point at which a statistically significant deviation between stop- and matched go-trial ERPs could be detected in a given participant. For this, single-trial amplitudes were subjected to sample-wise truth-label switching montecarlo permutation tests (10,000 iterations). The resulting p-values were then corrected to a family-wise error rate of $p < .05$ (one-sided) using the FDR procedure. The first sample point at which the P3 on stop-trials significantly exceeded the go-trial-ERP (i.e., the point at which the difference wave between stop- and matched go trials was significantly greater than 0) was selected as P3 onset. We also quantified the P3 peak latency (most positive deflection in the ERP difference wave between stop- and matched go-trials in the first 500ms following the stop-signal).

Some participants had a significant fronto-central P1 wave that preceded the N2/P3 complex. In order to avoid detection of the onset of that earlier positive wave instead of the P3 (which would bias our results to finding earlier – but inaccurate – P3-onsets), we defined minimum latencies for P3 onset and peak detection. For participants with visual stop-signals, the minimum latency was set to 200ms, for auditory stop-signals, the minimum latency was set to 120ms. Visual inspection revealed that these values prevented the erroneous detection of the P1 in all participants whose data showed that ERP, and furthermore, that none of the participants' veridical P3 onset took place before those minimum latencies (or immediately at the boundary). The selection procedure for the P3 peak and onset latencies is illustrated in Figure 2.

Statistical testing

In order to test our hypotheses, we quantified five variables in each participant: SSRT, P3 onset latency in successful stop-trials, P3 onset latency in failed stop-trials, P3 peak latency in successful stop-trials, and P3 peak latency in failed stop-trials. Prior to hypothesis testing, each of these variables was tested for outliers using Grubbs' test at $p < .05$. Outliers were removed from further analyses. We then tested the hypotheses as follows: Hypothesis 1 (P3 onset latency correlates with SSRT) was tested by means of a Pearson correlation between P3 onset latency on successful stop-trials and SSRT. Hypothesis 2 (P3 onset latency correlates more strongly with SSRT than P3 peak latency) was tested in two stages. First, the Pearson correlation between P3 peak latency on successful stop-trials and SSRT was measured. Then, the magnitude of this correlation was tested against the magnitude of the correlation between P3 onset and SSRT using a method to compare correlation coefficients based on overlapping samples (Zou, 2007). Hypothesis 3 (P3 onset latency is earlier for successful vs. failed stop trials) was tested by comparing the mean P3 onset latency on successful stop-trials to the mean P3 onset latency on failed stop-trials, using a paired samples t-test.

Results

Behavior

Average GoRT was 519ms (SEM: 7.5); average FsRT was 444ms (SEM: 7.0). All participants exhibited a $p(\text{stop})$ between .4 and .6, indicating the efficacy of the SSD staircase algorithm. Furthermore, GoRT was longer than FsRT in all participants, indicating the validity of the race model. Average SSRT was 228.8ms (SEM: 4.5; range: 142 – 312 ms). The distribution of SSRT values contained no outliers. Average SSD was 290ms (SEM: 8.6). Miss rates and error rates were low (miss rate: 1.1%, SEM: .2; error rate: .46%; SEM: .08). Data for the three different versions of the task (1. manual responses, visual stop-signal; 2. manual responses, auditory stop-signal; 3. verbal responses, visual stop-signal) can be found in Table 1 (sample 2 and sample 4 were grouped because both samples consisted of manual responses and visual stop-signals).

P3 onsets

In order to qualify as a P3 component, *either* successful stop-trials or failed stop-trials (or both) had to show a significant P3 (see Methods). Out of the 55 participants for whom such a component was found, all 55 showed a significant P3 for successful stop-trials, and 50 also showed a significant P3 for failed stop-trials. None of the participants showed a significant P3 for failed stop-trials but no significant P3 for successful stop-trials. One participant's successful-stop P3 onset was classified as an outlier and was excluded from further analysis (this participant also had no significant failed-stop P3). This left a final sample of 54 participants that showed a significant successful-stopping P3, out of which 50 participants also showed a significant failed-stopping P3.

Hypothesis 1: P3 onset latency correlates with SSRT—In the sample of 54 participants, the average P3 onset for successful stop-trials was at 225.3ms (SEM: 4.5). SSRT was 227.5 (SEM: 4.8). Across participants, P3 onset latency on successful stop-trials correlated strongly with SSRT ($r = .60$, $p < 10^{-5}$, Pearson correlation, Figure 3A). This means that the earlier the P3 reached significance on successful stop-trials in a given participant, the faster they stopped.

Hypothesis 2: P3 onset correlates with SSRT better than the P3 peak does—The P3 peak for successful stop-trials occurred at 297.6ms (SEM: 8.6) on average. Like the P3 onset, the P3 peak on successful stop-trials correlated significantly with SSRT ($r = .37$, $p < .01$, Pearson correlation, Figure 3B). However, this correlation was significantly lower compared to the correlation between the P3 onset and SSRT ($p < .05$; one-sided), showing that P3 onset latency is indeed a better predictor for the speed of stopping compared to the P3 peak. Further support for this finding comes from a partial correlation analysis between p3 peak latency and SSRT. This reveals that if the variance explained by the p3 onset latency is accounted for, there is no longer a significant correlation between the p3 peak latency and SSRT ($r = .069$; $p = .62$).

Hypothesis 3: P3 onset is earlier for successful compared to failed stop-trials—Out of the 50 participants who had both a significant successful stop-trial and failed-stop

trial P3, the onset of the failed-stop P3 was at 259.9ms (SEM: 6.0) on average. The successful-stop P3 onset latency (225.2ms in this sample of $N = 50$ [SEM: 4.5]) was earlier than the failed-stop P3 onset in 43 out of those 50 cases ($p < 10^{-7}$, binomial test). The mean difference in latency between the two onsets was 34ms in this sample ($t(49) = 6.9$, $p < 10^{-8}$, paired t-test; cohen's d : .90). This shows that the timing differences in P3 onset clearly reflect differences in stopping success: when the action was successfully stopped, the P3 onset occurred significantly earlier compared to when stopping failed.

Discussion

We used single-trial permutation statistics and an individual differences approach in a large sample of stop-signal task data to investigate the temporal relationship between the fronto-central P3 ERP and the timing of successful response inhibition. We found that the onset latency of the P3 on successful stop-trials was highly correlated with the speed of the stopping process (as measured by SSRT), and also that this correlation between P3 onset and SSRT was significantly stronger than the correlation between P3 peak and SSRT. We further found that the onset of the P3 occurred significantly earlier on trials in which participants successfully stopped compared to when they failed, underlining the key importance of the timing of the onset of the P3 in determining the success of stopping. From this, we conclude that the timing of the P3 is directly related to the *success* of response inhibition within participants, as well as to the *timing* of successful response inhibition between participants.

On average, the P3 onset in this study preceded SSRT by only 2–3ms. This is in line with the latency range predicted by modeling work and animal electrophysiology, which showed that response inhibition takes place immediately before the end of SSRT (Boucher, Palmeri, Logan, & Schall, 2007). Notably, the criterion we used here to determine the onset of the P3 is relatively conservative, i.e., it probably overestimates the P3 onset latency in favor of statistical reliability. One could argue that the 'true' onset of the P3 actually occurs when the successful stop-P3 starts to deviate from the go-ERP, i.e., even before this deviation becomes significant. Indeed, if we defined the P3 onset latency as the time-point at which the difference wave between successful stop trials and matched go-trials became positive (and did not return to zero before significance was reached), it becomes even more evident that the P3 onset latency is clearly before SSRT: the average P3 onset latency according to this more progressive quantification was ~18ms before SSRT (which was a statistically significant difference between SSRT and P3 onset latency; data not shown). Thus, a major implication of this study is that the P3 does occur in time to reflect response inhibition.

The approach used here provides several key advantages over prior studies. First, the unprecedented sample size (for an EEG study of the stop-signal task) provided a larger than usual degree of statistical power. This also enabled us to use an individual participants approach instead of the group-level comparisons that most regular ERP studies are based on. Second, by using several different versions of stop-signal task, which included different stop-signal modalities (auditory and visual) as well as motor response effectors (verbal and manual), we observed a sizable variance in SSRT, which further aided our attempt at an individual participants approach. Third, independent component analysis served to disentangle the ERP signature of stopping from other ongoing EEG processes that could

potentially be superimposed on the stopping-ERP, such as motor ERPs (Bekker, Kenemans, Hoeksma, Talsma, & Verbaten, 2005). The increase the single-trial signal to noise ratio brought about by using this technique (Wessel & Ullsperger, 2011) enabled us to use permutation statistics to quantify the exact time-point at which the P3 reached significance *in each individual participant*. This allowed us, for the first time, to directly relate the exact millisecond timing of the onset of an ERP in individual participants to their SSRT.

Apart from the P3, other ERPs are often reported in the context of stop-signal tasks. This is because stopping action is a complex behavioral sequence, which requires several psychological processes: at a minimum, successful stopping requires the perceptual processing of the stop-signal (primary auditory or visual processing), the attentional detection of that signal, and finally, response inhibition. In accordance with this, the fronto-central P3 (which we here argue to be a measurement of the motor inhibition process) is preceded by several other ERPs, some of which are similarly increased for successful vs. failed stopping, but probably do not reflect the response inhibition process. First, the P3 is usually preceded by a fronto-central N2, especially in Go/NoGo-type paradigms (Eimer, 1993). However, we believe that this N2 is unlikely to reflect the success of a motor inhibition process, as contrasts between successful and failed stop trials in the stop-signal task usually show that, if anything, the N2 tends to be increased for *failed* stop-trials (Dimoska, Johnstone, & Barry, 2006; Greenhouse & Wessel, 2013; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004; Ramautar, Kok, & Ridderinkhof, 2006; Senderecka, Grabowska, Szewczyk, Gerc, & Chmylak, 2012). Hence, we believe that the N2 is most likely to reflect attentional processes related to the stop-signal (Schroger, 1993). Second, an increased right fronto-lateral N2 is often reported for successful compared to failed stop-trials (Liotti, Pliszka, Higgins, Perez, & Semrud-Clikeman, 2010; Pliszka, Liotti, & Woldorff, 2000; Schmajuk, Liotti, Busse, & Woldorff, 2006), and is hence a potential candidate to reflect the response inhibition process (like the P3). This is in line with a right-lateralized network for response inhibition in the stop-signal task, for which there is ample evidence from other imaging domains, as well as lesion studies (for a review, see Aron, Robbins, & Poldrack, 2014). In our current study, we did indeed observe a fronto-lateral N2 wave in the ERP based on all non-artifact ICs (see Figure 1). However, as can be seen from the figures, this ERP was not right-lateralized. Importantly, though, it has to be mentioned that the right fronto-lateralized N2 has so far only been observed in children and adolescents, for studies of response inhibition in ADHD; and not yet reported in healthy adults. It is possible that in adults, fronto-lateral stopping-related activity cannot be easily measured using EEG. One reason for this could be increases in cortical folding from childhood to adulthood (Gogtay, et al., 2004; Zilles, Palomero-Gallagher, & Amunts, 2013). As EEG is only susceptible to dipolar activity that is perpendicular to the scalp, increases in cortical folding in frontal brain regions across development could change the electrical dipole-structure in right inferior frontal cortex, making it difficult to measure EEG activity from this area in adults. Lastly, early sensory ERPs can be selectively increased on successful compared to failed stop-trials (Bekker, Kenemans, Hoeksma, Talsma, & Verbaten, 2005; Greenhouse & Wessel, 2013; Lansbergen, Bocker, Bekker, & Kenemans, 2007). In conclusion, we argue that while multiple candidate ERPs exist that potentially map onto psychological processes associated with action-stopping in the stop-signal task our data

support the theory that the P3 specifically reflects the response inhibition sub-process associated with action stopping, since earlier ERPs are either clearly mapped onto other processes (sensory N1), not selectively increased for successful vs. failed stopping (fronto-central N2), or are not usually observed in adults (right fronto-lateral N2). However, the processes reflected in these ERPs likely contribute to the sequence of psychological processes that constitute to successful action stopping.

Apart from the ERP approach, several recent studies have looked for alternative signatures of successful response inhibition in human scalp EEG. These studies mainly reported fronto-central time-frequency signatures in the theta (5–8Hz) and delta (1–4Hz) frequency bands, which show an increase on successful compared to failed stop trials, similar to the P3 (Lavallee, Herrmann, Weerda, & Huster, 2014; Nigbur, Ivanova, & Sturmer, 2011; Schmiedt-Fehr & Basar-Eroglu, 2011; Wessel & Aron, 2013; Yamanaka & Yamamoto, 2010). However, while such time-frequency signatures have their utility, the ERP method has several advantages. First, ERPs can be derived without the advanced knowledge of digital signal processing necessary to appropriately conduct time-frequency analyses. Second, the low computational effort necessary to generate ERPs makes them potentially useful for brain-computer interfaces, in which quickly derived neural signals are needed for online feedback. Third, the high time-resolution of ERPs allows for the testing of hypotheses that pertain to the relative timing of neural and psychological processes with millisecond precision. The current study is just one example that exploits this high temporal precision to test specific hypotheses about the relative timing of brain activity and a psychological process. Unlike ERPs, time-frequency signatures, especially in lower frequency bands such as the delta/theta range, cannot be measured with such temporal resolution, and do not allow inferences such as the ones made in the current study.

Of course, the P3 is not exclusive to the stop-signal task. Notably, fronto-central positive voltage deflections in the ERP around the 300ms time-range are commonly observed following unexpected or rare events (novels/oddballs; Courchesne, Hillyard, & Galambos, 1975; Squires, Squires, & Hillyard, 1975a; Squires, Squires, & Hillyard, 1975b). P3-like potentials have also been associated with decision-making (Squires, Donchin, Squires, & Grossberg, 1977) and information processing (Duncan-Johnson & Donchin, 1982), and are elicited in many different experimental paradigms (for a review, see Polich, 2007). While it has been argued that the P3 reflects “inhibition of ongoing activity” following psychologically significant events of many types (Polich, 2007; also see: Wessel & Aron, 2013), this does not necessarily mean that the occurrence of a P3-ERP signifies the presence of an inhibitory mechanism in *any* given context or task. Still, the data presented here strongly suggest that, within the context of the stop-signal task, the P3 is a clear-cut neural marker of the speed of a (response) inhibition process.

Linking the P3 with successful response inhibition provides a fruitful test-bed for studies of response inhibition that require easily-derived clinical markers (for a review, see: Robbins, 2007; Sprengelmeyer, Lange, & Homberg, 1995; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989; van den Wildenberg, et al., 2006), that aim to assess different pharmacological compounds (Logemann, Bocker, Deschamps, Kemner, & Kenemans, 2013; Overtom, et al., 2003), and that aim to test theories of the inter-relation between inhibitory control, conflict,

attention, and memory (Chatham, et al., 2012; Huster, Enriquez-Geppert, Lavalée, Falkenstein, & Herrmann, 2013). We have provided conclusive evidence that the onset latency of the fronto-central P3 ERP a) correlates highly with the speed of stopping across participants, b) correlates more highly with the speed of stopping than does the P3 peak, and c) is highly sensitive to the success of the stopping itself. Furthermore, our results show that the P3 onset is not too late to reflect successful stopping, and confirm the utility of the P3 as a neural marker of response inhibition.

References

- Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. *Trends Cogn Sci*. 2014; 18:177–185. [PubMed: 24440116]
- Bekker EM, Kenemans JL, Hoeksma MR, Talsma D, Verbaten MN. The pure electrophysiology of stopping. *Int J Psychophysiol*. 2005; 55:191–198. [PubMed: 15649550]
- Bekker EM, Overtom CC, Kenemans JL, Kooij JJ, De Noord I, Buitelaar JK, Verbaten MN. Stopping and changing in adults with ADHD. *Psychol Med*. 2005; 35:807–816. [PubMed: 15997601]
- Bell AJ, Sejnowski TJ. An information-maximization approach to blind separation and blind deconvolution. *Neural Comput*. 1995; 7:1129–1159. [PubMed: 7584893]
- Benjamini Y, Hochberg Y. Controlling the False Discovery Rate – a Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B-Methodological*. 1995; 57:289–300.
- Boucher L, Palmeri TJ, Logan GD, Schall JD. Inhibitory control in mind and brain: an interactive race model of countermanding saccades. *Psychol Rev*. 2007; 114:376–397. [PubMed: 17500631]
- Chatham CH, Claus ED, Kim A, Curran T, Banich MT, Munakata Y. Cognitive control reflects context monitoring, not motoric stopping, in response inhibition. *PLoS ONE*. 2012; 7:e31546. [PubMed: 22384038]
- Courchesne E, Hillyard SA, Galambos R. Stimulus novelty, task relevance and the visual evoked potential in man. *Electroencephalogr Clin Neurophysiol*. 1975; 39:131–143. [PubMed: 50210]
- Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*. 2004; 134:9–21. [PubMed: 15102499]
- Delorme A, Palmer J, Onton J, Oostenveld R, Makeig S. Independent EEG sources are dipolar. *PLoS ONE*. 2012; 7:e30135. [PubMed: 22355308]
- Dimoska A, Johnstone SJ, Barry RJ. The auditory-evoked N2 and P3 components in the stop-signal task: indices of inhibition, response-conflict or error-detection? *Brain Cogn*. 2006; 62:98–112. [PubMed: 16814442]
- Dimoska A, Johnstone SJ, Barry RJ, Clarke AR. Inhibitory motor control in children with attention-deficit/hyperactivity disorder: event-related potentials in the stop-signal paradigm. *Biol Psychiatry*. 2003; 54:1345–1354. [PubMed: 14675798]
- Duncan-Johnson CC, Donchin E. The P300 component of the event-related brain potential as an index of information processing. *Biol Psychol*. 1982; 14:1–52. [PubMed: 6809064]
- Eimer M. Effects of attention and stimulus probability on ERPs in a Go/Nogo task. *Biol Psychol*. 1993; 35:123–138. [PubMed: 8507742]
- Etchell AC, Sowman PF, Johnson BW. “Shut up!” An electrophysiological study investigating the neural correlates of vocal inhibition. *Neuropsychologia*. 2012; 50:129–138. [PubMed: 22108442]
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF 3rd, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A*. 2004; 101:8174–8179. [PubMed: 15148381]
- Greenhouse I, Wessel JR. EEG signatures associated with stopping are sensitive to preparation. *Psychophysiology*. 2013

- Huster RJ, Enriquez-Geppert S, Lavalée CF, Falkenstein M, Herrmann CS. Electroencephalography of response inhibition tasks: functional networks and cognitive contributions. *Int J Psychophysiol.* 2013; 87:217–233. [PubMed: 22906815]
- Johnstone SJ, Barry RJ, Clarke AR. Behavioural and ERP indices of response inhibition during a Stop-signal task in children with two subtypes of Attention-Deficit Hyperactivity Disorder. *Int J Psychophysiol.* 2007; 66:37–47. [PubMed: 17604142]
- Jutten C, Herault J. Blind Separation of Sources .1. An Adaptive Algorithm Based on Neuromimetic Architecture. *Signal Processing.* 1991; 24:1–10.
- Kok A, Ramautar JR, De Ruiter MB, Band GP, Ridderinkhof KR. ERP components associated with successful and unsuccessful stopping in a stop-signal task. *Psychophysiology.* 2004; 41:9–20. [PubMed: 14692996]
- Lansbergen MM, Bocker KB, Bekker EM, Kenemans JL. Neural correlates of stopping and self-reported impulsivity. *Clin Neurophysiol.* 2007; 118:2089–2103. [PubMed: 17652017]
- Lavalée CF, Herrmann CS, Weerda R, Huster RJ. Stimulus-Response Mappings Shape Inhibition Processes: A Combined EEG-fMRI Study of Contextual Stopping. *PLoS ONE.* 2014; 9:e96159. [PubMed: 24763435]
- Lee TW, Girolami M, Sejnowski TJ. Independent component analysis using an extended infomax algorithm for mixed subgaussian and supergaussian sources. *Neural Comput.* 1999; 11:417–441. [PubMed: 9950738]
- Liotti M, Pliszka SR, Higgins K, Perez R 3rd, Semrud-Clikeman M. Evidence for specificity of ERP abnormalities during response inhibition in ADHD children: a comparison with reading disorder children without ADHD. *Brain Cogn.* 2010; 72:228–237. [PubMed: 19850394]
- Logan GD, Cowan WB, Davis KA. On the Ability to Inhibit Simple and Choice Reaction-Time Responses – a Model and a Method. *Journal of Experimental Psychology-Human Perception and Performance.* 1984; 10:276–291. [PubMed: 6232345]
- Logemann HN, Bocker KB, Deschamps PK, Kemner C, Kenemans JL. The effect of noradrenergic attenuation by clonidine on inhibition in the stop signal task. *Pharmacol Biochem Behav.* 2013; 110:104–111. [PubMed: 23792541]
- Naito E, Matsumura M. Movement-related potentials associated with motor inhibition under different preparatory states during performance of two visual stop signal paradigms in humans. *Neuropsychologia.* 1996; 34:565–573. [PubMed: 8736569]
- Nigbur R, Ivanova G, Sturmer B. Theta power as a marker for cognitive interference. *Clin Neurophysiol.* 2011; 122:2185–2194. [PubMed: 21550845]
- Onton J, Westerfield M, Townsend J, Makeig S. Imaging human EEG dynamics using independent component analysis. *Neurosci Biobehav Rev.* 2006; 30:808–822. [PubMed: 16904745]
- Overtom CC, Kenemans JL, Verbaten MN, Kemner C, van der Molen MW, van Engeland H, Buitelaar JK, Koelega HS. Inhibition in children with attention-deficit/hyperactivity disorder: a psychophysiological study of the stop task. *Biol Psychiatry.* 2002; 51:668–676. [PubMed: 11955467]
- Overtom CC, Verbaten MN, Kemner C, Kenemans JL, van Engeland H, Buitelaar JK, van der Molen MW, van der Gugen J, Westenberg H, Maes RA, Koelega HS. Effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with Attention Deficit Hyperactivity Disorder. *Behav Brain Res.* 2003; 145:7–15. [PubMed: 14529800]
- Pliszka SR, Liotti M, Woldorff MG. Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biol Psychiatry.* 2000; 48:238–246. [PubMed: 10924667]
- Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol.* 2007; 118:2128–2148. [PubMed: 17573239]
- Ramautar JR, Kok A, Ridderinkhof KR. Effects of stop-signal probability in the stop-signal paradigm: the N2/P3 complex further validated. *Brain Cogn.* 2004; 56:234–252. [PubMed: 15518938]
- Ramautar JR, Kok A, Ridderinkhof KR. Effects of stop-signal modality on the N2/P3 complex elicited in the stop-signal paradigm. *Biol Psychol.* 2006; 72:96–109. [PubMed: 16157441]

- Robbins TW. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philosophical Transactions of the Royal Society B-Biological Sciences*. 2007; 362:917–932.
- Schmajuk M, Liotti M, Busse L, Woldorff MG. Electrophysiological activity underlying inhibitory control processes in normal adults. *Neuropsychologia*. 2006; 44:384–395. [PubMed: 16095637]
- Schmidt R, Leventhal DK, Mallet N, Chen F, Berke JD. Canceling actions involves a race between basal ganglia pathways. *Nat Neurosci*. 2013; 16:1118–1124. [PubMed: 23852117]
- Schmiedt-Fehr C, Basar-Eroglu C. Event-related delta and theta brain oscillations reflect age-related changes in both a general and a specific neuronal inhibitory mechanism. *Clin Neurophysiol*. 2011; 122:1156–1167. [PubMed: 21115266]
- Schroger E. Event-related potentials to auditory stimuli following transient shifts of spatial attention in a Go/Nogo task. *Biol Psychol*. 1993; 36:183–207. [PubMed: 8260565]
- Senderecka M, Grabowska A, Szewczyk J, Gerc K, Chmylak R. Response inhibition of children with ADHD in the stop-signal task: an event-related potential study. *Int J Psychophysiol*. 2012; 85:93–105. [PubMed: 21641941]
- Sprengelmeyer R, Lange H, Homberg V. The pattern of attentional deficits in Huntington's disease. *Brain*. 1995; 118(Pt 1):145–152. [PubMed: 7895000]
- Squires KC, Squires NK, Hillyard SA. Decision-Related Cortical Potentials during an Auditory Signal-Detection Task with Cued Observation Intervals. *Journal of Experimental Psychology-Human Perception and Performance*. 1975a; 1:268–279. [PubMed: 1202150]
- Squires NK, Donchin E, Squires KC, Grossberg S. Bisensory stimulation: inferring decision-related processes from P300 component. *J Exp Psychol Hum Percept Perform*. 1977; 3:299–315. [PubMed: 864401]
- Squires NK, Squires KC, Hillyard SA. 2 Varieties of Long-Latency Positive Waves Evoked by Unpredictable Auditory-Stimuli in Man. *Electroencephalogr Clin Neurophysiol*. 1975b; 38:387–401. [PubMed: 46819]
- Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD. Effects of methylphenidate on inhibitory control in hyperactive children. *J Abnorm Child Psychol*. 1989; 17:473–491. [PubMed: 2681316]
- van den Wildenberg WP, van Boxtel GJ, van der Molen MW, Bosch DA, Speelman JD, Brunia CH. Stimulation of the subthalamic region facilitates the selection and inhibition of motor responses in Parkinson's disease. *J Cogn Neurosci*. 2006; 18:626–636. [PubMed: 16768365]
- Verbruggen F, Logan GD. Models of response inhibition in the stop-signal and stop-change paradigms. *Neurosci Biobehav Rev*. 2009; 33:647–661. [PubMed: 18822313]
- Wessel JR, Aron AR. Unexpected Events Induce Motor Slowing via a Brain Mechanism for Action-Stopping with Global Suppressive Effects. *J Neurosci*. 2013; 33:18481–18491. [PubMed: 24259571]
- Wessel JR, Danielmeier C, Morton JB, Ullsperger M. Surprise and error: common neuronal architecture for the processing of errors and novelty. *J Neurosci*. 2012; 32:7528–7537. [PubMed: 22649231]
- Wessel JR, Ullsperger M. Selection of independent components representing event-related brain potentials: a data-driven approach for greater objectivity. *Neuroimage*. 2011; 54:2105–2115. [PubMed: 20965258]
- Yamanaka K, Yamamoto Y. Single-trial EEG power and phase dynamics associated with voluntary response inhibition. *J Cogn Neurosci*. 2010; 22:714–727. [PubMed: 19413474]
- Zilles K, Palomero-Gallagher N, Amunts K. Development of cortical folding during evolution and ontogeny. *Trends Neurosci*. 2013; 36:275–284. [PubMed: 23415112]
- Zou GY. Toward using confidence intervals to compare correlations. *Psychological Methods*. 2007; 12:399–413. [PubMed: 18179351]

A) EVENT-RELATED POTENTIAL TIME-COURSES

B) EVENT-RELATED POTENTIAL TOPOGRAPHIES

Figure 1.

Event-related potentials (grand-average across all subjects), based on all non-artifact independent components, time-locked to the stop-signal. A) Averaged time courses for 9 anatomical ROIs: right frontolateral (electrode sites: AF8, F6, F8), fronto-polar (Fpz, Fp1, Fp2, AF3, AF4), left fronto-lateral (AF7, F5, F7), left central (FC6, FT8, C6, T8), fronto-central (FCz, Cz, FC1, C1, FC2, C2), right central (FC5, FT7, C5, T7), left posterior lateral (CP7, CP5, P9, P7, P5), medial occipital (Oz, POz, O1, O2, PO3, PO4), right posterior lateral (CP8, CP6, P10, P8, P6). B) Mean voltage topographies over 8 time points of interest: 0–50ms, 51–100ms, 101–150ms, 151–200ms, 201–250ms, 251–300ms, 301–350ms, 351–400ms). Voltage topographies are for the 64 channel montages only (N = 52).

P3 ONSET DETECTION (ILLUSTRATION)

Figure 2.

Illustration of the P3 onset detection procedure, exemplified on a single participant's successful stop data. The onset of the P3 is defined as the sample at which the positive ERP difference between stop and matched go-trials reaches significance at $p < .05$ (FDR-corrected).

CORRELATION BETWEEN SSRT AND P3 LATENCY

Figure 3.

Correlation between SSRT and P3 latency. A) P3 onset latency. B) P3 peak latency.

Individual markers represent individual participants. Black circles denote data with manual responses and visual stop-signals; Dark grey squares denote data with manual responses and auditory stop-signals, Light grey diamonds denote data with verbal responses and visual stop-signals. The solid line is the linear regression line (least-squares fit). The dashed line is the identity line.

Figure 4.

P3 onset latencies compared between successful and failed stop-trials. Markers as in Figure 3. The dashed line is the identity line. Any datapoint below the identity line denotes a participant whose P3 onset latency is shorter for successful stop-trials.

Table 1

Behavioral data split by stop-signal task type.

	GoRT	FsRT	SSRT	SSD
	<i>mean</i>	499.35	418.85	234.66
				264.70
	<i>sem</i>	9.02	7.29	4.48
				9.65
Manual responses / visual stop-signals	<i>min</i>	405.99	353.92	161.31
				155.73
	<i>max</i>	637.80	571.98	290.84
				405.50
	<i>mean</i>	536.42	465.52	191.71
				344.72
	<i>sem</i>	15.52	13.53	8.88
				19.32
Manual responses / auditory stop-signals	<i>min</i>	435.41	400.04	142.08
				243.05
	<i>max</i>	646.64	579.33	277.18
				482.00
	<i>mean</i>	556.96	493.31	254.28
				302.68
	<i>sem</i>	15.20	14.81	7.33
				14.13
Verbal responses / visual stop-signals	<i>min</i>	472.27	413.09	213.91
				192.73
	<i>max</i>	635.93	554.86	312.30
				351.82