Supporting the Link Between the Locus Coeruleus – Norepinephrine System, the P300, and the Attentional Blink

by

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Abstract

This paper provides evidence to support the hypothesis that the locus coeruleus – norephinephrine (LC-NE) system is the neurophysiological basis of both the attentional blink (AB) and the event related potential (ERP) component known as the P300. The LC-NE system is thought to provide a brief burst of processing facilitation in response to motivationally salient events. The AB refers to decreased accuracy for reporting the second of two targets (T1 and T2) inserted into a rapid serial visual presentation (RSVP). The LC-NE account of the AB holds that the AB is the result of a refractory-like period in LC-NE activity. The LC-NE account of the P300 suggests the P300 is the electrophysiological manifestation of the activity of the LC-NE system. I support the three-way link between these different aspects of brain activity by predicting differences in the AB dependent on characteristics of the P300 in response to T1 (T1-P300).

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This work is aimed at supporting a theorized link between the activity of a neuromodulatory system called the locus coeuruleus-norepinephrine (LC-NE) system, a cognitive phenomenon called the attentional blink (AB), and an electrophysiological correlate of brain activity called the P300. This three-way relationship was most thoroughly asserted and supported in two articles authored by Sander Nieuwenhuis and colleagues (Nieuwenhuis, Aston-Jones, & Cohen, 2005a; Nieuwenhuis, Gilzenrat, Holmes, & Cohen, 2005b), though the individual links between each phenomenon with the other had been suggested separately in other work (e.g. LC-NE system and the AB: Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999; AB and the P300: McArthur, Budd, & Michie, 1999; LC-NE system and the P300: Pineda, Foote, & Neville, 1989). For an in depth discussion of the evidence in support of these links, please see the above-cited work. Here, I give a brief summary of this evidence accompanied by a description of each area under discussion, and then move on to present additional argument and experiment.

The locus coeruleus (LC) is a neuromodulatory nucleus in the pontine region of the brain stem, consisting (in humans) of approximately 10 000 to 15 000 norepinephrine (NE) containing neurons. The LC conducts its neuromodulatory activity through the release of NE over a widespread efferent projection system. It projects to virtually the entire central nervous system except the basal ganglia. LC projections provide the primary source of NE to the forebrain, and are the exclusive source of noradrenergic innervation to the hippocampus and neocortex. The LC receives its major afferent connections from the prefrontal cortex and the anterior cingulate cortex, which supports the view that LC activity can be mediated by high-level cognitive and

affective processes (Arnsten & Goldman-Rakic, 1984; Aston-Jones, Foote, & Bloom, 1984; Berridge & Waterhouse, 2003).

The LC is associated with two characteristic components of activity: tonic activity and phasic activity. Tonic activity consists of firing rates between 0 and 5 Hz, and is associated with the level of arousal and the sleep-wake cycle of an organism. Within the tonic component of LC activity, the relationship between LC firing rate and the behaviour of an organism parallels the Yerkes-Dodson curve relating arousal to performance (Yerkes & Dodson, 1908). Greater LC firing frequencies are associated with greater arousal, alertness, wakefulness, and vigilance up to about 3 Hz, when further increases in firing rate are associated with distractibility and erratic behaviour (Aston-Jones, Rajkowski, Kubiac, & Alexinsky, 1994).

LC phasic activity is characterized by bursts of rapid firing (up to 20 Hz) in response to task-relevant or especially salient environmental stimuli. These bursts tend to involve 2 to 3 action potentials approximately 100 ms to 150 ms following the eliciting event (in monkeys), The bursts are followed by a sudden period of suppressed firing (200-400 ms post-event) with gradual recovery by 800 ms post-event (Berridge & Waterhouse, 2003). The period of suppressed firing is due to the self-inhibitory nature of the LC-NE system. LC neurons are inhibited by the NE they release, reducing the chance that they will fire again for a brief refractory-like period (Aghajanian et al. 1977).

Although NE inhibits neurons in the LC it is generally accepted that the different types of noradrenergic receptors represented in neurons outside of the LC results in an increase in the responsivity of NE innervated neurons in the forebrain. This increase in responsivity occurs to both excitatory and inhibitory synaptic transmission (Berridge & Waterhouse, 2003). Although such an indiscriminate increase in responsivity is not thought to improve signal detection for a single neuron, Servan-Schreiber, Printz, and Cohen, (1990) have demonstrated that increasing

the responsivity of each neuron in a neural network results in more effective signal detection for the network. This has led to the characterization of the LC-NE system as a temporal attention filter, that selects for the occurrence of motivationally salient or unexpected events, responding with a NE release, which briefly facilitates processing of and responding to these events by speeding/improving signal detection throughout the cortex (Cohen, Aston-Jones, & Gilzenrat, 2004; Nieuwenhuis, Nieuwpoort, Veltman, & Drent, 2007; Aston-Jones & Cohen, 2005; Dayan & Yu, 2006).

Various characteristics of LC-NE system activity show striking similarities with characteristics of the P300 event related potential (ERP) component and the cognitive phenomenon known as the attentional blink (AB).

The P300 is a positive voltage occurring between 250 ms and 800 ms after presentation of a stimulus, typically peaking around 300 ms. It has a broad scalp distribution and is thought to represent the summation of activity from widely distributed areas (e.g. Kok, 2001; Johnson, 1993). The P300 is a prominent component that can often be observed within a single trial, whereas most ERP components require the averaging together of many trials before they emerge. The P300 has been strongly associated with the successful updating of working memory, or context updating (Donchin and Coles, 1988). The LC-NE theory of the P300 posits that the P300 is manifested due to the widespread changes in neural responsivity caused by a LC phasic burst, the resulting flood of NE into the forebrain (Nieuwenhuis et al., 2005a, 2005b). Under the LC-NE theory of the P300, the relationship of the P300 to context updating is that the LC-NE phasic burst (indexed by the P300) facilitates the updating of context by briefly strengthening and stabilizing relevant neural representations.

The AB occurs when two targets (T1 and T2) are inserted in a rapid serial visual presentation (RSVP) of distracters. When subjects must perceive and remember both targets for

report at the end of the trial, T2 is reported with significantly lower accuracy if it is presented between approximately 200 ms to 700 ms after onset of T1, than if it is presented within 100 ms of onset of T1, or later than 700 ms after onset of T1 (Shapiro, Raymond, & Arnell, 1994). Figure 1 (AB RSVP Task) illustrates the typical attentional blink task as it is utilized in this work, and figure 1 (AB Performance) illustrates the typical pattern of accuracy for T2 across time, (locked to onset of T1). Of particular interest is that the decrease in report accuracy for T2 does not occur if T2 is presented within 100 ms of T1. This characteristic of the phenomenon is known as lag-1 sparing (Chun & Potter, 1995). The LC-NE theory of the AB posits that successfully coding the rapidly presented targets in the typical attentional blink task requires NE facilitated processing in order to strengthen and stabilize the representation of the target amidst the ongoing interference of the distracters. The LC is able to release NE effectively for the first target, but its self-inhibitory property briefly arrests further NE release, lowering NE levels throughout the forebrain, and reducing the chance of and/or size of an additional LC phasic burst in response to T2. This period of inhibition lasts from approximately 200 ms to 800 ms after onset of T1, reducing accuracy for T2 if it is presented during this time. Lag-1 sparing occurs because within 100 ms of T1 there is still enough NE available from the T1 release to facilitate processing such that T2 is processed successfully without the need of additional NE.

The theorized link between the LC-NE system, the AB and the P300 is supported by observations that these three aspects of brain activity share a very similar temporal profile, generally similar antecedent conditions, and share a broad impact within the brain.

Although most research on the LC phasic activity involves single cell recordings from monkeys, it is reasonable to assume that the human LC-NE system behaves similarly across a similar timeframe. Keeping this point in mind, the temporal relationship between the LC-NE system, the P300, and the AB is almost perfect. Onset of both the AB deficit and the P300 begin

at approximately 200 ms, just when the LC begins its refractory period. Furthermore, all three phenomena tend to show their greatest effect early, and then undergo a gradual recovery from about 400 ms to 800 ms after onset of the eliciting stimulus. To my knowledge, no correlational work has been done relating the timing of the LC-NE system with either the AB or the P300. However, MacArthur, Budd, and Michie (1999) demonstrated a very strong, significant correlation between the AB and the P300 at each lag ($r = -.95, p < .01$), such that across lags, higher P300 amplitude corresponds to lower T2 accuracy.

The antecedent conditions for a LC phasic burst, an AB, and for a P300 are also very similar. One of the most well described characteristics of the P300 is that its amplitude is modulated by the frequency of the eliciting stimulus such that less frequent stimuli elicit a larger P300 (e.g. Donchin & Coles, 1988). The LC response to a stimulus is also larger when that stimulus is less frequent (Alexsinsky , Aston-Jones, Rajkowski, & Revay, 1990), and the depth of the AB is increased when the first target is an infrequent stimulus(Martens, Johnson, Elmallah, & London, 2003). The amplitude of LC response, the P300, and the depth of the AB are also all scaled to the motivational salience of a stimulus. The LC does not respond to task irrelevant stimuli such as a fixation cross at the start of a trial. However, it responds to task relevant stimuli when these stimuli must be categorized according to task demands, and it responds most strongly to target stimuli that require a response. (e.g. Aston-Jones, Rajkowski, & Kubiak, 1997). P300 amplitude shows this same pattern. A P300 is not observed for ignored or irrelevant (and uninteresting) stimuli, a small P300 is observed for task-relevant stimuli that do not require a response, and a larger P300 is observed for target stimuli that require a response (Duncan-Johnson, & Donchin, 1977). The AB, meanwhile, is typically only exhibited in response to target stimuli that require a response, but it can be elicited by distracter stimuli if they are more difficult to discern from targets (Barnard, Scott, Taylor, May, & Knightley, 2004).

Finally, the broad innervation of the LC-NE system and the proposed system-wide transient increase (and then decrease) in neuronal responsivity is consistent with the broad topology and suggested widely dispersed neural generators of the P300. Furthermore, all of the P300, the LC phasic response, and the AB are elicited by stimuli in multiple modalities (e.g. Berridge & Waterhouse, 2003; Hillyard, Squires, Bauer, & Lindsay, 1971; Arnell & Jolicœur, 1999).

In addition to the above evidence showing consistencies between the LC-NE system phasic activity, the P300 and the AB, there is additional, less general evidence supporting individual links between each subject with one of the others. First, and most briefly, there is evidence from lesion and pharmacological studies for a link between the LC-NE system and the P300. In squirrel monkeys, lesions of the LC significantly reduce the size of the P300 (Pineda, Foote, & Neville, 1989), and pharmacological manipulations which reduce LC firing also reduce the size of the P300 (Swick, Pineda, and Foote 1994).

Many ERP studies have highlighted the relationship between the P300 and the AB. Vogel, Luck, and Shapiro (1998) demonstrated that averaged across trials, the amplitude of the P300 is significantly reduced during the AB. This is in contrast to the lack of an impact of the AB on ERP components related to sensory processing (the N1 and the P1), nor on a later component thought to be related to semantic processing (the N400). Rolke, Heil, Streb, and Hennighausen (2001) specified that the P300 is present during the AB, but only for T2s that are correctly reported. Kranczioch, Debener, and Engel (2003) further specified that the P300 is present during the AB for correctly reported T2s at each lag except lag 1. This lack of a P300 for correct T2 s at lag 1 is a notable exception supportive of the view of the LC-NE theory of the AB, that no additional NE release is elicited or required to identify T2 at lag 1, because NE from the T1 release is still present in the system. A final relationship between the P300 and the AB is that the

size of the P300 to T1 is inversely related to accuracy for T2 (Shapiro et al. 2006) supporting the view that the AB is due to the refractory-like period of the LC, such that larger NE releases to T1, (manifesting a larger P300) will result in greater inhibition of the LC during the AB timeframe.

While both the LC-NE theory of the AB and of the P300 are supported by a wide range of research showing commonalities between these areas, the LC-NE theory of the AB has also generated new understanding of the AB phenomenon. In particular, the LC-NE theory of the AB has helped to explain several enigmatic findings in the AB literature (e.g. Nieuwenhuis et al., 2005a; Nieuwenstein, 2006; Warren et al., submitted). For example, Nieuwenhuis et al.'s (2005a) explanation of lag-1 sparing, though supported by the electrophysiological study of the AB described above (Kranczioch, et al., 2003), was contentious at the time of publishing. A competing theory of the AB had asserted that the distracter following T1 initiated the AB, rather than T1 itself (e.g. Di Lollo, Kawahara, Ghorashi, & Enns, 2005). The temporary loss of control (TLC) theory of the AB (Di Lollo et al., 2005) held that lag-1 sparing occurred because there was no distracter between T1 and T2 to initiate the blink. Nieuwenhuis et al. not only gave a reasonable account of lag-1 sparing as being dependent on the time between T1 and T2, they also demonstrated that when T2 was presented 100 ms after onset of T1 (typically lag 1), but with an additional distracter placed between T1 and T2, T2 continued to exhibit sparing, against predictions of the TLC theory. However, it should be noted here that lag-1 sparing does not occur when there is a switch in task set or location (Visser et al., 1999; but see Potter Staub, & O'Connor, 2002), a finding that the LC-NE theory of the AB does not account for. However, I hold that this finding does not represent an aspect of the AB phenomenon itself, but rather the introduction of additional tasks whose difficulty is also affected by SOA and whose effects obscure the AB. In such cases, the addition of a task or location switch for T2 to the AB

paradigm lowers the accuracy for identifying T2 at lag 1, not because the activity of the LC-NE system is impacted, but rather because switching tasks or locations requires time, and is thus most detrimental to report of T2 when T2 follows T1 most closely.

The LC-NE theory of the AB was also able to account for an additional inscrutable finding in the AB literature. When three targets (T1, T2, and T3) are inserted into an RSVP with no intervening distracters, T3 is reported with normal accuracy even when it is presented 200 ms after T1. This led to the interpretation that an AB had not occurred in such circumstances, and led to further support for the TLC theory, which claimed the lack of any distracters intervening between the three targets allowed T3 to be processed successfully even though it was presented 200 ms after T1. However, the TLC theory could still not explain Nieuwenhuis et al.s' (2005a) results. In contrast, the LC-NE theory could explain both Nieuwenhuis et al.s' (2005a) results, and the findings from three-target studies. Nieuwenstein (2006) proposed that when three targets are included in the AB paradigm, T2 can potentiate the LC response, allowing the LC to produce a phasic burst in response to T3 despite undergoing inhibition from a previous NE burst. Nieuwenstein supported his account with several temporal combinations of targets and distracters, showing across combinations that whenever T3 was immediately preceded by T2 it showed a benefit, despite distracters placed between T1 and T2.

Finally, one additional, troublesome finding in the AB literature was the inconsistent relationship between T1 difficulty, and the depth of the AB. Although many studies reported that increasing the difficulty of identifying T1 would result in reduced accuracy for identifying T2 (e.g Seiffert & Di Lollo, 1997; Visser & Ohan, 2007), other studies had reported no change (e.g. Shore, McLaughlin, & Klein, 2001). Warren et al. (submitted) appealed to the LC-NE theory to shed light on this issue. It is known that the LC system phasic response is delayed when the target stimulus is made more difficult to distinguish from distracters (Rajkowski et al.,

(2004). Furthermore, the onset of the P300 is delayed when categorization of a stimulus is made more difficult (Kok, 2001; Coles, Smid, Scheffers, & Otten, 1995; Kutas, McCarthy, & Donchin, 1977). Warren et al. thus predicted that such a manipulation should impact the AB, in the same way. We predicted that the delay would be manifested by a novel set of behavioural findings: An interaction between T1 difficulty, T2 accuracy, and lag such that a more difficult T1 would delay the AB, leading to better accuracy for T2 at early lags (within 200 ms of onset of T1), but worse accuracy at later lags (after 200 ms). This result is predicted by imagining the typical pattern of the AB (as seen in figure 1 (AB Performance)) shifted onward in time. This shift would result in the benefit associated with lag-1 sparing being extended, potentially improving accuracy for T2 at lag 2. In addition, this improvement in T2 accuracy at early lags should be accompanied by a decrease in accuracy for T2 at later lags due to the delayed recovery of T2 accuracy from 400 ms to 600 ms after T1 onset. Warren et al. increased the difficulty of identifying T1 by reducing its contrast, and demonstrated exactly this result (see figure 2). This predicted interaction helped explain the inconsistencies in previous research on the effect of T1 difficulty on the AB: Because of the cross-over interaction, observing the main effect of T1 difficulty on the AB would depend on what lags were probed.

The current study is a continuation of the work reported in Warren et al. (submitted). Warren et al. were the first to hypothesize how a delay in the AB would manifest itself behaviourally, and the first to then demonstrate the predicted results. Here I attempt to reproduce the finding of a delayed AB (improved accuracy for T2 at lags one and two, accompanied by worse accuracy for T2 at lags four and five), while strengthening the link between the LC-NE system, P300 and the AB by using the P300 as an index of the onset of an LC phasic burst, and as a predictor of a delayed AB. Subjects perform the typical AB task, while having their brain EEG activity recorded. T2 is presented at lags 1, 2, 4, and 5, with 1 and 2

representing early lags that should be improved when the AB is delayed, and 4 and 5 representing the later lags where T2 accuracy should be decreased when the AB is delayed. To produce a group of trials in which the AB should be delayed for comparison with a group of trials where the AB should not be delayed, I use single trial analysis of the P300. If the P300 is the electrophysiological manifestation of the LC refractory period, then trials where the onset of the P300 in response to T1 (T1-P300) is relatively slow should represent a slow LC response, and be associated with a delayed AB compared to trials associated with a quick T1-P300. Within subjects, for each trial, I determine the time of the onset of the T1-P300. The median T1-P300 onset is determined for each subject at each lag, and trials are categorized according to whether they are above (slow-onset) or below (quick-onset) the median. Accuracy for T2 at each lag is determined for each category of trials, and those accuracies are compared across subjects to assess whether slow-onset T1-P300 trials demonstrated a delayed AB in comparison to quick-onset T1-P300 trials. If the LC-NE theory of the P300 and of the AB is correct, the slow-onset T1-P300 should indicate a slow-onset LC response to T1, and produce behavioural results consistent with a delayed AB when compared to the quick-onset T1-P300 trials. That is, at early lags (lag 1 and lag 2), slow-onset T1-P300 trials should be associated with greater accuracy than quick-onset T1-P300 trials, but at late lags (lag 4 and lag 5) this relationship should be reversed.

There is a caveat to note regarding the above-described analysis. The effects predicted here hinge on natural variability in the onset of the T1-P300 within a single condition, without any experimental manipulation to actively create differences. There is no reason to assume that the onset of the T1-P300 will naturally show enough variability such that categorizing trials according to T1-P300 onset will create enough of a difference in the onset of the LC response to produce the kind of effects observed in Warren et al. (submitted), which were obtained by comparing difficult versus easy T1 trials. This experiment was thus risky, and at best I predict

effects much weaker than observed in Warren et al. Furthermore, the stable presentation rate of targets and distracters in an RSVP paradigm (approx. 10 items/s) creates steady oscillation at the rate of presentation in the EEG due to low-level sensory and perceptual processing of both the targets and the distracters. This can obscure signals related specifically to targets. Other researchers have addressed this concern by assessing ERP components through subtraction of the grand average waveform of the trials in the experimental condition from the grand average waveform of the control trials, effectively averaging out the regular oscillation and the effects of distracters, leaving only differences due to target manipulation (eg. Vogel and Luck, 1998). This method cannot be applied to single-trial analysis, and thus my data contained more noise than is generally suitable for an EEG study.

A further prediction of this work is based on the amplitude, rather than the onset of the T1-P300. The LC-NE theory of the AB and the P300 claims that the amplitude of the P300 indicates how much NE is available at any given time (with greater amplitude meaning less NE due to greater LC inhibition). Therefore, a T1-P300 with a large mean amplitude should predict reduced T2 accuracy. This prediction is consistent with findings from Shapiro et al., (2006). Shapiro et al. were able to show a significant, correlation between the amplitude of the T1-P300 and the depth of the AB between subjects, such that subjects who demonstrated larger T1-P300s also demonstrated a greater AB deficit. However Shapiro et al. were not able to reliably show this same relationship within subjects on a trial-to-trial basis. This may be due to the small number of subjects tested (n=10). In this study, 16 subjects participate, and I attempt to extend the findings of Shapiro et al. by demonstrating that within subjects, trials where the subject was able to correctly report T2 (hit-T2s) would be associated with smaller amplitude T1-P300s (less LC inhibition) than trials where the subject was unable to report T2 (miss-T2s). A further, related prediction is that when I categorize trials according to T1-P300 amplitude, (just as I

described the categorization according to T1-P300 onset), high amplitude T1-P300 trials will be associated with lower T2 accuracy (a greater AB), but higher T1 accuracy. This result is expected because the higher T1-P300 amplitude should be associated with a larger LC inhibition during the AB, but should also be preceded by a larger NE release which gives rise to the LC inhibition. Since target accuracy is thought to be governed by NE availability at the time, a greater NE release to T1 should result in greater T1 accuracy, followed by greater LC inhibition and lower T2 accuracy.

There is a final point to make regarding analysis of EEG data within the RSVP paradigm before turning to my method and results. Although I have taken steps to ensure that my calculation of T1-P300 characteristics (onset and amplitude) are not confounded by the P300 in response to T2 (T2-P300), a reliable description of the T1-P300 amplitude can not be obtained without looking at a wider and later time window than is required to assess T1-P300 onset. Therefore, while analysis of T1-P300 onset could be performed for all of lags 1, 2, 4, and 5, analysis of T1-P300 amplitude was performed only on lags 4 and 5. When T2 was presented at lags 4 and 5, the T2-P300 began long enough after onset of T1 to give enough room to attain a fairly reliable estimate of T1-P300 amplitude while avoiding the T2-P300 overlap.

Method

Subjects. Sixteen undergraduate students at the University of Victoria took part in the experiment for extra credit. All of them had normal or corrected-to-normal acuity.

Apparatus and stimuli. The stimuli consisted of black digits and uppercase letters presented in rapid succession on a neutral gray background (25.0 cd/m^2). The stimuli subtend on average 1° of visual angle horizontally. They were presented on a monitor refreshed at 85 Hz. The subjects viewed the stimuli from a distance of 55 cm.

Procedure. The experiment took approximately one hour to complete, and comprised one 20-trial practice block, followed by five 80-trial experimental blocks. Short breaks were provided between each block, and feedback was given telling the subjects their average accuracy for detecting the targets within the previous block.3

The critical events in a single trial are illustrated in Figure 1 (AB RSVP Task). Subjects triggered the beginning of each trial by pressing on the spacebar. At the beginning of each trial, a fixation cross was displayed on the center of the screen for one second, and was immediately replaced by an RSVP sequence. The sequence was made of 20 characters (18 digits as distracters and 2 letters as targets). Each stimulus was presented for 47.1 ms, followed by a blank gray screen displayed for an additional 47.1 ms. With this interstimulus interval (ISI), the sequence was presented at a rate of approximately 10 items/s. The 18 digits of the sequence were chosen randomly with replacement from the numbers 2 to 9, with the constraint that a number could not be repeated consecutively. The targets consisted of two letters drawn randomly without replacement from 18 of the 26 letters of the alphabet. We excluded the letters B, I, O, Q, S and Z because of their visual similarity to digits, as well as letters M and W because their width made them especially salient in comparison to other letters. The first target (T1) was randomly presented at any location between the 6^{th} and the 10^{th} frame inclusively. The second target (T2) could appear in the next frame after T1 (lag 1), or following 1, 3, or 4 distracters (lags 2, 4, and 5). There were always at least four distracters following the second target. Finally, two response screens sequentially appeared asking for the identity of the first and the second target. Subjects responded using the keyboard.

EEG Recording. The electroencephalogram (EEG) was recorded from 41 electrode locations using BrainVision Recorder software (Version 1.3, Brainproducts, GmbH, Munich, Germany), using the standard 10-20 layout and referenced to the average voltage across

channels. The electrooculograms (EOG) were recorded from electrodes situated above and below the right eye, and on the outer canthi of each eye. Electrode impedances were kept below 10 kΩ. The EEG data were sampled at 250 Hz, amplified (Quick Amp, Brainproducts, GmbH, Munich, Germany), and filtered through a passband of 0.017 HZ-67.5 Hz (90 dB octave roll off).

Data Analysis. Responses were coded as correct if the subject was able to report the target regardless of order.

The EEG data were filtered off-line through a (0.1 Hz-20 Hz passband) phase-shift-free Butterworth filter and re-referenced to linked mastoids. Occular artifacts were removed using the algorithm described by Gratton, Coles, and Donchin (1983). Trials in which the change in voltage at any channel exceeded 35 μV per sampling point were also discarded. In total, .67% of the data were discarded due to artifacts in the EEG. A 1400-ms epoch data (from 200 ms before T1 onset to 1200 ms after the onset of the target) was extracted from the continuous EEG for each trial, channel, and subject. These epochs were baseline corrected relative to the 200-ms segment preceding stimulus onset.

The EEG data from channel Pz (parietal mid-line, where the P300 is typically maximal), was exported and analyzed in two different ways. First, trials were divided by lag, (1, 2, 4, and 5) and categorized according to whether the subject had successfully reported T2 on that trial (hit- vs. missed-T2). I created event related components (ERP) by averaging the EEG data for hit-T2 versus missed-T2, for each target, at each lag. These ERPs were compared to look for amplitude differences in both the T1-P300 and the T2-P300.

Additionally, I used an algorithm to analyze the EEG data in response to T1 for each trial, looking for the most negative voltage occurring between 200 ms and 300 ms after onset of T1. This point was defined as the peak of the ERP component known as the N2, and taken as the onset of the P300. Trials were divided at the median for each subject, into quick-onset and slow-

onset T1-P300 trials. Furthermore, I used an identical categorization method to divide trials into high-amplitude and low-amplitude T1-P300 categories. The T1-P300 amplitude measure was taken by calculating the average voltage between 300 ms and 600 ms after onset of T1 (only on trials where T2 was presented at 400 ms and 500 ms after onset of T1). The pattern of the AB was then examined and compared across these categories.

The nature of the RSVP task results in a large degree of overlap between EEG activity associated with T1 and EEG activity associated with T2. For example, when T2 occurred at lag 1 (100 ms after T1), the EEG activity recorded from 200 ms after onset of T1 to 600 ms after onset of T1 was the same activity associated with 100 ms after T2 to 500 ms after T2. This overlap made it very difficult to identify activity specific to one target. The critical risk of confound in this study is that EEG activity associated with T2 will differ systematically according to whether the subject was able to report T2. This systematic difference could mistakenly be attributed to activity associated with T1, because of the overlap in EEG activity from both targets, especially at early lags. However, this possible confound could fully be addressed in relation to the T1-P300 onset analysis, and partially for the T1-P300 amplitude analysis: Examination of the results from several studies suggest that difference in EEG activity associated with missed versus hit trials do not appear until after 200 ms post T2 onset (e.g. Vogel et al., 1998; Rolke et al., 2001; MacArthur et al., 1999). If this is true, then my measure of T1-P300 onset cannot be confounded by any systematic differences in the EEG response to missed- versus hit-T2s because the information used for categorization never overlapped with more than the first 200 ms of EEG activity to T2. To be clear, my measure of T1-P300 onset looked at the EEG activity from 200 ms after T1 onset to 300 ms after T1 onset. When T2 followed at lag 1, this time window corresponded to 100 ms to 200 ms after T2 onset, and when T2 was presented at lag 2 the window corresponded to 0 ms to 100 ms after T2 onset. At lags 4 and 5, The T1-

P300 onset time window did not overlap with T2 EEG activity at all. Therefore, as long as there is no systematic difference between missed and hit-T2 EEG activity with the first 200 ms of T2 onset, that small bit of overlap associated with lags 1 and 2 will not confound the T1-P300 onset measure. I begin my statistical analysis with a test of this concern.

Although my measure of T1-P300 onset is likely not confounded by the T2-P300, my measure of T1-P300 amplitude requires a later and wider time-window (300 ms to 600 ms after T1 onset). This meant that when T2 was presented at lags 1 and 2, the T1-P300 amplitude data was confounded by the T2-P300. For that reason, lags 1, 2, 4 and 5 were all included in the T1-P300 onset analyses, but only lags 4 and 5 were included in the T1-P300 amplitude analyses.

Results

Test of overlap between T1- and T2-P300. I was be able to confirm that within the first 200 ms of target onset, no systematic electrophysiological differences occurred between missed and hit targets. I looked at the first 200 ms of EEG recordings locked to T1 onset looking at hit- versus missed-T1s. I only looked at trials where T2 followed at lag 4 and lag 5 (400 ms and 500 ms after T1) so that there was no overlap of this time window with T2 EEG activity. I averaged the EEG amplitude from 0 ms to 200 ms. A repeated-measures one-way anova with hit- or miss-T1 as the repeated measure factor revealed no significant difference in amplitude [$F(1,15) = 1.79, MSE = .41, p = .20$]. This is in contrast to the significant differences in amplitude of EEG recorded between 200 ms and 400 ms post stimulus [$F(1,15) = 22.74, MSE = 2.26, p < .05$].

T1-P300 Amplitude data conditionalized on T2 report. To test whether I had replicated and extended earlier findings relating the P300 and the AB, I divided trials into hit- versus missed-T2s. Only trials where T1 was correctly reported were included in this analysis. Figure 3 plots the EEG amplitude data across time in response to T1, comparing hit- versus missed-T2. Looking only at lags 4 and 5, A three-way anova on P300 amplitude with target (T1 and T2), lag

(4 and 5), and hit/miss (hit-T2 vs. missed-T2) as repeated measures factors revealed no significant effects. There was a trend toward the predicted a target by hit/miss interaction such that hit-T2s should be associated with a larger mean T2-P300 amplitude but smaller mean T1-P300 amplitude P300 [$F(1,15) = 2.970$, $MSE = 3.597$, $p = .11$]. According to my a priori prediction based on the results of Shapiro et al. (2006) that the T1-P300 would be smaller for hit-T2 than missed-T2, I performed a two-way anova on T1-P300 amplitude with lag and hit/miss as repeated measures factors. This analysis confirmed that the T1-P300 was larger for hit- than missed-T2s [$F(1,15) = 5.176$, $MSE = 2.254$, $p < .05$]. An additional two-way anova on T2-P300 amplitude with lag and hit/miss as repeated measures factors revealed no effect of hit- or missed-T2 on T2-P300 amplitude [$F(1,15) = .367$, $MSE = 2.765$, $p = .55$], but instead, a lag by hit/miss interaction indicating at lag 4, the T2-P300 was larger for missed- than hit-T2s, but the reverse was true for lag 5 [$F(1,15) = 10.630$, $MSE = 1.215$, $p < .05$]. Further examination of two, one-factor anovas of T2-P300 amplitude at lag 4 and 5, with hit/miss as the repeated measures factors demonstrated that the difference between hit- and missed-T2s was not significant at lag 4 [$F(1,15) = 1.902$, $MSE = 1.757$, $p = .19$], but was significant at lag 5 such that hit-T2s were associated with larger T2-P300s than missed-T2s [$F(1,15) = 4.764$, $MSE = 2.222$, $p < .05$].

T2 accuracy conditional on T1-P300 onset. According to AB convention, analysis of T2 accuracy was performed only on trials where T1 was reported correctly, and targets were considered accurately reported regardless of which order they were reported in (see Hommel & Akyurek, 2005 for a discussion of the impact of this convention). Figure 4 shows the behavioural effects resulting from the P300 onset categorization. Trials were ordered according to the onset of the T1-P300 and divided at the median into quick-T1-P300 trials and slow-T1-P300 trials. The plot of the behavioural effects implies that an attentional blink was demonstrated in both the slow-T1-P300 and quick-T1-P300 conditions. This impression was confirmed by a

three-factor ANOVA with target (T1 vs. T2), lag (1, 2, 4, and 5) and T1-P300 onset (quick vs. slow) as repeated-measures factors, revealing a significant effect of target such that T2 was reported with significantly lower accuracy than T1 [$F(1,15) = 47.337, MSE = .565.580, p < .05$], and further, a significant interaction of target and lag indicated this deficit in reporting T2 varied across lags [$F(3,45) = 38.264, MSE = .167.918, p < .05$] according to the typical AB pattern. There was also a significant effect of lag [$F(1,15) = 15.785, MSE = .118.249, p < .05$]. A two factor ANOVA on T2 accuracy with lag and onset as repeated-measures factors revealed no significant interaction between onset and lag [$F(3,45) = 1.059, MSE = 44.430, p = .38$]. However, my a priori prediction for this analysis was a cross-over interaction such that trials associated with slow-onset T1-P300s would demonstrate improved T2 accuracy at early lags (1 and 2), accompanied by decreased T2 accuracy at late lags (4 and 5). To further test this prediction I amalgamated T2 accuracy data across lag 1 and 2 into an early-lags condition, and T2 accuracy data across lags 4 and 5 into a late-lags condition. A two factor ANOVA with general lag (early-lags vs. late-lags,), and onset as repeated measures factors again demonstrated no significant interaction between onset and general lag [$F(1,15) = .124, MSE = .23.544, p = .73$]. This result was against my prediction, though the differences were in the predicted direction (early-lags/quick: 82.57%, early-lags/slow: 82.97%, late-lags/quick: 63.44%, late-lags/slow: 62.99%). Had the interaction been significant, it would have been composed of better accuracy at early-lags for the slow-onset P300 trials, and better accuracy at late-lags for the quick-onset P300 trials. One-factor anovas for each of these effects revealed no significant main effect of P300 onset early-lags [$F(1,15) = .09, MSE = 15.36, p = .77$], nor at late-lags [$F(1,15) = .06, MSE = 25.93, p = .81$]. A power analysis of these anovas using G*Power3 software (Faul, Erdfelder, Lang, & Buchner, 2007), suggested that I had adequate power (>.80) to detect medium effect sizes (differences of .5 standard deviations), but medium effect sizes would have

been represented by differences of 4% in the early-lags condition, and 12% in the late-lags condition.

T2 accuracy conditional on T1-P300 amplitude. As with the onset-categorized data, a three-factor ANOVA with target (T1 and T2), lag (4 and 5) and T1-P300 amplitude (high vs. low) as repeated-measures factors suggested the standard AB effect was observed with the T1-P300 amplitude categorized data. T2 was reported with significantly lower accuracy than T1 [$F(1,15) = 41.102$, $MSE = .839.240$, $p < .05$]. Because I was only looking at lags 4 and 5, no interaction of target and lag was expected or observed [$F(1,15) = .414$, $MSE = .21.992$, $p = .53$], and thus, observation of a standard AB could not be confirmed according to the conventional analysis of demonstrating a drop in T2 accuracy between 100 and 700 ms post-T1 onset, relative to T2 accuracy prior to 100 ms, or after 700 ms. However, given the limited number of lags and corresponding lack of temporal resolution in looking at the pattern of the AB, it is reasonable to take the difference in accuracy between T1 and T2 as acceptable evidence that an AB had occurred. Finally, consistent with my prediction, an interaction of target and amplitude was observed, such that a high-amplitude T1-P300 was associated with better accuracy for T1, but worse accuracy for T2 [$F(1,15) = 20.700$, $MSE = 18.086$, $p < .05$]. This effect can be seen in figure 5, which plots the mean accuracy for T1 and T2 across the high- and low-P300 conditions. Further single-factor anovas of each of these component main effects revealed that the difference between high- and low-amplitude T1-P300 trials was not quite significant for T1 accuracy [$F(1,15) = 3.111$, $MSE = 12.096$, $p = .10$], but was significant for T2 accuracy [$F(1,15) = 13.695$, $MSE = 32.909$, $p < .05$].

Discussion

This work has extended findings relating the P300 to the AB, and the LC-NE system to both the P300 and the AB, however it has failed to replicate two findings from several previous

ERP studies of the AB. First, the amplitude of the T1-P300 was larger than the amplitude of the T2-P300 (Vogel et al., 1998; Rolke et al., 2001; MacArthur et al, 1999), but this difference was not significant. Second, the T2-P300 amplitude for hit-T2 trials was larger than the T2-P300 for miss-T2 trials (Rolke et al., 2001; MacArthur et al, 1999), but again, this difference was not significant. The deviation of my results from the work identified above highlights an important difference in my methodology. Because I was primarily interested in performing single-trial analysis of the T1-P300, I did not include a control condition that could be used to eliminate some of the noise generated by the distracters and that could have eliminated noise in the T2-P300 by subtracting out the T1-P300 waveform. For example, Vogel et al. (1998) examined the T2-P300 by subtracting trials that included a frequent T2, from trials that included a rare T2, exploiting target frequency effects on the P300. The resulting difference wave eliminated noise due to distracters and T1. Techniques such as this are very effective in eliminating noise, and are likely the reason behind the difference in significance between my analysis of the T2-P300, and those specified above. In this work, the analysis of the T2-P300 was only incidental to the major predictions, and my failure to replicate the specified results is not of major concern.

A novel finding that extends the work of Shapiro et al. (2006) concerns the relationship between the amplitude of the T1-P300 and the accuracy of reporting T2 within subjects. Shapiro et al. were able to demonstrate this relationship between subjects, as a significant correlation, such that subjects who demonstrated higher amplitude T1-P300s showed worse T2 accuracy during the period of the AB. However, Shapiro et al. failed to demonstrate this same relationship within subjects. I have demonstrated this relationship within subjects in two ways: First, hit-T2s were associated with lower amplitude T1-P300s than miss-T2s, and second, high amplitude T1-P300 trials were associated lower T2 accuracy. This is a powerful result in support of the LC-NE theory of the AB and the P300. It should be noted that my results are also superficially

different from Shapiro et al. in that I used EEG recordings in my study whereas Shapiro et al. used MEG recordings.

The primary hypothesis of this work was that a relatively slow-onset P300 would indicate a delayed LC response, and produce behavioural results interpretable as a delayed AB. Under the LC-NE theory of the AB, the AB deficit is caused by the lack of NE available to facilitate processing 200 ms to 500 ms after a first NE release. I have held that under certain circumstances, NE can be available to facilitate processing up to 200 ms after onset of T1, whereas under normal circumstances NE has usually dissipated by 200 ms with deleterious effects on T2 accuracy at this time. Specifically, if the LC response takes longer than average, the resulting NE release and subsequent reuptake should be delayed such that NE may still be available to facilitate processing of T2 when it is presented at 200 ms. In such a case, the recovery period of the AB should be delayed as well because the entire process from the LC firing to the NE release and then reuptake is shifted onward in time. Therefore, accuracy for T2 should shift from being better when T2 falls within 200 ms of T1, to worse when T2 falls more than 200 ms after T1 in the delayed condition. Against this prediction, categorizing AB trials on the basis of T1-P300 onset did not produce these results. In the introduction I discussed reasons why the novel results sought in this work would be small and elusive. Even with this consideration, the failure to confirm my primary hypothesis is troubling. If the effect of T1-P300 is real, I will have to find a way to greatly reduce the noise in the EEG in order to find it. This issue will be addressed by running the study again, not only with a larger sample size to increase the chance of demonstrating significant results, but with additional manipulation to increase the variability of the LC-NE response. Accordingly, the replication will be extended to contain a manipulation of T1 difficulty such as was employed in Warren et al. With such a design, I hope that I will be able to show a delay in the P300 in the difficult condition, (as was predicted in that

article), and also, within both the difficult and the easy condition, I will be able to see an impact of categorizing trials according to T1-P300 onset. In particular, I anticipate that the difficult condition of this proposed study will contain more variability in the onset of the T1-P300 due to the expected overall delay, and that this increase in variability will make categorization by T1-P300 onset more statistically powerful.

It should be noted that there are differences between my interpretation of, and Nieuwenhuis et al's (2005b) theory of the relationship between the LC-NE system and the P300. Nieuwenhuis et al. claimed that the LC phasic response is critical in generating the P300. I take the more conservative view that the LC phasic response at the very least mediates the amplitude and onset of the P300. Furthermore, Nieuwenhuis et al. claim that the P300 is a manifestation of a system wide *increase* in neural responsivity resulting from an LC-NE system phasic response. In contrast, I claim that the P300 represents the system-wide *decrease* in neural responsivity that would coincide with a decrease in NE availability due to the LC refractory-like period. This difference has almost no impact on predicted observations because it is assumed the LC refractory-like period is strongly correlated with the LC phasic response, i.e. the bigger the phasic response, the bigger the refractory-like period. As such, there is almost no implication in making the shift to my interpretation of the theory, except that my interpretation allows that behavioural responses in a reaction time task can be facilitated by LC phasic activity even when they occur before the actual onset of the P300 (i.e. within 250 ms of the eliciting stimulus). The observation of behavioural responses preceding onset of the P300 has been a deterrent to some researchers accepting the LC-NE theory of the P300 (e.g. Olav Krigolson, personal communication). As well, the timing of the three phenomena seems much more consistent with the relation I describe, and in fact, it is unclear why Nieuwenhuis et al. have gone with a different interpretation.

My interpretation of the LC-NE theory of the P300 has two important implications for theories of the P300. First, the robust effects of target frequency on the amplitude of the P300 have been the inspiration for prominent theories of the P300. For example, perhaps the most accepted theory of the P300 is that it represents context updating. Under this theory, the P300 is larger for infrequent than frequent targets because infrequent targets require a larger revision of context (Donchin & Coles, 1988). However, given that the phasic response of the LC-NE system should be metabolically demanding (Aston-Jones & Cohen, 2005), if the LC-NE system is behind the P300, frequency effects on the P300 may simply be due to the biological limitations of the system in producing frequent phasic bursts. Second, if the P300, represents the refractory-like period of the LC and associated system-wide decrease in NE, and not the initial phasic burst in response to a target and associated system-wide increase in NE, it stands to reason that an earlier component should be observable paralleling an LC phasic burst. As such, the N2 component is a possible candidate for being the electrophysiological manifestation of a brief NE flood into the forebrain. For one, it is a briefer component, occurring on a similar timeframe as an LC phasic burst. Second, it is a voltage deflection in the opposite direction of the P300 which corresponds to an opposite change in NE availability than is theorized to produce the P300. Finally, it is known to be highly correlated with P300 activity, as the LC phasic burst should be highly correlated to the subsequent refractory-like period. However, the N2 has recently been dissociated from the P300 in specific circumstances (for a recent review see Folstein & Van Petten, 2008), and a large amount of empirical evidence will be needed before an LC-NE theory of the N2 can be strongly supported.

The LC-NE theory of the AB and of the P300 has been supported by the work in this paper. Predictions based on these theories have led to the demonstration of novel results highlighting the relationship between the T1-P300 and the AB. The utility of the LC-NE theory

of the AB in delineating the AB phenomenon and explaining enigmatic results was discussed in the introduction. The integration of the LC-NE theory of the P300 with the LC-NE theory of the AB can only demonstrate even greater utility. In particular, the activity of the LC-NE system has been difficult to assess in human subjects because of the prohibitively invasive nature of the necessary research techniques (such as single-cell recording). Pharmacological manipulations of NE have had some success, but accepting a one-to-one-to-one relation between the P300, the AB, and the LC-NE system will open a whole new set of methodologies for studying the function, or perhaps even malfunction of this system in humans.

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Figure Captions

Figure 1. Graphic representation of the critical portion of one trial of the AB task is labeled AB RSVP Task. Actual events involved 20 stimuli, 20 interstimulus intervals, and a beginning fixation cross. Stimuli were displayed for 47.1 ms each. Blank ISI screens were also displayed for 47.1 ms each. A plot of T2 accuracy across lags is labeled AB Performance, and is representative of typical AB performance, not any specific results. Each lag represents a step of 100 ms onward in time

Figure 2. Plot of T2 performance across time as a function of T1 difficulty. This plot is taken from Warren et al., (submitted). Lags occurred every 94.2 ms and accuracy of T2 was calculating using only trials where T1 was reported correctly. Error bars represent 95% confidence intervals for the interaction of difficulty and lag.

Figure 3. EEG activity recorded from channel Pz, locked to T1 onset for hit versus missed T2 trials. The difference waveform (missed-T2 waveform subtracted from hit-T2 waveform) is plotted as well. Negative is plotted upward. Scalp distribution of the difference wave is shown to the right.

Figure 4. Plot of target performance across time as a function of T1-P300 onset. Lags occurred every 94.2 ms and accuracy of T2 was calculated using only trials where T1 was reported correctly. Error bars represent 95% confidence intervals for means at each lag, in each condition.

Figure 5. Graph of performance on each target as a function of T1-P300 amplitude. Only trials where T2 followed at lag 4 and 5 were included in the analysis. Error bars represent 95% confidence intervals for the interaction of target and T1-P300 amplitude.

Figure 1.

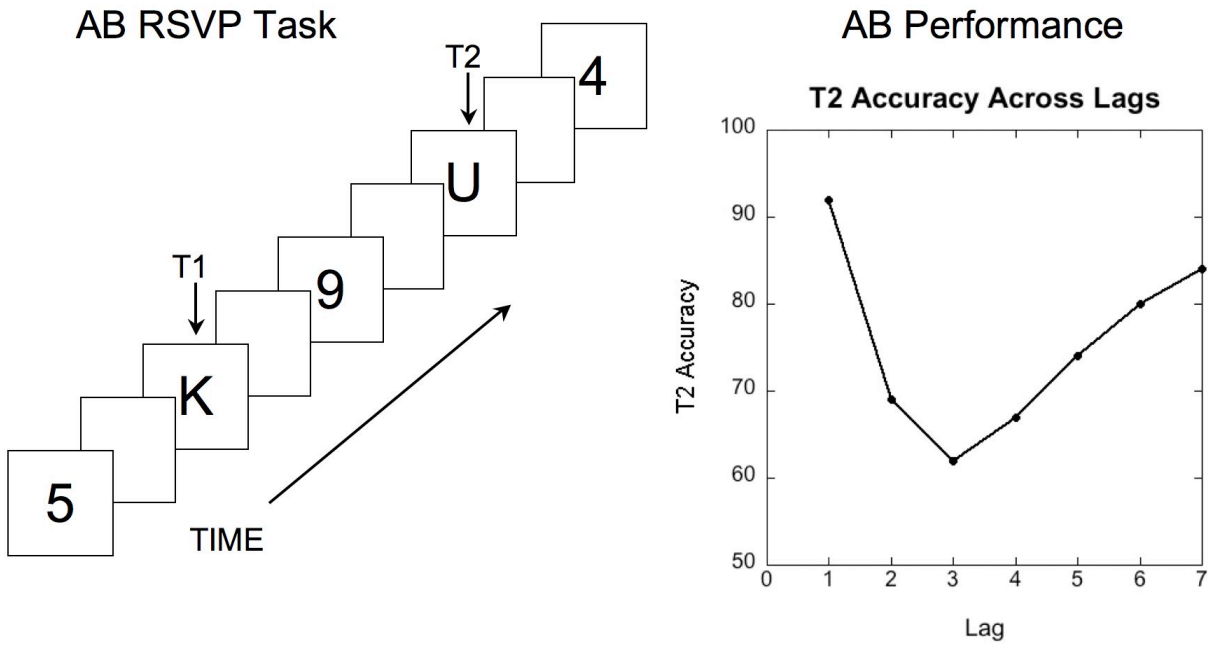

AB RSVP Task
T2
4
U
T1
9
K
5
TIME
AB Performance
T2 Accuracy Across Lags
T2 Accuracy
100
90
80
70
60
50
0
1
2
3
4
5
6
7
Lag

Figure 2.

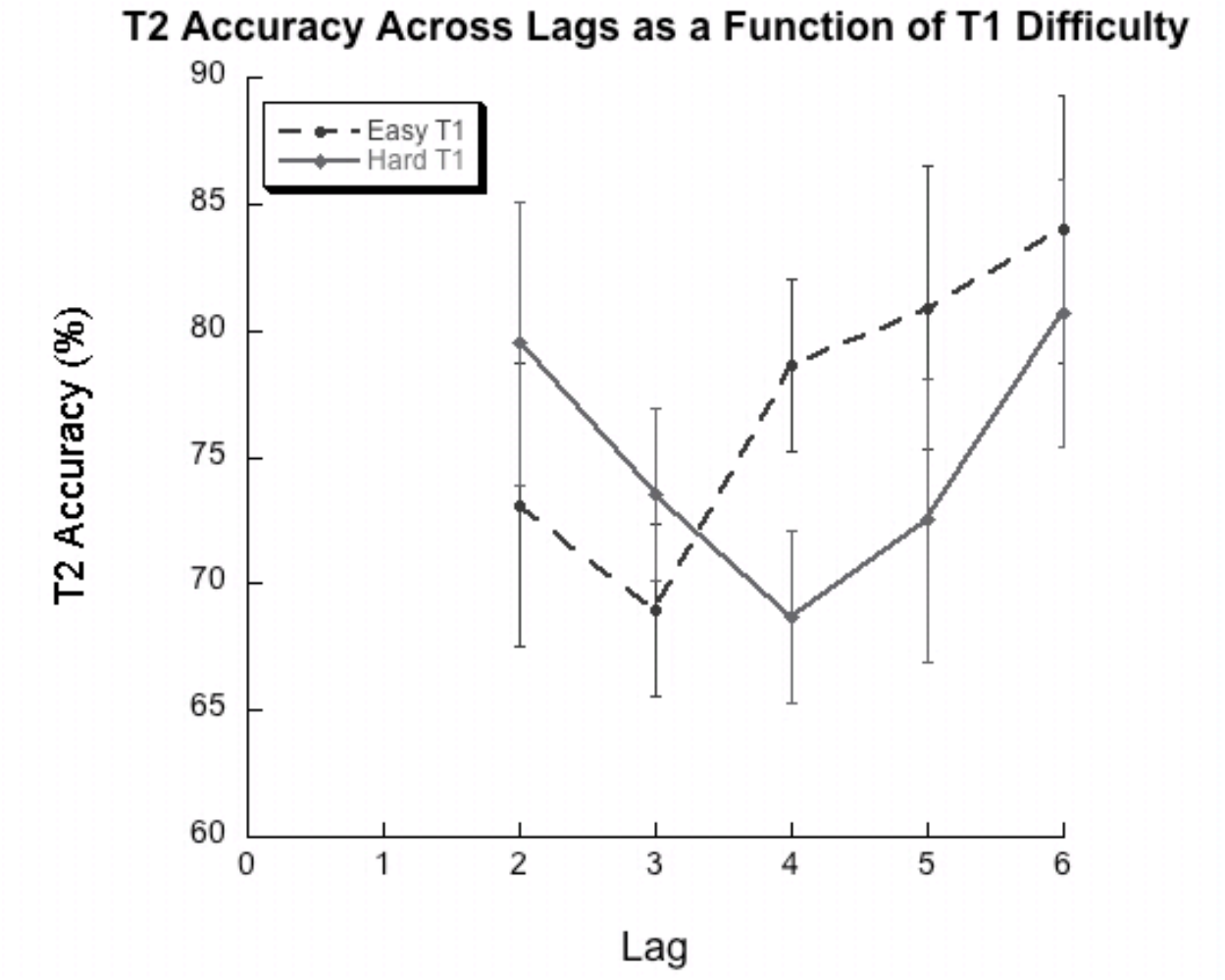

T2 Accuracy Across Lags as a Function of T1 Difficulty
T2 Accuracy (%)
90
85
80
75
70
65
60
Easy T1
Hard T1
0
1
2
3
4
5
6
Lag

Figure 3.

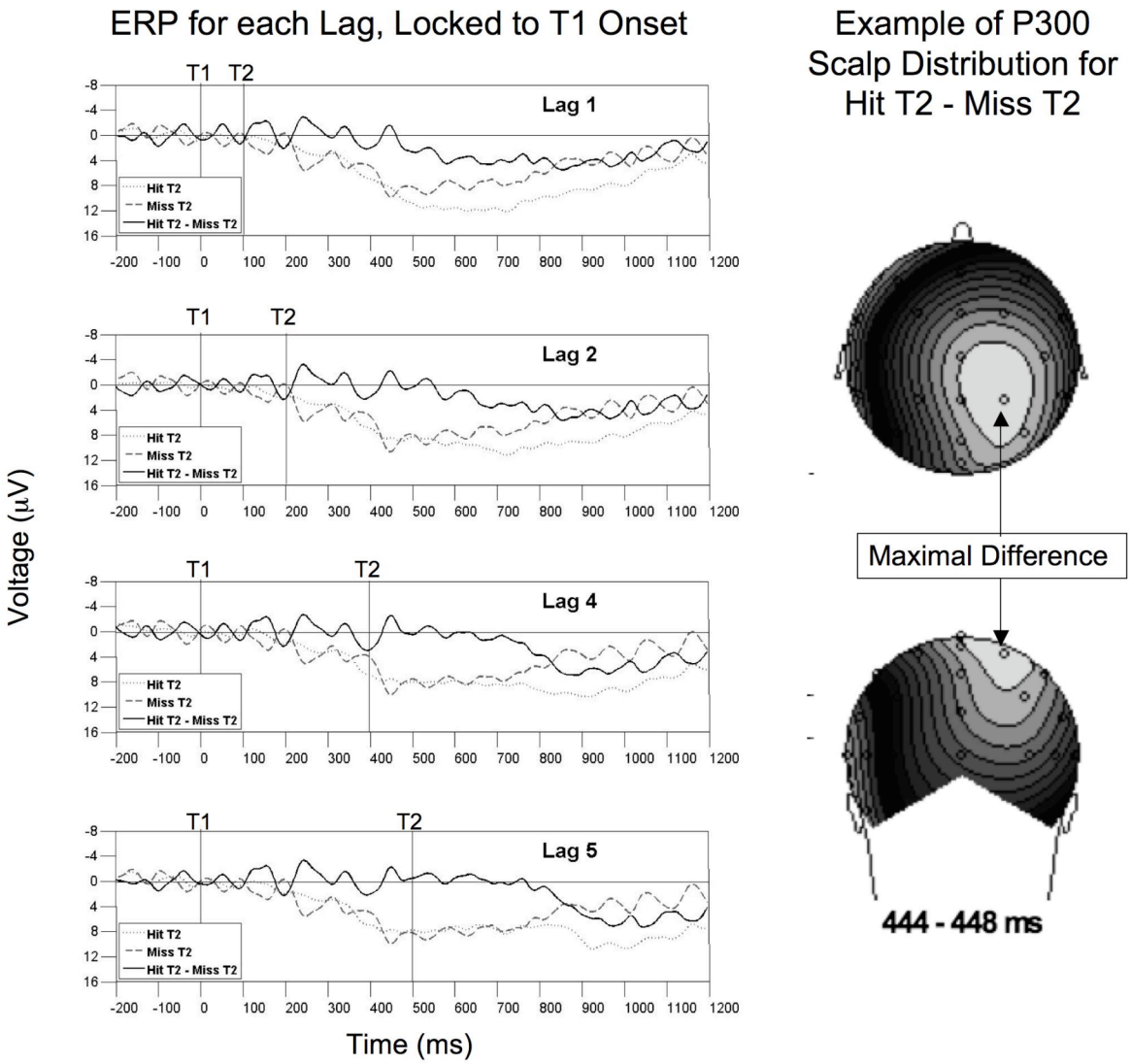

ERP for each Lag, Locked to T1 Onset
T1
T2
Lag 1
Lag 2
Lag 4
Lag 5
Hit T2
Miss T2
Hit T2 - Miss T2
Voltage (μV)
Time (ms)
Example of P300 Scalp Distribution for Hit T2 - Miss T2
Maximal Difference
444 - 448 ms

Figure 4.

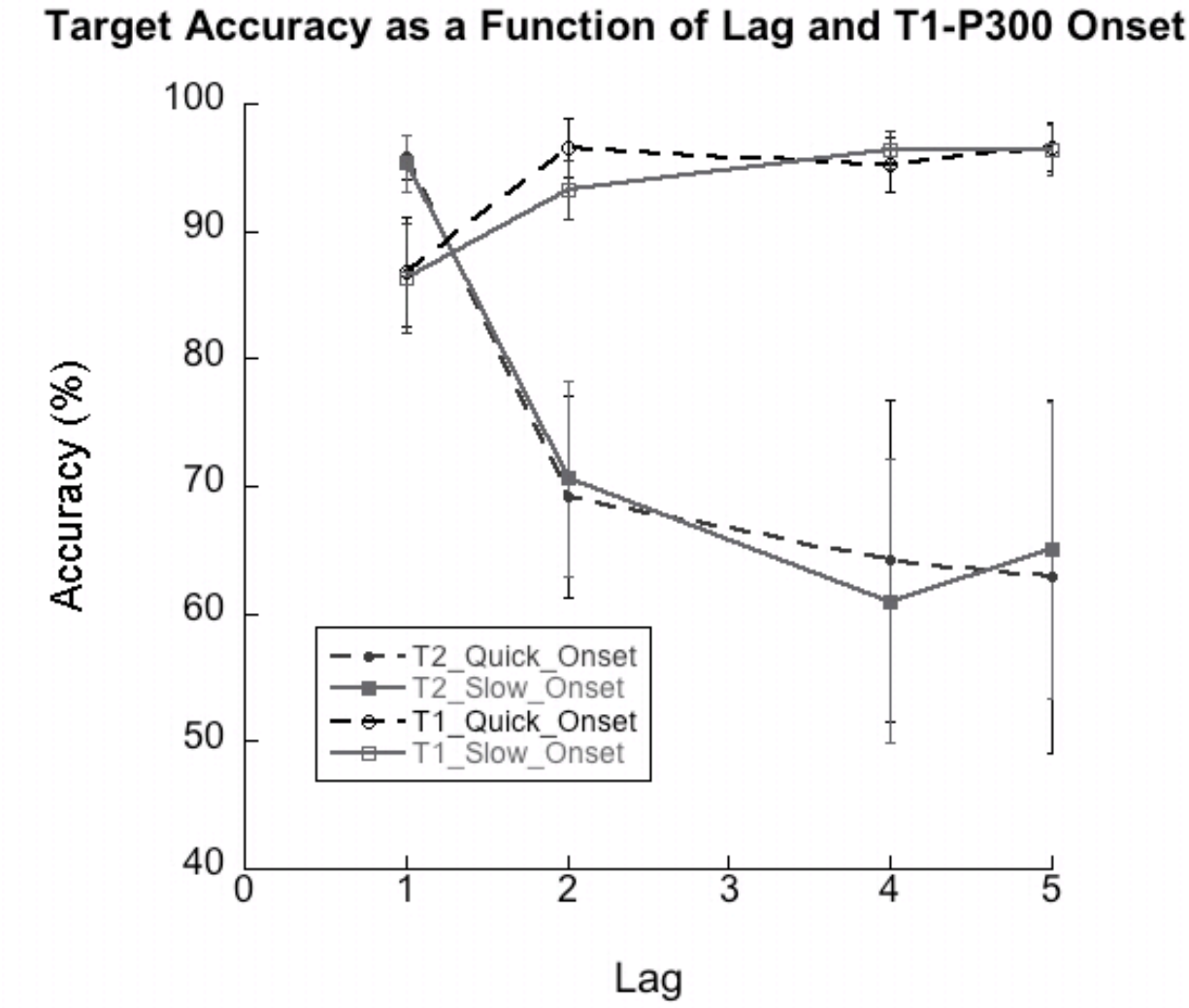
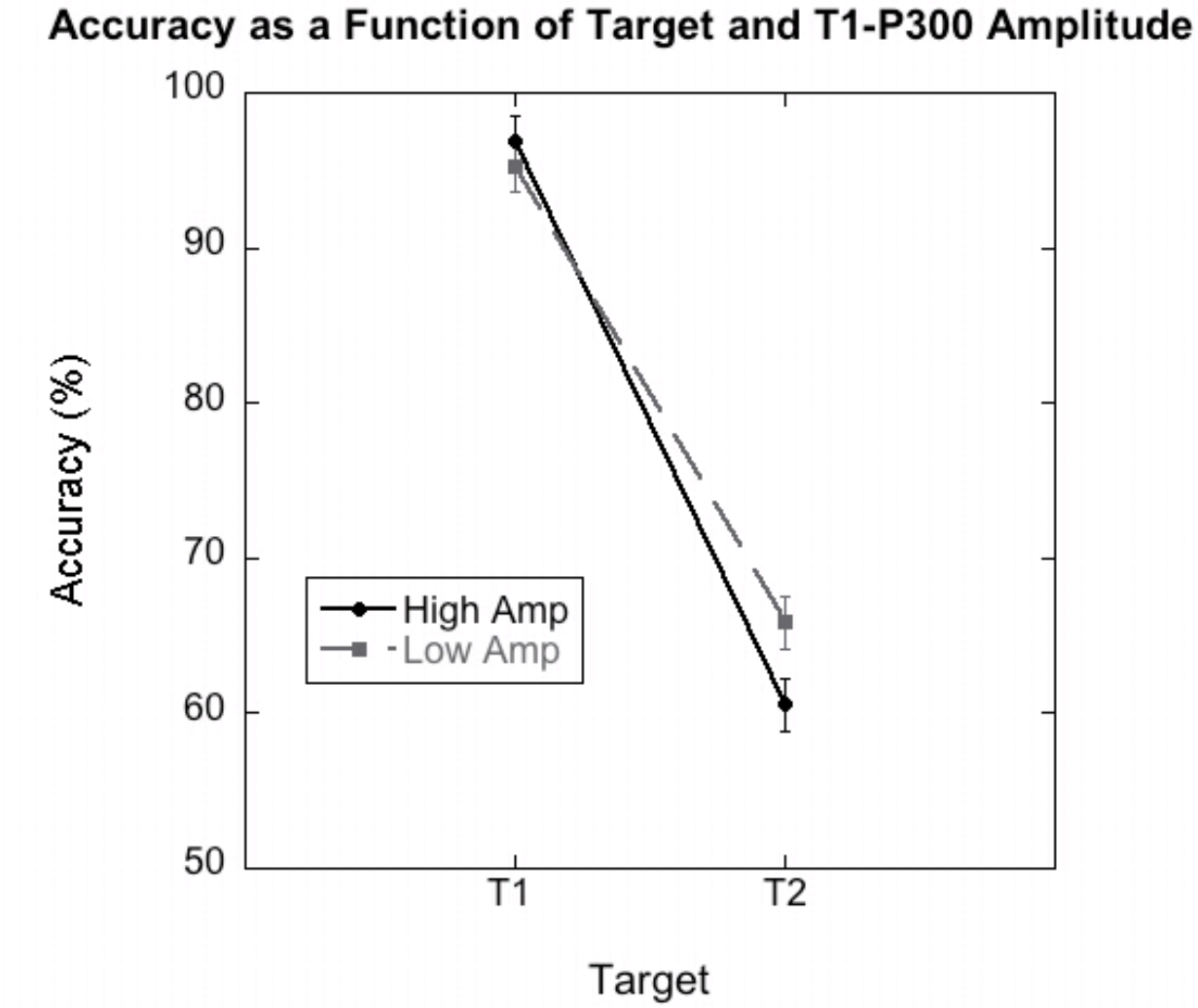

Target Accuracy as a Function of Lag and T1-P300 Onset
Accuracy (%)
100
90
80
70
60
50
40
0
1
2
3
4
5
Lag
T2_Quick_Onset
T2_Slow_Onset
T1_Quick_Onset
T1_Slow_Onset

Figure 5.


Accuracy as a Function of Target and T1-P300 Amplitude
100
90
80
70
60
50
Accuracy (%)
High Amp
Low Amp
T1
T2
Target