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Can working memory predict target-to-target interval effects in the P300?

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Keywords

p300, effects, interval, target, predict, working, memory, can

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Can working memory predict target-to-target interval effects in the P300?

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Abstract

It has been suggested that the P300 component of the ERP is an electrophysiological index of memory-updating processes associated with task-relevant stimuli. Component magnitude varies with the time separating target stimuli (target-to-target interval: TTI), with longer TTIs eliciting larger P300 amplitudes. According to the template-update perspective, TTI effects observable in the P300 reflect the updating of stimulus-templates in working memory (WM). The current study explored whether young adults' memory-task ability could predict TTI effects in P300. EEG activity was recorded from 50 university students (aged 18-25 years) while they completed an auditory equiprobable Go/NoGo task with manipulations of TTIs. Participants also completed a CogState® battery and were sorted according to their WM score. ERPs were analysed using a temporal PCA. Two P300 components, P3b and the Slow Wave, were found to linearly increase in amplitude to longer TTIs. This TTI effect differed between groups only for the P3b component: The high WM group showed a steeper increase in P3b amplitude with TTI than the low WM group. These results suggest that TTI effects in P300 are directly related to WM processes.

Keywords: Late Positive Complex (LPC); P300; P3b; Slow Wave (SW); Event-related potentials (ERPs); Target-to-target interval (TTI); Sequence effects; Interstimulus interval (ISI); Memory; Attention.

1. Introduction

The P300 (or late positive complex), first described by Sutton et al. (1965), is a large centroparietal positivity in the event-related potential (ERP) that occurs approximately 300 ms post-stimulus (Picton, 1992; Pritchard, 1981). This late positivity has been shown to differ in scalp topography and latency depending on the experimental design, suggesting that multiple sources are producing different and independent components, rather than a single entity (Ritter et al., 1968; Vaughan & Ritter, 1970). These components include P3a, P3b (the classic "P3" to target stimuli), Novelty P3, and a late Slow Wave (SW; Courchesne et al., 1975; Squires et al., 1975). Here we use the label "P300" when discussing the single entity/global response peak, rather than these independent components. The P300 has been associated with a range of cognitive processes including decision making (Johnson & Donchin, 1982), memory (Johnson et al., 1985), and orienting (Donchin et al., 1984), and has been extensively examined as an electrophysiological response to target stimuli in oddball tasks (Duncan-Johnson & Donchin, 1977).

In the oddball context, P300 amplitude varies with different stimulus presentation characteristics, including global and local target probability (Duncan-Johnson & Donchin, 1977; Gonsalvez et al., 1995; Johnson & Donchin, 1980; Squires et al., 1976, 1977), interstimulus-interval (ISI; Fitzgerald & Picton, 1981; Polich, 1990a, 1990b), and the target-to-target interval (TTI; Gonsalvez et al., 1999). Previous studies have suggested that, in this context, TTI is an important determinant of P300 measures, and is *independent* of other stimulus manipulations, including probability, sequence, and ISI (Croft et al., 2003; Gonsalvez et al., 1999, 2007; Gonsalvez & Polich, 2002; Steiner et al., 2013). For example, Gonsalvez and Polich (2002) demonstrated that when stimulus sequence and ISI were controlled, P300 amplitude increased, and latency and response time (RT) decreased, to

longer TTIs. These findings suggest the greater importance of target timing over sequence and general ISI manipulations.

Perhaps due to the wide range of conditions in which the P300 is elicited (e.g., habituation and passive paradigms, oddball, choice-reaction time (CRT), and continuous performance tasks; Falkenstein et al., 1991; Johnson & Donchin, 1980; Riccio et al., 2002; Rushby et al., 2005; Wronka et al., 2008), there is a lack of consensus on what the P300 represents, other than that it is an electrophysiological measure of "information processing" (Donchin et al., 1983). However, in the oddball and Go/NoGo context, it has been suggested that the P300 is generated by working memory (WM) processes (Squires et al., 1976), and that variations in amplitude and latency result from a range of different variables including task difficulty (Kok, 2001), psychopathology (Slaets & Fortgens, 1984), and age (Vesco et al., 1993). It has also been suggested that these variations in P300 might index individual differences in memory-updating processes (Gonsalvez et al., 1995). However, the link between P300 and memory is not fully understood, and there is evidence to suggest that brain regions directly related to memory processes may only be involved in the generation of one P300 component, P3a (for a summary, see Verleger, 2008).

Previous research investigating individual differences in memory and ERPs primarily has focused on between-group differences in amplitude and latency of the global P300 (i.e., not underlying independent components; e.g., Karis et al., 1984; Polich et al., 1990b). Some of these studies have explored aspects of memory such as recall (Fabiani et al., 1986), deficits in clinical (Chapman et al., 2007, 2011; Polich et al., 1986, 1990a; e.g., Alzheimer's disease), and subclinical groups (Pató & Czigler, 2011; Pfefferbaum et al., 1984; e.g., normal ageing, early-stage dementia), and individual differences in healthy adults (Polich et al., 1983), and have reported similar patterns: P300s with small amplitudes and prolonged latencies are seen for poor versus good memory performance (Polich, 1989; Vesco et al., 1993). The P300 has

been explored in this context by some of these studies under the premise that it is an index of immediate memory processes (Donchin & Fabiani, 1990; Polich, 1989; Squires et al., 1977). For example, Karis et al. (1984) explored the relationship between P300 amplitude and recall performance in a healthy population by presenting words to participants, some of which were distinctive (i.e., smaller or larger in font size). Distinctive words were used on the assumption that attention should be enhanced to salient events, resulting in stronger WM representations of those events. Karis et al. (1984) found that successful recall of distinctive words was associated with larger P300 amplitudes during the encoding phase than words that were not able to be recalled. This finding suggests that "events that elicit a P300 are remembered better than events that do not…" (Donchin, 1981, p. 509), and also implies that there is a relationship between WM and P300 amplitude. However, the specific nature of this relationship (direct/indirect) and the mechanisms underpinning it are not known.

Evidence suggests that the P300 is sensitive to differences in memory functioning between groups of young, healthy adults. For example, Polich et al. (1983) demonstrated that P3a and P3b latencies from an auditory oddball task were negatively correlated with memory digit-span scores (i.e., prolonged P300s were linked to lower digit span scores). In another study, Polich et al. (1990b) showed that digit span predicted differences in P300 amplitude and latency in children in several auditory oddball tasks. Together, these findings suggest that the global P300 and its components may be able to be predicted by individual differences in memory. Although these previous studies provided a valuable contribution by identifying a relationship between P300 and WM, there are some aspects that require clarification and extension. For instance, testing for a relationship between grand mean ERP peak data and memory scores from one measure (i.e., digit span) may be suboptimal for exploring the relationship between P300 and memory. That is, Polich et al. (1983, 1990b) did not take into account performance across different WM tests (e.g., N-back tasks). Furthermore, Polich et

al. (1983) explored P300 latency, not amplitude, and Polich et al. (1990b) quantified global P300 measures, and consequently did not explore whether separate P300 components (P3a etc.) are sensitive to individual differences in memory ability. The present study aimed to clarify, enhance and extend this literature.

Several theoretical perspectives addressing the functional significance of the P300 posit that it represents some form of immediate *memory-updating* (e.g., Gonsalvez et al., 2007; Squires et al., 1976, 1977) and/or is related to event *expectancy* (e.g., the context-updating vs. context-closure debate; Donchin & Coles, 1988; Verleger, 1988). In brief, the context-updating hypothesis (Donchin & Coles, 1988) asserts that expectancies are established by a model of the context of the environment, and when events violate those expectancies, the model is updated, with "P300... elicited by the processes associated with maintenance of... [that] model" (p. 370). Verleger (1988) separated this hypothesis into "expect" and "update", where the representation of a stimulus in WM is "updated" after it has decayed over time. Verleger (1988) introduced the context-closure account – P300 is elicited by awaited events in a structured and repetitive task "when a perceptual epoch is closed" (p. 351). Ten years on, Sommer et al. (1998) noted a key difference between these perspectives in relation to subjective probability (not relative frequency, as outlined in Donchin, 1981) and argued that "P300 appears to reflect mainly passive expectancies" (p. 150), a view contradicting Verleger's (1988) assertions. In light of the evidence suggesting that the P300 is not a strategic response (unconscious expectancies: Sommer et al., 1998; response selection: Verleger, 1997), Verleger (1998) withdrew the context-closure hypothesis.

Earlier TTI papers (Gonsalvez et al., 2007) attempted to account for P300 TTI effects by adopting a framework similar to the context-updating hypothesis (Donchin & Coles, 1988) and Verleger's (1988) "update" hypothesis: a template-update model. Template-update differs from both context-updating (Donchin & Coles, 1988) and context-closure (Verleger,

1988) hypotheses as it rejects the notion that P300 amplitudes are related to revised expectancies of target and nontarget stimuli (both “unexpected” or “awaited”).

Template-update assumes that templates are a profile of neural activation generated by a stimulus and that TTI results are related to the integrity of those templates in WM. The template is affected by both degradation, occurring as a function of the time between matching-stimulus presentations, and WM update, activated to refresh the neural model/template of the stimulus. This important aspect of the model is shared with Verleger’s (1988) “update” interpretation. However, Verleger’s (1988) criticisms of “update” related to P300 playing a direct role in memory processes (e.g., “the close relationship of the P300 and working memory postulated by context updating has not been demonstrated so far… P300 is unlikely to reflect the activity of working memory”; p. 344). In contrast, a key tenet of template-update is that TTI effects are what directly reflect memory-updating processes, rather than the P300 itself (which may be influenced by a range of other factors such as arousal). This particular aspect of template-update, that TTI-related changes (observable in P300 amplitude) reflect WM capabilities, is a novel prediction that has not been tested, and the aim of the present study is to directly test this hypothesis.

This prediction is made because template-update assumes that individuals with high compared to low WM ability have stronger encoding abilities and/or richer associative networks, and consequently larger P300 amplitudes when templates are initially encoded. Compared to individuals with poor WM, those with good WM may also have better mechanisms to retain templates over time, resulting in less decay and smaller P300 differences during time frames critical to template decay. The latter is difficult to test because of differing initial encoding values, and the possibility that larger decay values may represent the decay from a greater number of networks rather than faster decay *per se*. However, based on the assumption that individuals with high WM ability encode templates

more strongly to begin with, it can be predicted that the difference between this strong initial encoding value (best estimated at long TTIs – 15 s or more) and the value when there is minimal update (i.e., short TTIs – 1 s), will be greater for persons with high compared to low WM ability (i.e., a steeper gradient).

The current study explored whether the TTI/P300 relationship could be predicted by memory differences in a healthy population of young adults. To control for possible age-related memory changes, only participants aged 18-25 years were recruited. To elicit P300s, an auditory equiprobable Go/NoGo task was utilised, in which TTI was manipulated. This paradigm was carefully constructed to control for global probability, stimulus sequence, and ISI. WM was tested with a customised CogState® battery. Participants were selected to form two groups (high- vs. low-WM) based on their CogState® performance across WM subtests, and their TTI-determined ERPs were assessed. Although previous TTI research (Croft et al., 2003; Gonsalvez et al., 1999, 2007; Gonsalvez & Polich, 2002; Steiner et al., 2013) has employed baseline-to-peak measures to assess the P300, it is reasonable to suggest that P300 components (e.g., P3a, P3b, SW) are differentially responsive to manipulations of TTI. Thus, the current study sought to clarify this by applying a principal components analysis (PCA). In line with Polich et al. (1983, 1990b), it was hypothesised that WM should directly affect one or more components of the P300. Additionally, template-update (Gonsalvez et al., 2007) predicted that there would be differences in the TTI-determined P300 amplitudes between the high versus low WM groups. Specifically, it was hypothesised that as TTI increased, individuals with good compared to poor WM would show a greater increase in P300 amplitude due to stronger initial encoding values. In accordance with the previous TTI research in two-stimulus oddball tasks (Gonsalvez & Polich, 2002; Gonsalvez et al., 2007), it was also predicted that RT would decrease as TTI increased.

2. Method

2.1 Participants

Fifty young undergraduate students from the University of Wollongong participated in this study in return for course credit. The sample included 24 males and 26 females (47 right-handed, 3 left-handed), with a mean age of 19.7 (*SD* = 1.9) years. All provided informed consent prior to commencing the experiment, and were free to withdraw at any time without penalty. Recruited individuals self-reported no neurological or psychiatric illnesses, and no use of psychotropic medication. Self-reports also indicated that participants had refrained from psychoactive substances for at least 12 hours and from tea, coffee, alcohol, and cigarettes for at least 2 hours prior to testing. All participants had normal or corrected-to-normal vision and self-reported normal hearing.

2.2 Procedure

Participants were required to complete a demographic and screening questionnaire, and were fitted with EEG recording apparatus. The experiment took place in an air-conditioned room with a background illuminance of 470 lux. Air flowing from the air-conditioning was redirected away from participants to reduce blinking and subsequent eye-movement artefact. Prior to the experiment, participants completed an electrooculogram (EOG)/EEG calibration task (Croft & Barry, 2000).

Participants were seated 60 – 80 cm in front of a 19" Dell LCD monitor (REV A00) and instructed to fixate on a 10 x 10 mm grey cross (luminance = 7.0 cd/m^2) displayed in the centre of a black background (luminance = 0.4 cd/m^2). Acoustic stimuli were delivered binaurally through Sony MDR V700 circumaural stereo headphones, and consisted of 1000 and 1500 Hz tones of 50 ms duration (15 ms rise/fall time), at 60 dB SPL.

The experiment consisted of a unique task that was broken into four different blocks (approximately 4.5 min each), with short rest intervals between blocks to minimise fatigue effects. To avoid global probability effects, the task was an equiprobable oddball (Go/NoGo)

paradigm (global $p = 0.50$), where target and nontarget stimuli were counterbalanced between participants (1000 and 1500 Hz tones). When designing the paradigm, the presentation of TTI was randomised and silence was added to maintain stimulus equiprobability (see Figure 1 for a sample of the stimulus sequence). Care was taken to vary the local probability and density of targets, nontargets, and silence to minimise possible expectancy effects or participant strategies related to sequence and ISI. The stimulus order was fixed across subjects, with specific presentations of eight TTIs (1, 2, 3, 5, 7, 10, 12, 15 s); a total of 264 stimuli were presented over the 4 blocks (132 targets, 132 nontargets). Exactly 20 trials for each of the five intervals of major interest (1, 2, 5, 10, and 15 s) were presented with equal probability. Thus, stimulus order was semi-random with a variable SOA that was no less than 1 s for successive stimuli (TT, NN, TN, NT). Between target presentations, for TTIs longer than 1 s, there was silence or nontarget/s (or a combination of the two for TTIs > 2 s). To balance possible speed/accuracy trade-offs, participants were instructed to "respond to target stimuli with a button press, as quickly and as accurately as possible." The response was made with the dominant hand on a Logitech® Precision game controller.

Figure 1 about here.

After completing the ERP task outlined above, participants completed a customised CogState® research battery (a computerised neuropsychological test battery) that was ~ 30 min in duration. The battery comprised 10 subtests that examine a range of cognitive abilities, including: International Shopping List, Continuous Paired Associate Learning Task, Detection Task, Identification Task, One Card Learning Task, One Back Task, Two Back Task, Monitoring Task, International Shopping List: Delayed Recall, and Continuous Paired Associate Learning: Delayed Recall; these tasks measure verbal and visual learning and memory (short-term and long-term), processing speed, visual attention and vigilance, and working memory, and have acceptable criterion and construct validity in a

neuropsychological context (see www.cogstate.com; Maruff et al., 2009; Pietrzak et al., 2009). This procedure was approved by the joint South Eastern Sydney/Illawarra Area Health Service and University of Wollongong Health and Medical Human Research Ethics Committee.

2.3 Materials and Apparatus

EEG data were recorded continuously from A2 and 30 scalp sites (Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, O1, Oz, O2) using an electrode cap with tin electrodes. A1 was used as a reference and the cap was grounded by an electrode located midway between Fp1/Fp2 and Fz. The data were acquired using a Neuroscan Synamps 2 digital signal-processing system and Neuroscan 4.3.1 Acquire software, and recorded DC – 70 Hz. The CogState® battery was administered on this computer after the ERP task (Dell Optiplex computer with a 19" Dell LCD monitor; REV A00). The display and stimulus markers were controlled by a linked stimulus computer using Neurobehavioral Systems Inc. Presentation V 13.0 Build 01.23.09 software.

EOG was recorded using tin cup electrodes placed 2 cm above and below the left eye for vertical movements, and on the outer canthus of each eye for horizontal movements. Impedance was less than 5 kΩ for cap, EOG and reference electrodes. Scalp and EOG potentials were amplified with a gain of 500 and digitised at a rate of 1000 Hz.

2.4 Data Extraction

The EEG data were EOG corrected using the RAAA EOG Correction Program (Croft & Barry, 2000). For each trial, data were extracted offline using Neuroscan Edit software, re-referenced to digitally-linked ears, low pass filtered (0.1 – 30 Hz, zero-phase shift, 24 dB/Octave), epoched from 100 ms pre- to 750 ms post-stimulus, and baseline corrected using the pre-stimulus interval. For each condition, averages were computed for each subject for

each of the five intervals of major interest. All participants had low error rates (< 5 %) and trials containing incorrect responses, both commission (false alarms) and omission errors (misses) were excluded from further analysis.

WM was measured for each participant by forming a composite score (similar to Lim et al., 2012) derived by averaging standardised scores from three subtests in the CogState® battery that specifically measure WM (One Card Learning Task, One Back Task, Two Back Task). The 50 participants were then sorted according to their composite scores. Participants scoring in the top and bottom thirds formed high and low WM groups (N = 17 for each group) that were retained for further analysis. These groups were significantly different on WM, with the high group (M = 0.63, SD = 0.18) scoring higher composite WM scores than the low group (M = -.81, SD = .85; F = 45.82, p < .001, η_p^2 = .59).

2.5 Principal Components Analysis

The averaged post-stimulus data (0-750 ms) from 30 scalp locations for each interval and condition were submitted to a temporal PCA using Dien's ERP PCA toolkit (v. 2.23; Dien, 2010) in MATLAB® (The Mathworks, R14SP3). Data for the PCA were down-sampled to 250 Hz (187 time-points/variables), to reduce computation time and improve the ratio of cases/components. Factors for all conditions were quantified simultaneously, hence there were 10,200 observations (34 participants × 2 stimulus types × 5 intervals × 30 sites). The PCA used the unstandardised covariance matrix with Kaiser normalisation, and all 187 unrestricted factors underwent Varimax rotation, following Kayser and Tenke (2003). PCA factors were identified as ERP components based on their latency, topography, and polarity. Although this quantification procedure was performed for all components post-stimulus, this study was interested in testing hypotheses pertaining to the target P300, thus only identifiable P300 component target responses were retained for analysis.

2.6 Statistical Analyses

Separate mixed-model MANOVAs were carried out on the virtual ERP amplitudes for each of the identified P300 components at 9 central sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4), with the between-subjects factor of WM (High vs. Low), and within-subjects factor of TTI (1, 2, 5, 10, and 15 s); within TTI, weighted linear and quadratic contrasts were assessed. For each component, the first analysis also examined stimulus type (Target vs. Nontarget); only the effects of topography and stimulus type, and their interaction, are reported. The second analysis examined topography, group, and TTI for target responses only. Each analysis included an examination of topography involving the sagittal plane: Frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4); and the coronal plane: Left (F3, C3, P3), midline (Fz, Cz, Pz), and right (F4, C4, P4). Planned contrasts compared regions within each plane: Sagittal plane (frontal vs. parietal, and central vs. mean of the frontal and parietal) and coronal plane (left vs. right, and midline vs. mean of the left and right sites), and their interactions. The topographic distribution of peak amplitudes can be examined most efficiently by utilising these orthogonal planned contrasts. No Bonferroni-type α adjustment was required as contrasts were planned, and the number of contrasts did not exceed the degrees of freedom for effect (Tabachnick & Fidell, 1989). RT to target stimuli was also assessed between groups and over the five interval levels (within subjects) with a mixed-model MANOVA, again with weighted linear and quadratic contrasts over interval. The violations of sphericity assumptions associated with repeated-measures analyses do not affect single degree of freedom contrasts, so Greenhouse-Geisser-type correction was not necessary (O'Brien & Kaiser, 1985). All *F*-tests are reported with (1, 32) degrees of freedom.

3. Results

3.1 Grand Mean ERPs

Grand mean ERPs (100 ms pre- to 1000 ms post-stimulus) over the 34 participants from the midline sites (Fz, Cz, Pz) are shown for targets and nontargets in the left panel of

Figure 2A. In the uppermost panel, the dashed waveform (uncorrected) is the mean activity (across all subjects, groups, and stimulus types) at Fz pre-EOG artefact correction. This serves to illustrate any contamination to be dealt with by the EOG artefact correction procedure (Croft & Barry, 2000). Figure 2B shows the grand means to targets (left panel) and nontargets (right panel) for the high and low WM groups. The upper three panels of Figure 3 show the grand mean ERPs to targets from the midline sites over the five intervals. Here, as intervals increase, an increase in the area under the curve for the P300 complex is apparent, suggesting that any amplitude differences are not a result of shifting latency variability.

The lower panel of Figure 3 shows pre-corrected vertical EOG for the five TTIs. The dissimilarity between the pre-corrected VEOG and the ERP waveforms, especially in the P300 latency range, indicates that EOG artefact correction was successful, and that EOG artefact did not contribute to the P300 data.

Figures 2 and 3 about here.

3.2 PCA Outcomes

From the 187 temporal factors extracted, the first twelve each explained more than 1% of the variance, and together they explained 90.5 %. The sums of these virtual temporal components at the midline sites are displayed in the right panel of Figure 2A. Comparison with the ERPs in the left panel suggests a good fit with the original data.

The temporal factor loadings for the twelve ERP components are displayed as a function of time in Figure 4. The y-axis indicates the factor loadings (unscaled correlations between each factor and the ERP waveform; Tabachnick & Fidell, 1989), multiplied by the standard deviation of the ERP at each time-point to convert to μV. The percentage of the total variance and the latency for each rotated component is also indicated. The topographic headmaps of the virtual temporal components, averaged across stimulus type, group, and

interval, are displayed above. These components (Factors 1-12, contributing to the virtual ERPs; right column Figure 2A) were tentatively identified, in terms of their polarity, latency, sequence, and topography. Seven of the twelve factors were identified as P1, N1-1 (the dominant frontocentral component of the N1 identified by Näätänen & Picton, 1987), Processing Negativity (PN; temporal negativity occurring late in the N1 latency range, following Näätänen & Picton, 1987), P2, N2, P3b (strong parietal positivity and large response to targets), and the classic SW. The other five were less distinguishable, but some resembled real components and were thus cautiously labelled as N1-3 (again following Näätänen & Picton, 1987, a small and early "true" N1 component), unidentified N2 (uN2; occurring before the identifiable frontally-negative N2), unidentified P3 (uP3; similar overall topography to the frontal P3a, but occurring *after* the large target P3b at a time range similar to that of the Novelty P3; Courchesne et al., 1975), an unidentifiable late component (Un), and a very late negativity (VLN). As specific predictions were made in regard to the P300 complex, only the three components identifiable as part of this complex (P3b, uP3, SW) were analysed further. The sum of these three virtual components is illustrated with dashed lines at the site of maximal P300 amplitude (Pz) in the right panel of Figure 2A. The good fit with the P300 in both the virtual ERPs (sum of the twelve virtual factors; right column) and the actual ERPs (original data; left column) indicates that these three components explain a substantial amount of the variance in the P300 complex and that their analysis is justified. The data reported below are in an order corresponding to the latency of the component.

Figure 4 about here.

3.3 TTI effects

To aid interpretation of results, trends analysed across TTIs are denoted as "linear intervals" or "quadratic intervals". The direction of difference between variables is indicated by "<" and ">", and interactions between effects by "×".

3.3.1 Factor 3: P3b

Figure 4 shows that across stimulus type, group, and interval, P3b demonstrated the typical strong parietal topography, with amplitudes larger parietally than frontally (frontal < parietal: $F = 150.86$, $p < .001$, $\eta_p^2 = .83$; also see Figure 6A), and lower centrally than the mean of frontal and parietal sites (central < mean frontal/parietal: $F = 55.95$, $p < .001$, $\eta_p^2 = .64$). These effects were greatest at the midline (frontal < parietal × midline > mean left/right: $F = 58.75$, $p < .001$, $\eta_p^2 = .65$; central < mean frontal/parietal × midline > mean left/right: $F = 15.98$, $p < .001$, $\eta_p^2 = .33$).

Across group and interval, P3b amplitudes were greater to targets than nontargets ($F = 6.75$, $p = .014$, $\eta_p^2 = .17$; see Figure 5A), particularly for the strong parietal maximum (frontal < parietal × target > nontarget; see Figure 6A): $F = 10.08$, $p = .003$, $\eta_p^2 = .24$; central < mean frontal/parietal × target > nontarget: $F = 14.04$, $p = .001$, $\eta_p^2 = .30$). The greater central reduction for targets than nontargets was larger at the midline (central < mean frontal/parietal × target > nontarget × midline > mean left/right: $F = 6.04$, $p = .020$, $\eta_p^2 = .16$), and in the right hemisphere (central < mean frontal/parietal × target > nontarget × left < right: $F = 11.10$, $p = .002$, $\eta_p^2 = .26$); there was also an overall right hemisphere enhancement that was greater for targets (left < right × target > nontarget: $F = 8.21$, $p = .007$, $\eta_p^2 = .20$).

As illustrated in Figure 5B Column 1, across interval, target P3b amplitudes were more positive for the high than the low WM group in the midline (midline > mean left/right × high > low: $F = 3.91$, $p = .057$, $\eta_p^2 = .11$) and for the central reduction/right hemisphere enhancement (central < mean frontal/parietal × left < right × high > low: $F = 4.47$, $p = .042$, $\eta_p^2 = .12$). There was no main effect of group on target P3b amplitudes.

Figure 5B also illustrates that as TTI increased, across group target P3b amplitudes increased in a linear fashion (linear intervals: $F = 10.50$, $p = .003$, $\eta_p^2 = .25$). This increase was most prominent at the midline (linear intervals × midline > mean left/right: $F = 5.63$, $p =$

.024, η_p^2 = .15), and in the parietal region (linear intervals × frontal < parietal: F = 16.10, p < .001, η_p^2 = .33; Figure 6B). The parietal increase was particularly apparent in the right hemisphere (linear intervals × frontal < parietal × left < right: F = 7.54, p = .010, η_p^2 = .19) and the midline (linear intervals × frontal < parietal × midline > mean left/right: F = 21.64, p < .001, η_p^2 = .40). Importantly, Figure 6C demonstrates that this linear increase in parietal target P3b amplitudes was greater for the high than the low WM group (linear intervals × frontal < parietal × high > low: F = 6.67, p = .015, η_p^2 = .17).

Figures 5 and 6 about here.

3.3.2 Factor 8: uP3

As demonstrated in Figure 4, across stimulus type, group, and interval, uP3 had a midline topography (midline > mean left/right: F = 4.11, p = .051, η_p^2 = .11), dominant in the frontal region (midline > mean left/right × frontal > parietal: F = 15.04, p < .001, η_p^2 = .32). uP3 amplitudes were smaller centrally (central < mean frontal/parietal: F = 4.27, p = .047, η_p^2 = .12), especially in the left hemisphere (central < mean frontal/parietal × left > right: F = 5.20, p = .029, η_p^2 = .14).

Figure 5A shows that across group and interval, uP3 was strongly parietal to targets and frontal to nontargets (frontal < parietal × target > nontarget: F = 44.15, p < .001, η_p^2 = .58). There was no main effect of stimulus type.

Across interval, a central reduction in uP3 to targets was larger in the midline for the high than the low group (central < mean frontal/parietal × midline > mean left/right × high > low: F = 4.28, p = .047, η_p^2 = .12; see Figure 5B, Column 1). There was no main effect of group on uP3 amplitudes.

Across groups, as TTI increased, target uP3 amplitude decreased (linear intervals: F = 6.62, p = .015, η_p^2 = .17), before increasing at the longest TTI (quadratic intervals: F = 4.65, p = .039, η_p^2 = .13; see Figure 5B). These effects were prominent for the central

reduction/midline enhancement (linear intervals × central < mean frontal/parietal × midline > mean left/right: $F = 7.25$, $p = .011$, $\eta_p^2 = .18$; quadratic intervals × central < mean frontal/parietal × midline > mean left/right: $F = 15.00$, $p = .001$, $\eta_p^2 = .32$), with the overall decrease greater at the midline (linear intervals × midline > mean left/right: $F = 4.58$, $p = .040$, $\eta_p^2 = .13$). TTI effects did not differ with group.

3.3.3 Factor 1: SW

As seen in Figure 4, across stimulus type, group, and interval, SW demonstrated the typical frontal negativity and parietal positivity (frontal < parietal: $F = 102.87$, $p < .001$, $\eta_p^2 = .76$), with central amplitudes being more positive than the mean of frontal and parietal sites (central > mean frontal/parietal: $F = 13.94$, $p = .001$, $\eta_p^2 = .30$). The defining parietal positivity/frontal negativity difference was larger in the left hemisphere (frontal < parietal × left > right: $F = 11.13$, $p = .002$, $\eta_p^2 = .26$), and greatest at the midline (frontal < parietal × midline > mean left/right: $F = 78.99$, $p < .001$, $\eta_p^2 = .71$).

Figure 5A shows that the difference between the parietal positivity and frontal negativity was larger for targets than nontargets (frontal < parietal × target > nontarget: $F = 63.54$, $p < .001$, $\eta_p^2 = .66$), particularly in the left hemisphere (frontal < parietal × target > nontarget × left > right: $F = 12.83$, $p = .001$, $\eta_p^2 = .29$), and at the midline (frontal < parietal × target > nontarget × midline > mean left/right: $F = 34.48$, $p < .001$, $\eta_p^2 = .52$). There was a greater reduction at the vertex for targets than nontargets (central < mean frontal/parietal × midline < mean left/right × target > nontarget: $F = 15.40$, $p < .001$, $\eta_p^2 = .32$). There was also a central reduction that was greater in the left hemisphere for targets and in the right hemisphere for nontargets (central < mean frontal/parietal × left > right × target > nontarget: $F = 4.81$, $p = .036$, $\eta_p^2 = .13$).

Across intervals, Figure 5B Column 1 shows that for targets, the parietal positivity/frontal negativity difference and central enhancement were greater in the left-

hemisphere for the high than the low WM group (frontal < parietal × left > right × high > low: $F = 3.25$, $p = .081$, $\eta_p^2 = .09$; central > mean frontal/parietal × left > right × high > low: $F = 4.48$, $p = .042$, $\eta_p^2 = .12$).

As TTI increased, the central right enhancement showed a linear increase (Figure 5B; linear intervals × central > mean frontal/parietal × left < right: $F = 8.09$, $p = .008$, $\eta_p^2 = .20$), as did the midline parietal positivity/frontal negativity difference (linear intervals × midline > mean left/right × frontal < parietal : $F = 4.71$, $p = .037$, $\eta_p^2 = .13$), but this peaked and plateaued after the 2 s interval (quadratic intervals × midline > mean left/right × frontal < parietal: $F = 9.83$, $p = .004$, $\eta_p^2 = .23$). Target SW TTI effects did not differ between the WM groups.

3.3.4 RT

Mean RTs as a function of TTI are shown in Figure 7 separately for the two WM groups. Across group, RT increased up to the 5 s TTI before decreasing (quadratic intervals: $F = 38.40$, $p < .001$, $\eta_p^2 = .55$). There was also a marginal group difference, where the low group elicited longer RTs with TTI increments than the high group (linear intervals × high < low: $F = 3.34$, $p = .077$, $\eta_p^2 = .09$). There was no group main effect.

Figure 7 about here.

4. Discussion

The current study explored whether WM could predict TTI effects in components of the P300 in young, healthy adults. Participants completed a battery of cognitive tests and a carefully constructed auditory equiprobable Go/NoGo task with manipulations of TTI. Participants were sorted according to their WM, and their TTI-determined P300s were analysed. Our TTI-P300 component and RT findings were consistent with previous research exploring TTI effects on the global P300 complex (Croft et al., 2003; Gonsalvez et al., 1999, 2007; Gonsalvez & Polich, 2002; Steiner et al., 2013), with TTI effects apparent in RTs,

target P3b and SW responses. These TTI effects differed between groups for the P3b component only, with the high WM group eliciting a steeper increase in P3b amplitude than the low group, a novel finding that provides support for the template-update model.

A number of components were visually identifiable in the grand mean ERPs (P1, N1-1, P2, N2, P3b, and SW), and several others emerged with the PCA (N1-3, PN, uN2, uP3, an unidentifiable component, and a VLN). Only the components identifiable as part of the P300 complex (P3b, uP3, SW) were retained for analysis, as no predictions could be made about memory-related differences in TTI effects for the other ERP components. To better understand the mechanism of TTI effects, future research should seek to examine where the sequential processing that leads to TTI effects in P300 components begins, that is, whether systematic TTI effects are also present in earlier ERP components (e.g., P1, PN, N2). Further research is also required to establish the validity and utility of the VLN identified here, particularly in the light of Verleger and Möcks' (1987) suggestion that such a late component may reflect misallocation of variance from a monotonic trend in the data. We note however, that when the epoch is extended to 1 s post-stimulus (see Figure 2), the VLN component resolves (at Fz and Cz), especially for nontargets, suggesting that it is most likely a real component. The possibility that the VLN is related to response processing should also be considered due to its strong left hemispheric bias (see Figure 4) and our predominantly right-handed sample. This could imply contralateral motoric contribution and should be considered in conjunction with the left-hemispheric reduction in P3b, a finding similar to Jentzsch and Sommer (2001). Those authors suggested that a reduction in P3(00) amplitude in the hemisphere contralateral to the responding hand may be related to an overlapping negative-going readiness potential.

As apparent in Figure 2B, WM appeared to have a direct effect on the global P300, with larger P300s for the high compared to the low memory group; a finding in line with

previous research (Polich et al., 1983, 1990b). In the current study, however, this main effect failed to reach statistical significance in the P3b, uP3, and SW components. Visual inspection of the grand means (Figure 2A) also reveals P300 differences for the two stimulus types (i.e., Target > Nontarget). Although not tested here, this difference is most likely attributable to the specific nature of the equiprobable task (see Barry & Rushby, 2006). That is, the lack of a probability bias towards one stimulus type places no strict demand on response requirements (e.g., inhibition vs. rare target detection). Thus, larger P300s to targets can be attributed to the only difference between stimulus types: task-relevance (not probability). This stimulus-related difference was also apparent in P3b, uP3, and SW components.

Two of the three P300 components identified here, P3b and SW, demonstrated a linear increase in target response amplitudes with extensions of TTI. The uP3, however, did not demonstrate this increase. This finding contributes to research examining inter-target interval effects on the P300 as it suggests that multiple components in this complex are responsive to this particular stimulus manipulation, emphasising the importance of separating the P300 into its various components, rather than treating it as a unitary construct. The target P3b seen here shared the characteristics of the P3b (paretial scalp distribution, latency ~ 300 ms, large target response) previously identified by Barry and Rushby (2006) in an equiprobable Go/NoGo task. Given this component is generally enhanced to target stimuli, it was not unexpected that an increase in P3b amplitude to longer TTIs was observed here. It is also not surprising that TTI effects are apparent in the classic SW, given that these effects were identified in previous P300 peak-data studies and the SW contributes substantially to the P300 complex. Although the uP3 was greater parietally for targets and frontally for nontargets, the uP3 was not a readily identifiable component, making any WM, TTI or stimulus-related differences difficult to interpret. The uP3 explained a small proportion of

the overall variance (2.2%), and the possibility that this component is merely noise should not be ruled out.

Following on from the previous point, it should also be noted that the P3a component (typical frontocentral positivity occurring ~ 60 – 80 ms *prior* to the P3b, often associated with an attentional shift; Nieuwenhuis et al., 2005; Polich, 2007) was not identifiable in the data presented here; an unexpected result, given that the P3a component is identifiable in equiprobable Go/NoGo tasks (Barry & Rushby, 2006). This may be an outcome of the unique paradigm employed here, where stimuli were interspersed with silence, making the sequence unpredictable (Figure 1). It is reasonable to suggest that the ambiguous nature of the task resulted in high attentional demands overall (i.e., no regular switching of attention), and this may have contributed to the lack of an identifiable P3a component.

As predicted, the P3b component evidenced a steeper increase in amplitude to TTI increments in the high compared to the low WM group. This is a unique finding that supports the template-update model (Gonsalvez et al., 2007) and provides a direct link between the TTI/P300 relationship and WM. That is, individuals with poor WM may not have effectively updated their neural representation of events (due to inadequate encoding/updating, or fast decay processes); this could be related to activation of associative networks that are less effective. A further prediction of this model would be that a steeper TTI-P300 function would also be seen for younger compared with older adults, due to the deterioration of WM capabilities among the latter group. Importantly, the present result was found while using a paradigm where probability, stimulus sequences, and ISI were controlled, which implies that these results are not directly related to subjective probability/expectancy (Donchin, 1981; Donchin & Coles, 1988; Squires et al., 1977; Verleger, 1988). This suggests that "update" is not occurring for the context (as suggested by Donchin & Coles, 1988), but for the template or memory-trace. That is, the link between TTI

and memory is direct and independent of subjective probability, as the template-update model predicts.

Furthermore, the finding that TTI effects in the P3b are related to WM, and the lack of a group main effect, suggests that TTI effects are a *direct* outcome of memory-update, but that an omnibus measure of P3b amplitude (across TTIs) is a less sensitive metric. That is, if overall P3b amplitudes represent a cumulative measure of template activation, this is likely to be influenced by both an element of template-update/decay and basal levels of activation, determined by non-memory factors such as individual trait differences in activation levels, attention, and arousal (e.g., greater P300 amplitudes seen for high vs. low intensity tones, Gonsalvez et al., 2007). This first element is better captured by a function of P3b changes associated with TTI. Following on, there is a substantial body of evidence to suggest that the P3b is generated in areas of the temporal and parietal cortex (for a review, see Polich, 2007), and that these structures are not directly linked to memory (Verleger, 2008; Verleger et al., 1994). Thus, it is possible that in the current study WM affected the TTI mechanism and this process, in turn, modulated the P3b. That is, processes that have been linked to both P3b elicitation and the functional role of temporal-parietal brain regions (Corbetta et al., 2000; Downar et al., 2002; Todd et al., 2005), such as attention and decision-making (Nieuwenhuis et al., 2005; Polich, 2007; Verleger, 2008; Verleger et al., 2005), may also be linked to the TTI-mechanism. Further research that clarifies the neural substrates underlying TTI effects is required.

In sum, the current study extended previous research investigating temporal effects on the global P300 by examining TTI effects in components of the P300 using a PCA: both P3b and SW components demonstrated TTI effects. Importantly, this study found that WM predicted TTI effects in the P3b, with the high WM group eliciting a steeper increase in P3b amplitude to longer TTIs than the low WM group. This is a valuable finding that indicates a

link between TTI effects and WM, and confirms a prediction derived from a template-update model. By offering a mechanism for TTI effects, the template-update perspective facilitates the exploration of memory-update, without reference to subjective probability, and can be employed as a framework to guide future clinically-based research (e.g., populations with memory deficits, such as Alzheimer's disease).

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Figure Legends

Figure 1. Example of the stimulus sequence: T = Targets; N = Nontargets; silence is indicated by the shaded rectangles. The arrow below illustrates time, with each increment (shown here as rectangles) representative of the 1 s SOA. An example of three sequential TTIs is indicated above: TTI = 5, 1, and 10 s.

Figure 2. Panel A: ERPs at midline sites for targets and nontargets (left column). The pre-EOG corrected data at Fz, averaged across all participants, groups, and stimuli, is overlayed in the dashed line in the uppermost panel. Virtual ERPs derived from the sum of the twelve temporal PCA factors (right column). The dashed lines mark the sum of three virtual P300 components (P3b, uP3, SW) at the site where the P300 component is maximal (Pz). Panel B: Average ERP waveforms for high and low groups. Larger P300 complexes are visible for the high than the low group to both targets (left panel) and nontargets (right panel).

Figure 3. Grand average target ERP waveforms from midline sites for the five TTIs. Interval effects in the P300 component are apparent at Pz. Mean vertical EOG (VE) is displayed for each of the TTIs below before EOG correction.

Figure 4. Temporal PCA factor loadings scaled to μV as a function of time. The topographic headmaps and factor information for the virtual temporal components are displayed above. Headmaps are averaged across stimulus type, group, and TTI.

Figure 5. Panel A: Target and nontarget headmaps for P3b, uP3, and SW averaged across interval and group. Panel B: Headmaps for P3b, uP3, and SW target responses for the two WM groups averaged across interval (Column 1), and separately for the five TTIs (Columns 2

– 6).

Figure 6. Panel A: Mean P3b amplitude at frontal (F: F3, Fz, F4) and parietal (P: P3, Pz, P4) sites across all subjects, groups, and TTI, separately for targets and nontargets. Panel B: The difference between frontal and parietal target P3b amplitude (parietal minus frontal) across subject and group as a function of TTI. Panel C: Illustration of the sagittal × group × interval interaction. The fronto-parietal difference in target P3b amplitude is plotted separately for the two groups as a function of TTI. A steeper increase in P3b amplitude can be seen for the high compared to the low WM group.

Figure 7. Mean RT as a function of TTI separately for high and low groups. Groups are fitted with separate linear trends to demonstrate the between group difference in RT as a function of TTI (marginal group × linear trend interaction).

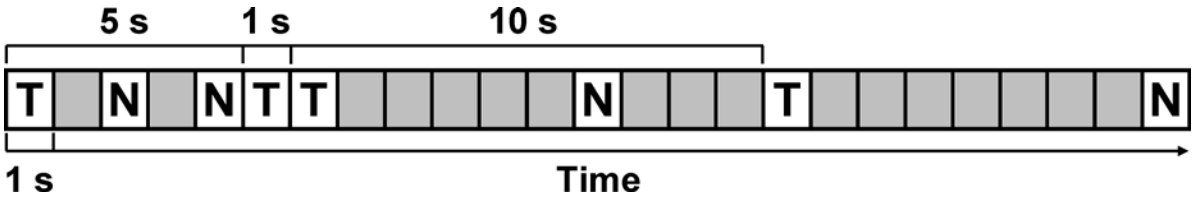

Figure 1

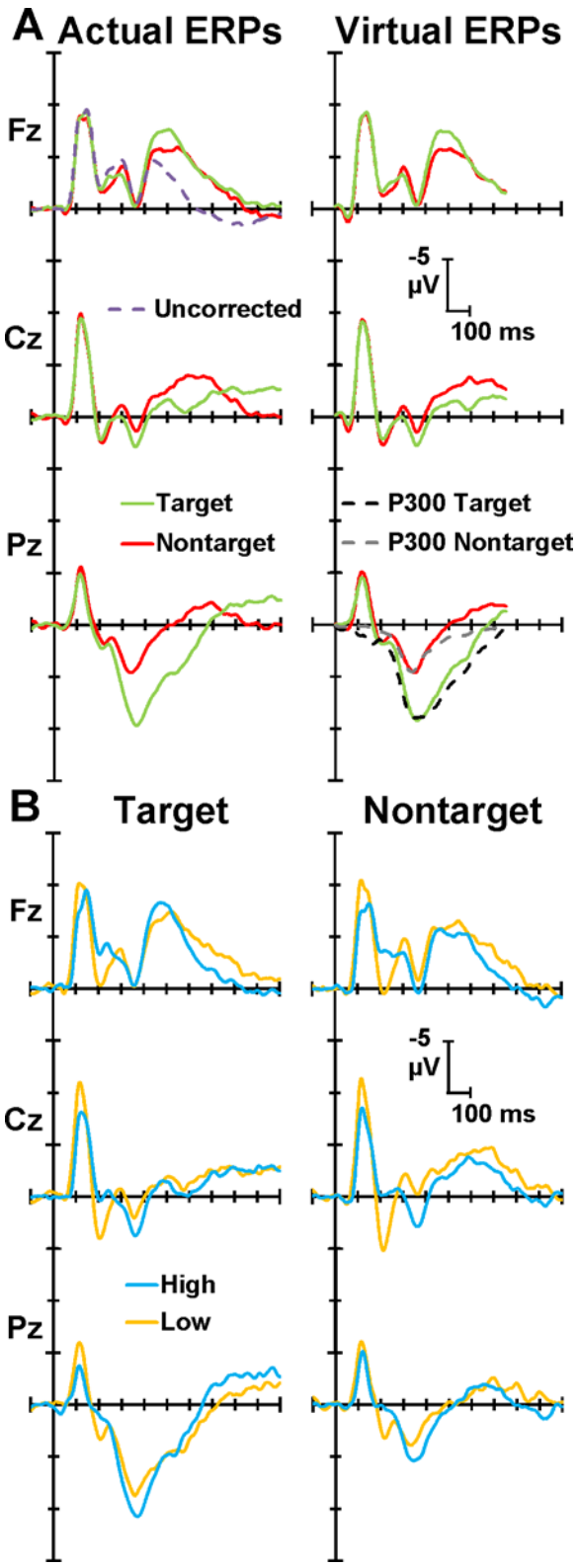
A
Actual ERPs
Virtual ERPs
Fz
Cz
Pz
Uncorrected
Target
Nontarget
-5
μV
100 ms
P300 Target
P300 Nontarget
B
Target
Nontarget
Fz
Cz
Pz
High
Low
-5
μV
100 ms

Figure 2

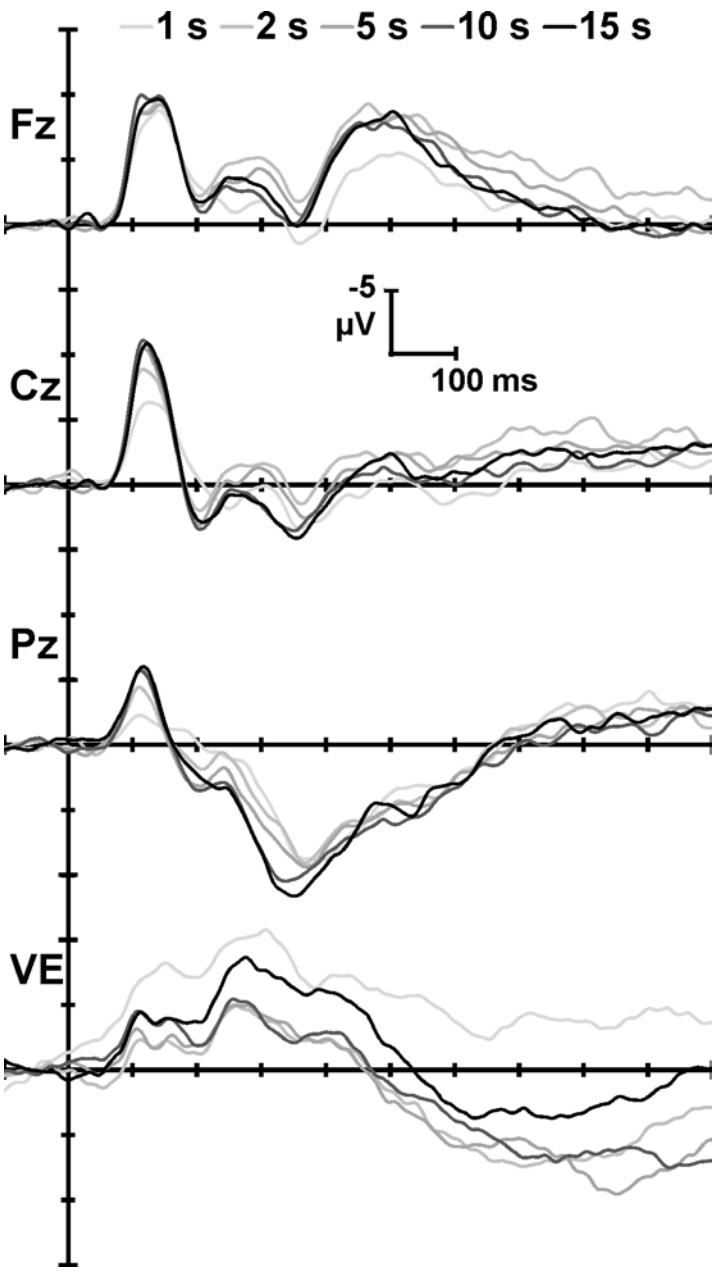

Figure 3

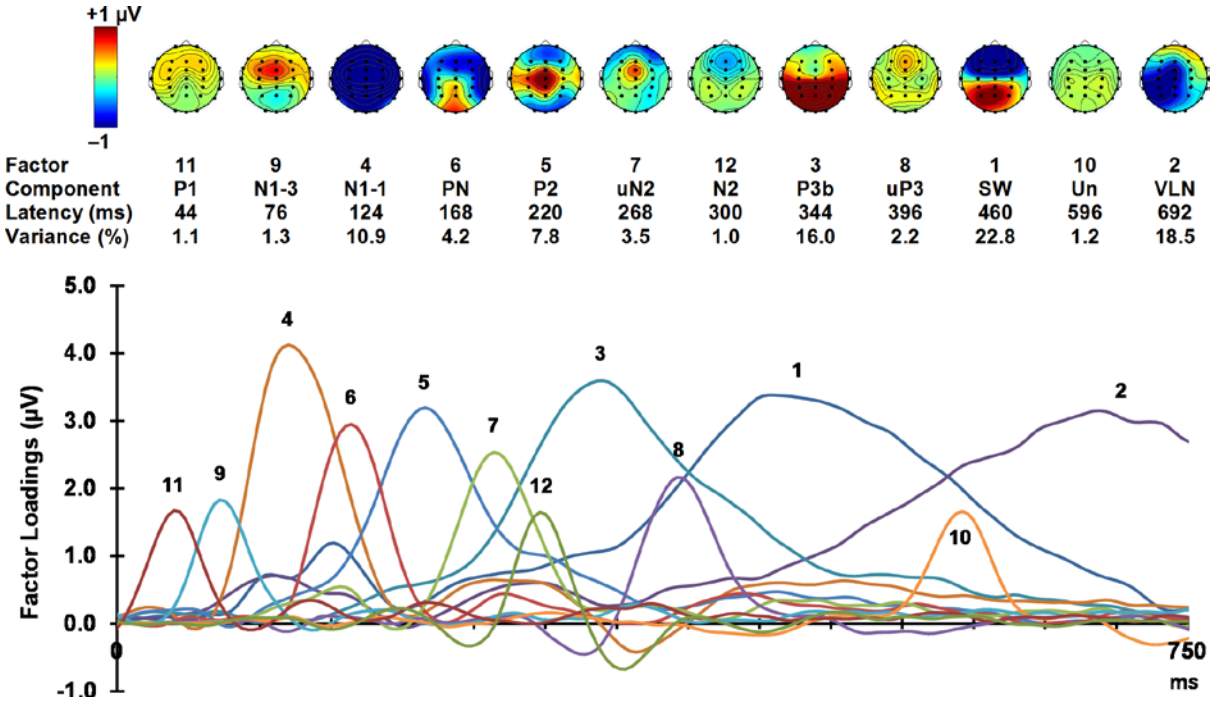
+1 µV
−1
Factor 11 9 4 6 5 7 12 3 8 1 10 2
Component P1 N1-3 N1-1 PN P2 uN2 N2 P3b uP3 SW Un VLN
Latency (ms) 44 76 124 168 220 268 300 344 396 460 596 692
Variance (%) 1.1 1.3 10.9 4.2 7.8 3.5 1.0 16.0 2.2 22.8 1.2 18.5
Factor Loadings (µV)
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
0
750
ms

Figure 4

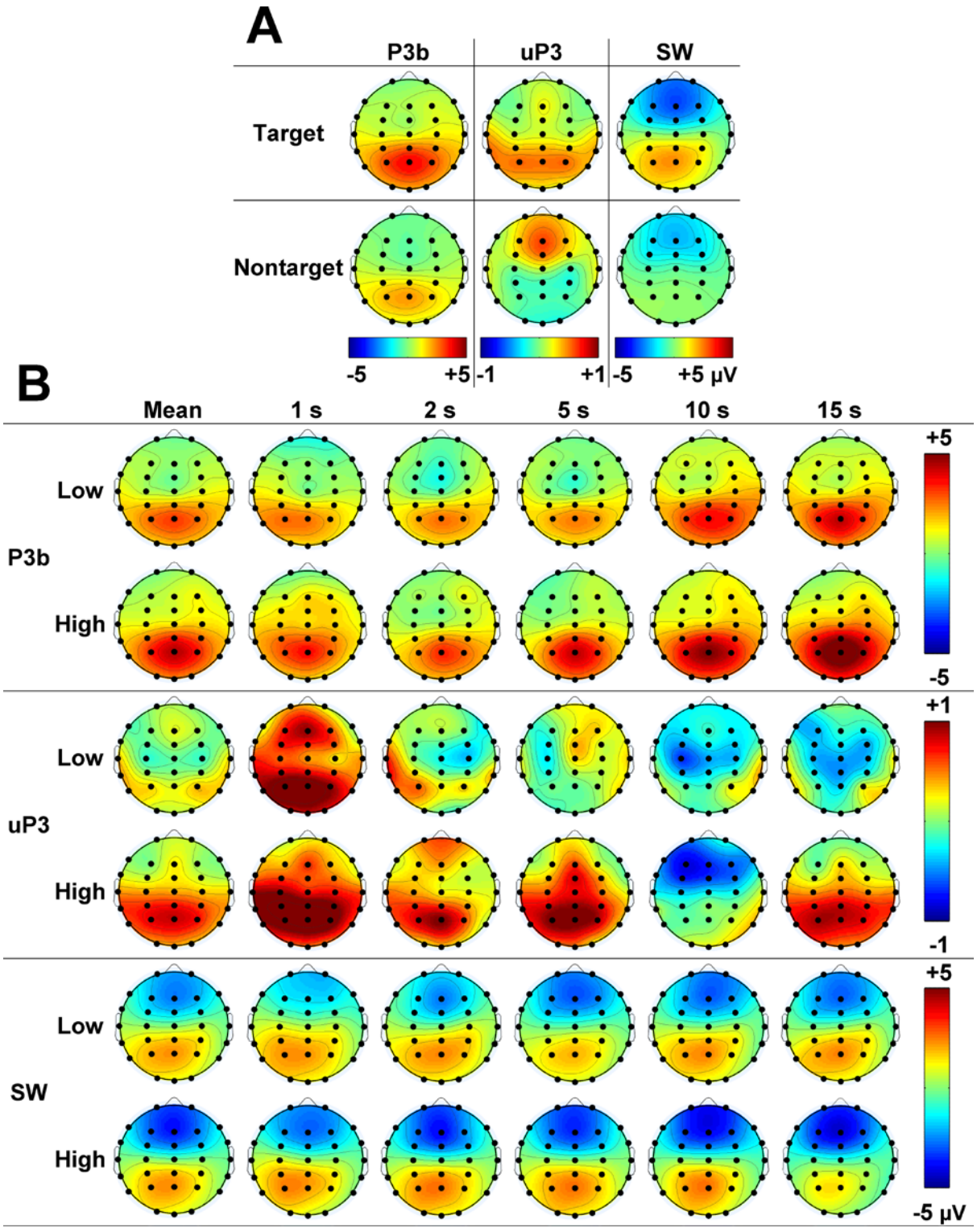
A
P3b
uP3
SW
Target
Nontarget
-5
+5
-1
+1
-5
+5 µV
B
Mean
1 s
2 s
5 s
10 s
15 s
P3b
uP3
SW
Low
High
+5
-5
+1
-1
-5 µV

Figure 5

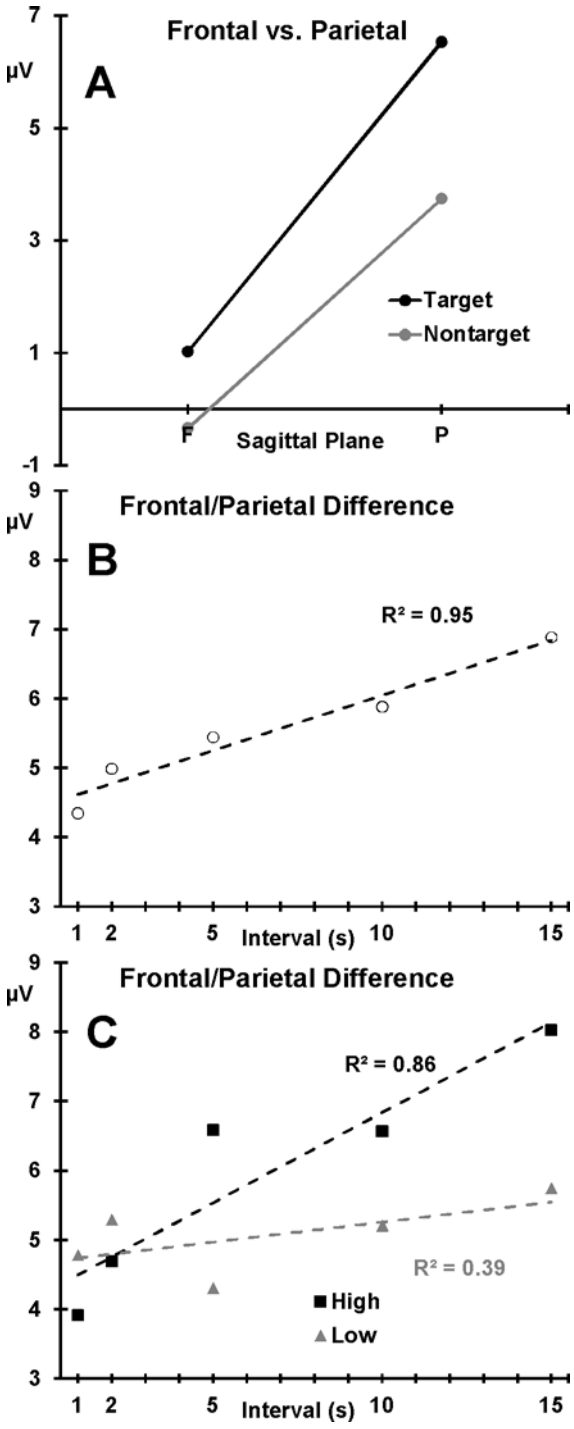
Frontal vs. Parietal
A
μV
7
5
3
1
-1
Target
Nontarget
F
Sagittal Plane
P
Frontal/Parietal Difference
B
μV
9
8
7
6
5
4
3
R² = 0.95
1
2
5
Interval (s)
10
15
Frontal/Parietal Difference
C
μV
9
8
7
6
5
4
3
R² = 0.86
R² = 0.39
High
Low
1
2
5
Interval (s)
10
15

Figure 6

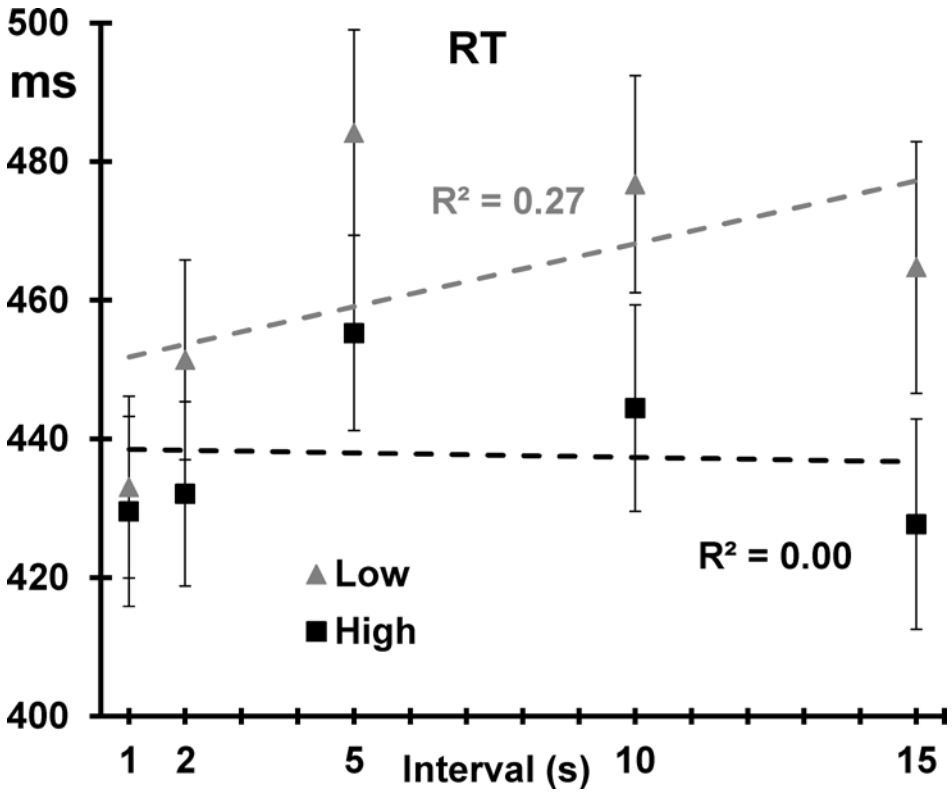
RT
500
ms
480
460
440
420
400
R² = 0.27
R² = 0.00
Low
High
1
2
5
10
15
Interval (s)

Figure 7