

Inter- and intra-individual coupling between pupillary, electrophysiological, and behavioral responses in a visual oddball task

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Abstract

Although the P3b component of the event-related brain potential is one of the most widely studied components, its underlying generators are not currently well understood. Recent theories have suggested that the P3b is triggered by phasic activation of the locus-coeruleus norepinephrine (LC-NE) system, an important control center implicated in facilitating optimal task-relevant behavior. Previous research has reported strong correlations between pupil dilation and LC activity, suggesting that pupil diameter is a useful indicator for ongoing LC-NE activity. Given the strong relationship between LC activity and pupil dilation, if the P3b is driven by phasic LC activity, there should be a robust trial-to-trial relationship with the phasic pupillary dilation response (PDR). However, previous work examining relationships between concurrently recorded pupillary and P3b responses has not supported this. One possibility is that the relationship between the measures might be carried primarily by either inter-individual (i.e., between-participant) or intra-individual (i.e., within-participant) contributions to coupling, and prior work has not systematically delineated these relationships. Doing so in the current study, we do not find evidence for either inter-individual or intra-individual relationships between the PDR and P3b responses. However, baseline pupil dilation did predict the P3b. Interestingly, both the PDR and P3b independently predicted inter-individual and intra-individual variability in decision response time. Implications for the LC-P3b hypothesis are discussed.

KEYWORDS

LC-NE, LC-P3, methods>EEG, methods>pupillometry, P3b

1 | INTRODUCTION

The P300 (P3b) is a positive-going ERP component. Its amplitude is primarily affected by the temporal frequency of a stimulus, such that stimuli that occur less frequently over time yield higher amplitude (more positive) responses compared to those that have occurred more frequently (see

Polich, 2007; Verleger, 2020). P3b amplitude is also known to be affected by attention and motivation (see Polich, 2007). The P3b is commonly elicited via the oddball task, in which the participant is required to differentiate between frequent “standard” stimuli and infrequent “deviant” stimuli (e.g., Donchin et al., 1978). The exact function of the P3b remains under considerable debate, but many theories suggest that the

activity underlying this response plays a vital role in facilitating response selection in decision tasks (e.g., O'Connell et al., 2012; Philiastides et al., 2014; Twomey et al., 2015; see Verleger, 2020 for a comprehensive review). The P3b's importance to response selection makes it a useful component for understanding the neural computations that underlie effective task performance.

Although much has been learned about both the eliciting conditions and functional significance of the P3b, its neurophysiological origins remain elusive. Early studies investigating the neural generators of the P3b did not lead to any conclusive or likely single generator (for review see Nieuwenhuis et al., 2005; although see Bledowski et al., 2004 & Verleger et al., 1994 for background on areas that make important contributions to the P3b). Instead, the evidence seems to suggest multiple cortical and subcortical regions that contribute to the scalp-recorded P3b response (e.g., Kirino et al., 2000; McCarthy et al., 1997; Pineda et al., 1989; Smith et al., 1990; Soltani & Knight, 2000). Thus, the P3b might better be described as reflecting the activity of a large-scale neuromodulatory system, and one promising candidate is the locus-coeruleus norepinephrine (LC-NE) system (Nieuwenhuis, 2011; Nieuwenhuis et al., 2005; Pineda et al., 1989).

The locus-coeruleus, located in the pons, is the brain's source of norepinephrine (NE; Berridge & Waterhouse, 2003). Adaptive Gain Theory (Aston-Jones & Cohen, 2005) suggests that this system plays an essential role in receiving environmental and contextual information about task goals and utility from the pre-frontal cortex, and then using this information to regulate arousal state and optimize behavioral performance. Research in primates has identified two modes of LC-NE activity: tonic and phasic firing. Tonic activity is roughly linearly related to general arousal level and quadratically related to behavioral performance, such that intermediate tonic activity levels predict the highest task performance (for reviews, see Aston-Jones & Cohen, 2005; Nieuwenhuis et al., 2005). Phasic activity is reflected by transient bursts of high-frequency (~20 Hz) activity superimposed on the tonic signals and is thought to relate to the processing of task-relevant stimuli. It occurs primarily during intermediate levels of tonic arousal after stimulus presentation and is tightly locked to response characteristics (for a review, see Nieuwenhuis et al., 2005). Because of its close relationship to task-related events, it is specifically this phasic response that researchers suggest may be reflected by the P3b response (Nieuwenhuis et al., 2005; Pineda et al., 1989).

In detailed reviews, Nieuwenhuis (2011) and Nieuwenhuis and colleagues (2005) outline evidence to support a theoretical framework arguing that the P3b reflects phasic LC-NE activity. Similarly to the P3b, the LC-NE phasic response is also elicited by an oddball paradigm (e.g., Aston-Jones et al., 1994, 1997; Rajkowski et al., 1994; Swick et al., 1994)

and is sensitive to attention and motivation (e.g., Berridge & Waterhouse, 2003; Kok, 1990, 2001; Mückschel et al., 2017; Polich & Kok, 1995; Pribram & McGuinness, 1975; Unsworth & Robison, 2017). Furthermore, lesions to the LC, direct manipulation of noradrenergic agents, and genetic influences on adrenergic pathways are all known to influence the amplitude of the P3b (Glover et al., 1988; Liu et al., 2009; Pineda et al., 1989; Swick et al., 1994). Recently, optogenetic stimulation of the LC-NE neurons in rats produced a P3b-like response (Vazey et al., 2018). Although there is compelling empirical support for the idea that the P3b may reflect phasic LC-NE activity, it has not been easy to directly confirm this hypothesis in humans. The LC-NE system is a difficult-to-reach imaging target (e.g., Astafiev et al., 2010; Elman et al., 2017; Murphy et al., 2014; though see recent developments in Chen et al., 2014; Dahl et al., 2019; Mather et al., 2020; Priovoulos et al., 2018), and activity in this structure can not be localized via surface M/EEG recordings. To assess whether or not phasic LC-NE activity generates the P3b, consideration of other biomarkers of LC-NE activity can be useful. One such candidate measure is the pupillary response to task-related stimuli.

There is strong evidence to suggest that the pupillary response directly maps onto tonic and phasic activity of the LC-NE system (de Gee et al., 2017; Murphy et al., 2014), such that the pupillary response has been used as a proxy for LC-NE activity in various studies (e.g., Gilzenrat et al., 2010; Nassar et al., 2012; Smallwood et al., 2011, 2012; however, see Joshi & Gold, 2020 for a description of other potential contributors to pupil size). Consistent with this LC-P3b theory, the PDR response is elicited under remarkably similar circumstances as the P3b response (Nieuwenhuis, 2011) and the LC phasic response. The oddball task, which is known to elicit a robust P3b response, also elicits a larger PDR to deviant stimuli compared to standards (e.g., Friedman et al., 1973; Gilzenrat et al., 2010; Hong et al., 2014; Korn & Bach, 2016; Liao et al., 2016; Marois et al., 2018; Quirins et al., 2018; Steiner & Barry, 2011; Wetzel et al., 2016). Similarly, the antecedent conditions that generate the PDR response are remarkably similar to the antecedent conditions that generate the P3b (e.g., Friedman et al., 1973; Kamp & Donchin, 2015; Murphy et al., 2011). Therefore, taking the PDR as an indirect proxy measurement for LC-NE activity, if the LC-P3b theory is correct, there should be a strong relationship between the P3b and the PDR. However, few studies have examined the two responses simultaneously.

To our knowledge, only two studies have examined the relationship between the P3b and pupil dilation in human subjects (Kamp & Donchin, 2015; Murphy et al., 2011), and both have failed to find evidence in support of a strong relationship between the P3b and PDR. However, it is worth noting a few potential limitations of the design and analyses of these prior studies that could obscure the

relationship between P3b amplitude and phasic pupil dilation. First, Kamp and Donchin (2015) used a non-canonical categorization task consisting of words and images, which is potentially problematic as conditions vary semantically and can elicit N400 responses at around the same time as the P3b response (e.g., Kutas & Iragui, 1998), potentially confounding the results. Moreover, the canonical two-stimulus oddball task elicits the strongest P3b and PDR responses in humans (e.g., Donchin et al., 1978; Friedman et al., 1973; Gilzenrat et al., 2010; Hong et al., 2014; Korn & Bach, 2016; Marois et al., 2018; Polich., 2007; Pritchard, 1981; Steiner & Barry, 2011; Wetzel et al., 2016) as well as robust LC-activity in animal studies (e.g., Aston-Jones et al., 1991, 1994; Rajkowski et al., 1994, 2004; Swick et al., 1994). To date, there has not yet been an investigation on the relationship between pupillary and ERP responses using a canonical, 2-stimulus visual oddball task. Moreover, although both previous studies used single-trial analytical techniques, neither chose an approach that also examines the contribution of individual differences (i.e., between-subject relationships). Within-subject, intra-individual effects and between-subject inter-individual effect represent independent sources of variability that both contribute to the variability in any given outcome measure (e.g., Boy & Sumner, 2014). Therefore, direct inclusion of both analytical techniques in addition to the univariate outcomes would be a useful extension of the literature. Moreover, our approach involved adopting linear mixed-effects models, which allows us to properly model between-subject and within-subject sources of variation via random effects (i.e., as opposed to Kamp and Donchin (2015), who fit a single linear regression model to the disaggregated data). Additionally, we modeled all single-trial predictors as continuous variables, rather than binning predictors, as this form of aggregation can result in issues such as reduced power to detect effects and increased false positives (e.g., MacCallum et al., 2002; Royston et al., 2006). Therefore, we conducted a standard, two-stimulus visual oddball task to simultaneously examine pupillary and ERP indices of task-related decision making. Importantly, we separately examined both inter-individual (i.e., between-subjects) and intra-individual (i.e., within-subjects) relationships between the P3b, PDR, and response behavior (decision response time).

2 | METHOD

2.1 | Participants

We recruited 36 participants (19 male, 17 female; mean age = 20 years, $SE = .27$) from the subject pool in the Department of Psychology at the University of Illinois.

Participants had normal or corrected-to-normal vision and no neurological disorders. All participants were right-handed native English speakers. Note that the handedness and native English speaker inclusion criteria were used because the same participants subsequently completed a language experiment that was unrelated to the current study. We dropped 13 participants due to either error within the eye-tracking system preventing data collection (two participants) or excessive artifact rejections due to blinking (greater than 50% of trials, 11 participants), for a final sample of 23 participants.

2.2 | Stimuli and procedure

Participants sat at a distance of 80 cm from a 21-inch CRT computer monitor in a quiet testing room with an ambient luminance of 65 lux. A chinrest was used to minimize head movements. Before the task, they were instructed to maintain their fixation on a fixation cross in the center of the screen and to reduce blinking as much as possible within each block. Stimuli were presented visually via SR-Research EyeLink experimental control software (SR-Research, Kanata, ON). Participants completed a standard two-stimulus oddball task (e.g., Luck et al., 2009). Stimuli were black letters and digits presented on a dark grey background to minimize the pupillary light reflex. Digits were randomly drawn from 1 to 9 (0 excluded because could be confused with O). Letters were randomly presented between A-K, excluding letters that may be perceptually ambiguous (e.g., B, I). Each stimulus subtended 1.07 degrees of visual angle at the viewing distance. Each stimulus was presented for 200 ms, followed by an inter-stimulus interval of 1,500 ms to allow for the slower latency of the pupil response. A total of 10 practice trials and 640 stimuli were presented. Experimental stimuli were divided into four blocks of 160 trials. In each half of the session, participants received one block in which digits appeared on 80% of the trials (and thus were standards), and letters appeared on 20% of the trials (and thus were deviants). In the other half of the blocks, the mapping was reversed, such that the letters appeared 80% of the time, and digits appeared on 20% of trials, with order counterbalanced across participants. Participants were asked to classify each stimulus as a standard or deviant by responding on a response pad with the right or left index finger. Response hand was counterbalanced across standard and deviant conditions across blocks, such that every combination of response hand and relative probability for each stimulus was tested for each participant in a separate block. This also helped us control for LC-NE activity elicited by voluntary movement (e.g., Yebra et al., 2019), as the participant was always responding to every stimulus, counterbalanced across the response hand.

2.3 | EEG and pupil recording

We recorded EEG from 26 evenly spaced (for montage, see Figure 1) silver-silver chloride electrodes embedded in an EasyCap (EasyCap, Herrsching, Germany). Electrodes were referenced online to the left mastoid. Additionally, we placed one electrode on the left infraorbital ridge to monitor for vertical eye movements and blinks, and another two electrodes on the outer canthus of each eye to monitor for horizontal eye movements. We kept electrode impedances below 5 k Ω . The continuous EEG was amplified with a BrainAmp DC (Brain-Vision, LLC, Morrisville, NC) amplifier (high-pass filtered: 0.02 Hz, low-pass filtered: 250 Hz) at a sampling rate of 1,000 Hz.

We recorded pupil data using an Eye-Link 1,000 desktop-mounted eye tracker at a sampling rate of 1,000 Hz. Each participant was calibrated and validated upon set up to ensure that no issues arose (i.e., glasses impeding the eye-tracker) that would prevent quality data collection. We found that we were able to perform valid eye-tracking on all subjects. Viewing was binocular, but only pupil dilation from the right eye was recorded. A fixation correction was presented between each trial to check that the system was still correctly calibrated. In cases where a minor drift occurred, the system auto-corrected before the beginning of the trial. In rare cases where calibration was lost, the experiment was paused, and the eye-tracking system was completely recalibrated before moving forward.

2.4 | EEG processing

All EEG analyses were done using the EEGLAB and ERPLAB toolboxes (Lopez-Calderon & Luck, 2014) in MATLAB (The MathWorks, 2014). Data were first down-sampled to 250 Hz, and bandpass filtered (0.1 to 30 Hz, roll-off slope: 12 dB/octave). An offline bipolar vertical ocular channel was created for artifact rejection by subtracting the left lower eye electrode from a prefrontal electrode directly above the left eye. Likewise, an offline bipolar horizontal ocular channel was created by subtracting the right horizontal eye channel from the left horizontal eye channel. Data were epoched from -100 ms to 1,500 ms relative to stimulus presentation. These epochs were sorted into separate bins for the deviant and standard stimuli for analyses. We performed further artifact rejection offline before averaging, by setting individual thresholds for blinks and eye movements through condition-blind visual inspection. These thresholds were applied to all trials within individual subjects equally. Data were re-referenced offline to the average mastoids. Artifact-free ERPs were averaged by stimulus type (deviant and standard) after subtracting the 100 ms pre-stimulus baseline.

To measure the P3b, we calculated mean amplitude at an a priori midline parietal channel (corresponding

approximately to position Pz in the International 10–20 system), where the P3b is typically maximal. An a priori measurement window size of 300 ms was used based on prior work (e.g., Luck et al., 2009). Because the P3b can show a considerable change in latency across task context, we used a collapsed localizer technique across both stimulus types on the grand-averaged ERP to select the temporal region of interest (tROI) (Luck & Gaspelin, 2017). Note that because this approach collapses across the effect of interest (the standard vs. deviant trials), this data-driven tROI selection does not bias subsequent analyses (Kriegeskorte et al., 2009). Using this approach, we identified a peak latency of 448 ms and selected a window of 298 to 598 ms. We extracted the mean amplitude of the deviant and standard waveforms from both the subject-averaged ERPs (for the univariate and individual difference analyses) and the individual trials for the intra-individual analyses (see below). Single trial-mean amplitudes were measured at the same channel and in the same time window on the individual trials after single-trial baseline correction (see Payne & Federmeier, 2017; Payne et al., 2015, for more detail).

2.5 | Pupil-data processing

All pupil data were processed using the R language for statistical computing (R Core Team, 2019). The pupil data were first epoched from 0 to 1,400 ms using the EyeLink DataViewer software. The epoched pupil data were then imported into R and processed in five steps. The first step was to remove any dilation speed outliers. For this, we followed a similar procedure to that outlined in Kret and Sjak-Shie (2019). Removing dilation speed outliers is vital because some eye-trackers will temporarily identify something as part of the pupil when it is not (i.e., eyelash, etc.). The second step was to identify and remove eye blinks. Eye blinks were identified as gaps in the data of at least 80 ms. Once the eye blinks were identified, 50 ms of data were removed on either side of the blink. If more than 50% of the data on a trial were missing after these first two steps, the trial would be rejected from further processing and analysis. The third step was to use linear interpolation to fill in gaps in the data. The fourth step was to filter the data using a low-pass 12 dB/octave Butterworth filter with a half-amplitude cut-off of 10 Hz. The fifth and final step was to baseline correct the data using a baseline period of 0–50 ms. Using a short, post-stimulus baseline with pupillometry data is justified, given the relatively slow changes of task-evoked pupillary dilation responses. Additionally, given the sustained nature of the PDR, we reduce the likelihood of baselining into an effect of interest from the previous trial by avoiding using a pre-stimulus baseline (though,

to be cautious, we do control for pre-stimulus pupil size as well, see data analytical plan below).

To select the appropriate time window for calculating the mean PDR amplitude, we used a mass univariate statistical technique often used in ERP research (Fields & Kuperberg, 2020; Groppe et al., 2011). Using the baseline-corrected data and ignoring experimental conditions, we ran a one-sample *t*-test at each time point, looking for time windows in which the data were significantly different from zero. The *t*-tests were corrected using the false discovery rate correction (Benjamini & Hochberg, 1995). Using this methodology, a time window of 560 ms to 1,400 ms was identified. This time window was used to calculate the mean pupil diameter amplitude for each subject (by condition) and for each individual trial. Trials marked for rejection in either the ERP pre-processing or pupil pre-processing pipeline were rejected in both modalities—therefore, we only included trials with useable data for both the P3b response and PDR. For all statistical analyses, we also excluded error trials, in order to avoid potentially confounding the P3b with the Pe response—a response locked component that occurs after error responses and has similar morphological characteristics to the P3b (Falkenstein et al., 2000; Overbeek et al., 2005).

The average number of trials included in ERP and pupil responses for each subject *after* excluding error trials and rejecting artifacts was 357.48 ($SE = 17.00$, range = 198–477) for standard trials and 87.26 ($SE = 5.35$, range = 42–119) for deviant trials.

2.6 | Data analysis plan

Our analytical plan included three stages of analysis. We first analyze and report the univariate responses to confirm the presence of an oddball effect in the P3b, PDR, and response times. Next, we report the inter-individual (between-subjects) relationships between the subject-average P3b, PDR, and RT. Finally, and importantly, we report the intra-individual analyses at the single-trial level to best understand the trial-to-trial dynamics of the P3b and PDR as it relates to behavior. In order to isolate the within-subjects variance, we subject mean-centered our predictors in the intra-individual analyses, allowing us to interpret trial-to-trial change directly in relation to each individual's own average (Enders & Tofighi, 2007), allowing us to avoid the “uninterpretable blend” (Raudenbush & Bryk, 2002, p. 139) of within- and between-subject contributions to the estimated fixed effect in the single trial analyses.

We ran all statistical models in R's (version 1.1.442) lme4 package (version 1.1-17) using the lmer function. Likelihood ratio tests, calculated using the “mixed” function from the “afex” package (version 0.22-1), were used

to test the significance of all fixed effects. To analyze the univariate data, we ran separate linear mixed-effects models for the RT data, PDR data, and P3b data as the response variables. Each model used a fixed effect of condition type (standard vs. deviant) and a random intercept for each subject.

2.6.1 | Inter-individual analyses

To understand the between-subjects relationships between response time, the PDR, and the P3b response, we ran linear mixed effect models on the subject-average PDR, RT, and P3b responses for the deviant and standard conditions. Subject was treated as a random intercept. We ran two models to explore the relationship between PDR amplitude and P3b amplitude, and each measure's relationship to behavior. Importantly, we focused on the interaction between each measure and stimulus type—deviant versus standard. We also included baseline pupil diameter as a covariate for both models, as previous work has documented relationships between baseline pupil size and the PDR (Murphy et al., 2011). For *Model 1*, we fit a linear mixed-effects model with PDR mean amplitude as the response variable, and with condition type (standard vs. deviant), P3b mean amplitude and their interaction as fixed effects. For *Model 2*, we fit a linear mixed-effects model with response time as the response variable and with condition type, P3b mean amplitude, the interaction between P3b amplitude and condition type, PDR mean amplitude, and the interaction between PDR amplitude and condition type.

2.6.2 | Intra-individual analyses

To analyze the intra-individual (within-subject) relationships between PDR, P3b amplitude, and response time, we fit two linear mixed-effects models (which we call *Model 3* and *Model 4*) that followed similar outlines as those described in the above section. Random intercepts by subject were fit for all models.¹ *Model 3* used single-trial PDR mean amplitudes as the response variable, with condition type (standard vs. deviant), single-trial P3b amplitude, and their interaction as fixed effects. For both *Model 3* and *Model 4*, we also included baseline pupil diameter as a control variable. All independent variables were subject-mean standardized to isolate

¹We did follow the advice for random slopes given by Barr and colleagues (2013) to “keep it maximal” and found that adding random slope effects did not significantly alter the outcomes of any of the models. Therefore, to be parsimonious and remain consistent in analyses across all models, we used a random intercept model for each rather than having different random slope structures for each model (see Bates et al., 2015).

intra-individual variability (Enders & Tofghi, 2007). For Model 4, we used single-trial response times as the response variable with condition type, single-trial PDR mean amplitude, the interaction between PDR amplitude and condition type, single-trial P3b mean amplitude, and the interaction between P3b amplitude and condition type. To facilitate the interpretation of significant interactions, we used the *emtrends()* function from the *emmeans* package in R (v1.4.3.01, Lenth et al., 2018) to calculate simple slopes and their corresponding 95% confidence intervals.

2.7 | Predictions

Before discussing hypotheses, we note here that, in all following statistical analyses, when we refer to the P3b, we specifically mean the EEG amplitude in microvolts during the P3b spatial-temporal window on a given trial. This is to say, while many studies examining individual differences in P3b effects choose the oddball *effect* (deviant- standard), we include condition (standard vs. deviant) as an independent variable in predicting P3b amplitude. This strategy was necessary for us to conduct single-trial analyses in the first place, as there is no difference “oddball effect” at the single-trial level, and we aimed for consistency when examining the between-subjects effect as well. Moreover, we note that P3b activity still occurs in standard trials at a lower amplitude (see Polich, 2012).

If the P3b and PDR are driven by the same underlying neural substrate, the LC-NE system, then we would predict that, for both inter-individual and intra-individual analyses, single-trial P3b amplitude would strongly and positively predict PDR amplitude, reflecting strong trial-to-trial relationships between these two signals. As for the relationship of each variable to response time, the literature has been less clear. Previous studies (i.e., Kamp &

Donchin, 2015; Murphy et al., 2011) that have examined the simultaneous effects of the PDR and P3b responses on response time have yielded mixed results. While Kamp and Donchin (2015) found independent positive effects of P3b and PDR latency on response time in both standard and deviant trials, they observed no relationships with amplitude. Moreover, Murphy et al. (2011) did not see reliable relationships between PDR and RT, but did observe a negative relationship between P3b amplitude and RT. Therefore, we predict that PDR and P3b responses will be related to response time at both the inter and intra-individual level, but we do not have strong directional predictions.

3 | RESULTS

3.1 | Univariate results

Participants, on average, responded more accurately to the standard trials compared to the deviant trials ($t(22) = 5.36$, $p < .01$, See Table 1), as expected. After removing error trials, we found a robust oddball effect (i.e., the difference between standard and deviant stimuli) for P3b amplitude, PDR amplitude, and response time (See Table 2; Figures 1–3), such that the EEG and pupil responses were larger and response time was slower for deviant stimuli. All descriptive statistics for the PDR, P3b, RT, and accuracy can be found in Table 1. Fixed-effect coefficients for each univariate oddball effect are presented in Table 2.

3.2 | Inter-individual analyses

Descriptive statistics for all inter-individual and intra-individual analyses can be found in Table 1, and coefficients can be found in Table 3. Before removing error trials, we examined

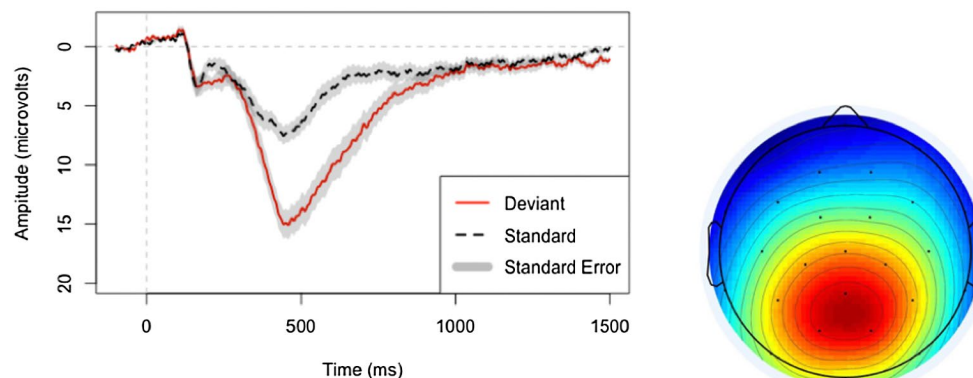


FIGURE 1 Left: Grand average P3b response to standard (dashed) and deviant (solid) stimuli at electrode MiPa (Midline parietal, the equivalent of Pz in 10–20 system). Negative is plotted up. Gray shades represent standard error of the mean (using inter-individual averages). Baseline is pre-stimulus, –100 ms to 0 ms. Right: Grand average scalp map of the difference wave (deviant—standard) of the P3b response from 298–598 ms

TABLE 1 Descriptive statistics for P3b, PDR, and RT

	Mean Pupil	SE pupil	Mean P3b	SE P3b	Mean RT	SE RT	Mean accuracy	SE accuracy
All trials—Standard	36.98	1.35	5.85	.10	470.34	1.52	.95	<.01
All trials—Deviant	89.00	2.76	11.17	.20	507.66	2.52	.85	<.01
Subject average—Standard	37.16	5.70	5.72	.61	469.19	16.87	.95	<.01
Subject average—Deviant	90.97	10.67	11.05	.88	505.43	14.86	.84	.02

TABLE 2 Univariate data. Condition differences on each outcome variable

	Beta estimates (unstandardized)	SE	χ^2	df	p
P3b amplitude	5.65	.22	618.38	1	<.001***
Pupil diameter	42.74	3.06	192.72	1	<.001***
Reaction time	52.62	2.87	331.32	1	<.001***

****p* < .001.

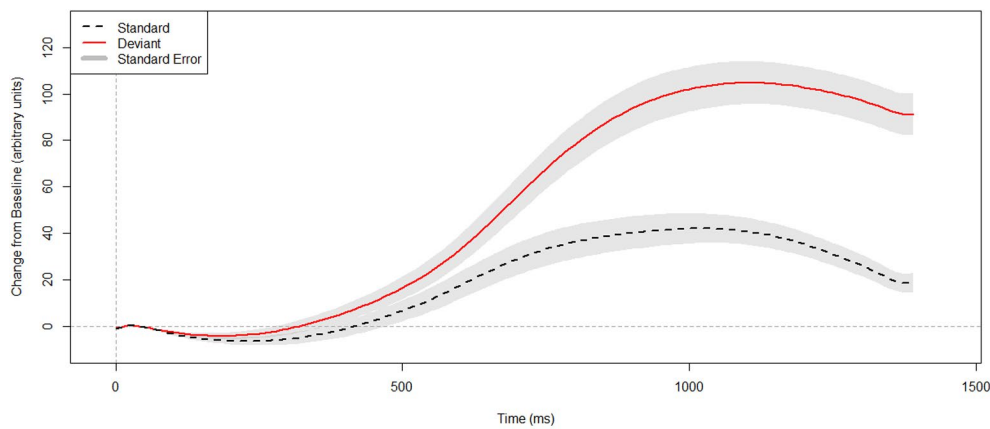


FIGURE 2 Grand average PDR response to standard (black) and deviant (red) stimuli. Standard error of the mean (using inter-individual averages) is shaded in gray. Positive is plotted up. Baseline is at stimulus, 0–50 ms

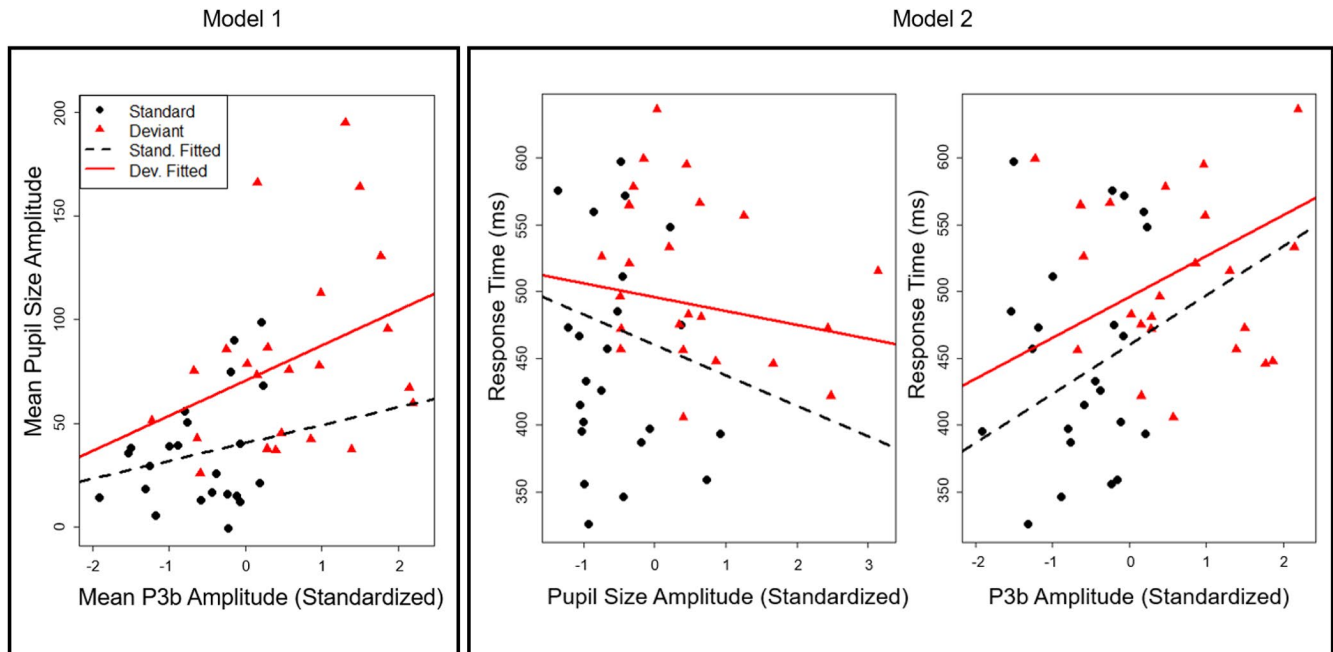


FIGURE 3 Model predicted best fit lines for P3b amplitude on pupil size (Model 1) and P3b amplitude and pupil diameter on response time (Model 2) at the inter-individual level

TABLE 3 Standardized coefficients for all four models

	Beta estimates (standardized)	SE	χ^2	df	p
Model 1: Inter-individual effects on pupil diameter					
Intercept	40.57	9.27	–	–	–
P3b amplitude	8.68	9.61	.81	1	.37
Condition	30.18	9.99	8.20	1	<.01*
P3b amplitude \times Condition	8.26	8.27	.96	1	.33
Model 2: Inter-individual effects on reaction time					
Intercept	460.34	16.57	–	–	–
P3b amplitude	36.75	11.22	8.38	1	<.01*
Pupil	–22.89	12.89	3.01	1	.08
Condition	35.47	12.03	7.95	1	<.01*
Pupil \times Condition	12.51	8.41	2.11	1	.15
P3b amplitude \times Condition	–6.14	7.90	.59	1	.44
Model 3: Intra-individual effects on pupil diameter					
Intercept	36.12	6.07	–	–	–
P3b amplitude	–.92	1.38	.99	1	.51
Condition	41.26	3.27	172.86	1	<.0001***
Baseline Pupil	–26.82	1.37	377.68	1	<.0001***
P3b amplitude \times Condition	1.85	3.07	.55	1	.55
Baseline Pupil \times Condition	–1.56	3.11	.04	1	.62
Model 4: Intra-individual effects on reaction time					
Intercept	470.72	15.71	–	–	–
P3b amplitude	3.33	1.31	6.43	1	.01
Pupil	9.61	1.34	51.62	1	<.0001***
Condition	57.69	3.20	320.57	1	<.0001***
Baseline pupil	7.84	1.34	34.34	1	<.0001***
Pupil \times Condition	–11.35	2.99	14.37	1	<.001**
P3b amplitude \times Condition	–15.97	2.93	29.72	1	<.0001***
Baseline pupil \times Condition	–9.42	3.05	9.56	1	<.01**

* $p < .05$; ** $p < .01$; *** $p < .001$.

whether an individual's average P3b or PDR amplitude influenced their average accuracy. After controlling for trial type, we did not find a significant effect of P3b or PDR amplitude on accuracy. All the following results have excluded error trials from analyses. For Model 1, we confirmed what was found in the univariate analysis of PDR—that PDR mean amplitude was predicted by stimulus type, such that deviant stimuli elicited a larger PDR response. However, PDR did not have a significant relationship with P3b amplitude, and the interaction between P3b amplitude and condition type did not predict PDR amplitude (see Figure 4, Model 1). Thus

we did not observe strong relationships between the P3b and PDR as a function of individual differences.

Our Model 2 analysis found that average response time was significantly slower for deviant stimuli than standard stimuli. There was a marginal but not statistically significant effect of PDR on RT such that larger average PDR amplitudes were associated with faster RTs (i.e., a numerical pattern opposite to our predictions). The interaction with stimulus type was not significant. We found that larger average P3b amplitude was associated with slower average response times overall (See Figure 4, Model 2). This effect was not qualified by an interaction with condition.

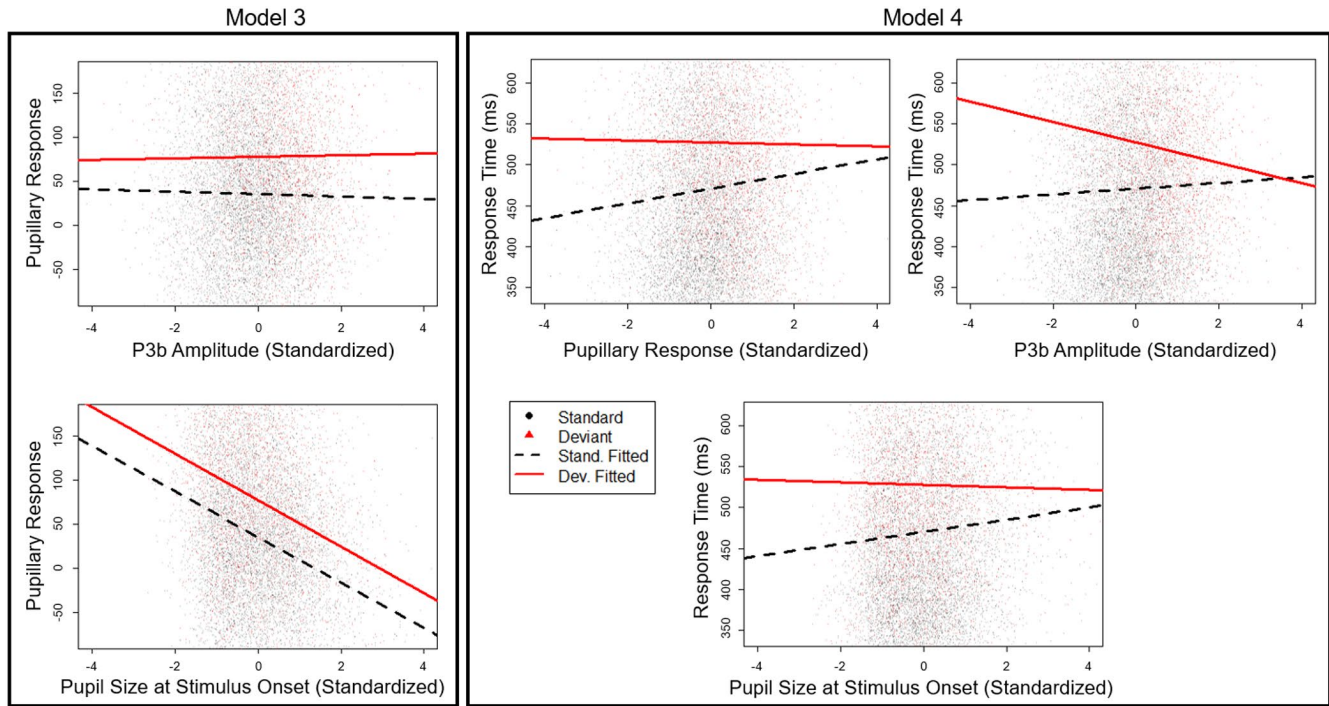


FIGURE 4 Model predicted best fit lines for P3b amplitude and baseline pupil size on the PDR (Model 3) and P3b amplitude, PDR diameter, and baseline pupil diameter on response time (Model 4) at the intra-individual level

3.3 | Intra-individual analyses

For all intra-individual analyses, baseline pupil size was included as a covariate into the models. For Model 3, we did find a main effect of baseline pupil size on the PDR, such that larger baseline pupil size predicted a smaller PDR. There was no interaction with stimulus type. After controlling for this covariate, we found that the results from Model 3 mirrored the results found in both the univariate and inter-individual analyses: PDR amplitude was predicted by stimulus type, such that PDR amplitude was larger for deviant stimuli. We found no evidence of intra-individual relationships between PDR amplitude and P3b amplitude, nor was this effect qualified by an interaction with stimulus type.

Model 4 also revealed a main effect of baseline pupil size on reaction time, such that a larger baseline pupil size was associated with slower RTs. This was qualified by an interaction with stimulus type. To interpret this interaction, we calculated the simple slopes for the PDR effect for both deviant and standard and their corresponding confidence intervals. For standards, a larger baseline pupil size predicted a significantly slower RT (simple slope estimate = 7.84 ; 95% CI = [5.22, 10.46]), but for deviants, baseline pupil size did not predict reaction time.

With baseline pupil size controlled for in the model, we also found that within-person fluctuations in PDR amplitude significantly predicted trial-to-trial variability

in RT. This effect was further qualified by an interaction with stimulus type. For standards, trials in which the PDR response was larger than the average for that subject had slower response times (simple slope estimate = 9.61; 95% CI = [6.99, 12.20]). For deviant stimuli, however, we found no relationship between PDR and RT. Furthermore, we found a main effect of P3b single-trial amplitude on RT, such that a larger P3b amplitude predicted a slower RT, consistent with the pattern seen in the individual differences. This was qualified by a significant interaction with stimulus type. For standard stimuli, a larger single-trial P3b amplitude predicted slower reaction time on that trial (simple slope estimate = 3.33; 95% CI = [.76, 5.90]). However, for deviant stimuli, trials that elicited a larger P3b amplitude than average were associated with a faster response time for that trial (simple slope estimate = -12.65; 95% CI = [-17.77, -7.53]).

Finally, in an exploratory analysis using the same linear mixed-effects structure as the Models 3 and 4, we examined whether or not baseline pupil diameter would significantly predict P3b response. We found a significant interaction between baseline pupil and trial type on P3b response ($\chi^2(1) = 24.69, p < .001$). For standard stimuli, trials that began with a larger than average baseline pupil size elicited a larger P3b response (simple slope estimate = .70; CI = [.50, .90]). For deviant stimuli, trials that began with a larger than average baseline pupil size elicited a smaller P3b amplitude (simple slope estimate = -.45; CI = [-.86, -.04]).

4 | DISCUSSION

The goal of the current study was to examine behavioral, electrophysiological, and pupillary responses to deviance in an oddball paradigm. In particular, our goal was to examine the relationships among each of these responses at the inter-individual and intra-individual level to test whether the phasic task-evoked PDR and the P3b are intercorrelated. Infrequent stimuli elicited a robust P3b, a substantial phasic pupil dilation response (PDR), and a slower RT, demonstrating a uniform “oddball” effect across all modalities. Consistent with prior work (Murphy et al., 2011), we found that baseline pupil diameter predicted the PDR and the P3b. However, we found no evidence of inter-individual or intra-individual relationships between the PDR and P3b. Thus, assuming that the PDR is a proxy for phasic LC-NE activity (e.g., Gilzenrat et al., 2010), these findings suggest complications for the LC-P3b hypothesis. Nevertheless, we did find evidence that PDR and P3b amplitudes each independently predicted behavior.

Kamp and Donchin (2015) found no relationship between the PDR and P3b amplitude. Moreover, neither PDR nor P3b amplitude predicted response time in their study (note, however, that latency measures did predict RT). Murphy et al. (2011) similarly did not find that the PDR and P3b were related. However, they found that larger P3b responses predicted faster RTs to deviant stimuli. We found that larger P3bs, relative to the subject's average, facilitated RTs to deviant stimuli at the single-trial level. We did not observe this relationship between the PDR and RTs for the deviant trials. We found, however, that for standards, both a larger P3b or PDR predicted slower RTs. Collectively, these findings suggest that these two physiological responses may reflect distinct but complementary functional stages that contribute to task-related decision making.

Three separate studies have now examined relationships between the PDR and P3b in an auditory oddball task, a word categorization task, and a visual oddball task. Despite substantial task and analytical differences across studies, none has found evidence for tight coupling between these two phasic responses. Nevertheless, two of the three studies have found that either the amplitude or latency of PDR and the P3b responses each independently predicted RT. Our current study extends this literature by clearly delineating variance in behavior driven by individual differences from variance driven by trial-to-trial within-person fluctuations. These results collectively suggest that, although the P3b response may not be directly coupled to PDR, both the P3b and the PDR have a hand in contributing to subsequent decision behavior. As Kamp and Donchin (2015) suggest, one explanation is that the activity of the (LC-NE mediated) PDR and the P3b each independently reflect separate points of the decision-making process. If this is the case, future work will benefit from utilizing a concurrent EEG and pupillometry design as in the current

study, combined with manipulations of various aspects of task demands, to better characterize the functional significance of these largely independent physiological responses to deviance. Interestingly, there does seem to be some preliminary evidence that pre-stimulus pupil size is related to the P3b response (Murphy et al., 2011), and we similarly found that pre-stimulus pupil diameter predicted P3b amplitude. This may represent a fruitful area for future research regarding the LC-NE system's relationship to the P3b response.

Finally, it is essential to note that other brain regions are involved in the pupillary response beyond the LC-NE system, such as the pretectal olivary nucleus and the superior colliculus (Joshi & Gold, 2020). Hence, although there is compelling evidence that LC activity modulates pupillary responses, and that LC activity and pupil diameter correlate in the oddball task in particular (Joshi & Gold, 2020; Murphy et al., 2014), the reverse inference that pupillary responses *directly reflect* LC activity alone is challenging to make confidently, and we acknowledge that pupillary responses may reflect contributions from other brain regions.

4.1 | Simpson's paradox

Our findings also demonstrated the importance of decomposing between-subject and within-subject covariation. In fact, we observed a complete reversal in the direction of the relationship between the P3b amplitude and RT when comparing effects at the between-subjects and within-subjects level. At the inter-individual level, individuals with larger P3b amplitudes showed *slower* responses to both standard and deviant stimuli. However, at the intra-individual level, on trials where the P3b was larger than average for that subject, response times were *faster* for deviant stimuli. Although one may expect and assume similar relationships at the between-subject and within-subjects level, these two levels of analysis reflect different sources of variance and can show completely opposing relationships, a phenomenon known more broadly as *Simpson's paradox* (Kievit et al., 2013; Simpson, 1951).

Why do we observe this inversion at the between-subjects and within-subjects level? We speculate here that inter- and intra-individual variability in the P3b may reflect different processes. Given the P3b's potential role as a neural index of evidence accumulation (e.g., Twomey et al., 2015), individual differences in P3b amplitude observed in the current study may reflect, in part, individual differences in decision criteria. There are reliable differences in the amount of information an individual requires before making a decision (e.g., Bogacz et al., 2006; Ratcliff, 1978), known as decision criteria. Decision criteria can vary within individuals as a function of task demands (e.g., Frazier & Yu, 2008; Karşilar et al., 2014), but also can represent stable individual differences (e.g., Bianco et al., 2020) in response caution. Under this hypothesis, an individual who

requires less evidence to make a decision only needs the P3b to build to a relatively low amplitude before they prepare to respond, whereas those who have higher stable response thresholds require more evidence, yielding a larger P3b before making their decision. Supporting this claim, studies that emphasize the importance of accuracy in various ways, requiring the participant to increase their response caution, do observe larger P3b's (e.g., Sutton et al., 1978; Yeung & Sanfey, 2004). At this inter-individual level, it is also worth noting that we observed no interaction between standard and deviant stimuli, suggesting that this reflects a more general individual difference in decision criterion that is invariant to stimulus type. Note that speed-accuracy trade-off studies, which can be considered as manipulations of criterion setting (Bogacz et al., 2006; Wickelgren, 1977), also find that the effects of decision caution apply to both standard and deviant stimuli. One might suspect that cautious individuals would theoretically be more accurate in their responses. However, we did not find evidence that average P3b amplitude predicted accuracy after controlling for trial type. This may simply be because our participants performed the task at very high levels of accuracy (on average 93%) with minimal variance (range = 86%–98%), making it harder to predict variance in this outcome variable.

In contrast, the within-subject P3b and RT relationship was not only in the opposite direction, but it also did not apply equally to standard and deviant stimuli. Instead, it appeared that on deviant trials specifically, a larger P3b to the stimulus facilitated RT. Rather than a general individual difference in response threshold, these data likely reflect the trial-to-trial dynamics of brain activity implementing stimulus-driven behavior. If we accept that there is a given evidence threshold to respond, then on larger-than-average individual P3b trials, this threshold—whatever it may be for a given individual—is reached more quickly, facilitating RTs to the deviants. We do not observe this relationship in the standard trials. Instead, we find that a larger P3b response predicts longer RTs. We speculate that larger P3b amplitudes to standards may represent trials in which participants nearly miscategorized stimuli as deviant before eventually making the correct response (i.e., these trials began accumulating evidence toward the wrong decision boundary before recovering). This is consistent with an evidence accumulation framework, which would suggest that, in general, one would be "biased" to respond to the standard, and therefore require less evidence to respond (e.g., Ratcliff, 1985; Ratcliff & McKoon, 2008), as evidenced by the quicker RTs to standards across the board. However, on trials in which the participant had a larger P3b, they may have required more evidence to make their decision, resulting in a longer RT.

5 | CONCLUSION

Three studies using different tasks have now failed to find evidence of strong relationships between the phasic PDR and the

P3b response. Assuming the PDR is a valid marker of phasic LC activity, our results are consistent with prior work in suggesting challenges to a strong interpretation of the LC-P3b hypothesis. Nevertheless, both physiological responses independently predicted response behavior, suggesting they may reflect distinct processes that contribute to optimal task-relevant performance. Critically, our results also highlighted the importance of decomposing inter-individual and intra-individual covariation. We observed a complete reversal in the relationship between P3b amplitude and RT at the inter-individual and intra-individual level, which we argue reflects distinct markers of decision making (i.e., individual differences in response caution vs. trial-to-trial variability in evidence accumulation). More broadly, we caution researchers to carefully consider both inter- and intra-individual sources of variation in multi-modal studies.

AUTHOR CONTRIBUTION

Sara B. LoTempio: Conceptualization; Formal analysis; Writing-original draft; Writing-review & editing. **Jack W. Silcox:** Data curation; Formal analysis; Methodology; Writing-original draft; Writing-review & editing. **Kara D. Federmeier:** Conceptualization; Funding acquisition; Project administration; Writing-review & editing. **Brennan R. Payne:** Conceptualization; Project administration; Writing-original draft; Writing-review & editing.

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