Title: A measure of the trigeminal blink reflex to parametric variation of mechanical stimulation

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Abstract
The primary goal of this study was to develop a parametric model that relates variation in trigeminal stimulation to properties of the blink response. We measured blink responses in 17 healthy, adult participants to air puffs delivered to the cornea and lateral canthus at five different, log-spaced intensities (3.5 - 60 PSI). Lid position over time was decomposed into amplitude, velocity, and shape components. We found that blink amplitude was lawfully related to log stimulus intensity, with the relationship well described by a Weibull cumulative density function. The parameters of the Weibull fit correspond to the slope of the function and the stimulus intensity required to produce half of a maximal blink response (the half-response threshold). There was a reliable decrease in half-response threshold for the contralateral as compared to ipsilateral blink response. This decrease was consistent across participants despite substantial individual differences in the half-response threshold and slope parameters of the overall sensitivity function, suggesting that the laterality effect arises in the neural circuit subsequent to individual differences in sensitivity. Overall, we find that graded mechanical stimulation of the trigeminal afferents elicits a graded response that is well described by a simple parametric model. We discuss the application of parametric measurements of the blink response to the detection of group differences in trigeminal sensitivity.

Key Words: trigeminal system; blink reflex; individual differences

Impact statement:

- There has been limited study of how variation in stimulus intensity influences the blink response. We describe how variation in the intensity of an air-puff stimulus relates to the amplitude of the blink response using a two-parameter model. The parameters of this model allow us to measure individual differences in the sensitivity of the trigeminal blink response, which may be used in future studies to identify population differences in this system.

1. Introduction

The blink reflex is an easily evoked, clinically relevant measure of brainstem function. The cornea of the eye and periorbital skin are innervated by the ophthalmic division (V1) of the fifth cranial nerve (CN V), also known as the trigeminal nerve. In the brainstem, the principal sensory nucleus of V receives light-touch sensation from V1, while the nucleus caudalis receives both light touch and nociceptive afferents (May and Porter, 1998). Both of these nuclei project to local brainstem circuits that serve reflexive functions, including eye blink (May and Warren, 2021).

There is a long history of quantitative measurement of the human blink reflex, with a frequent approach being unilateral electrical stimulation of the supraorbital nerve or cornea, and electromyographic (EMG) measurement of the binocular orbicularis oculi response. Generally, the amplitude or latency of the response is measured for a fixed stimulus intensity, or the threshold stimulus is found that evokes a criterion EMG response. There has, however, been relatively little study of the effect of variation in somatosensory stimulus intensity upon the evoked response. A focus upon measurement at response threshold can obscure individual and population differences. For example, two groups may initiate a physiologic response at the same threshold but differ in the amplification of that response with further increases in stimulus intensity. Examination of the sensitivity function that relates stimulus to response, and how this function interacts with other experimental variables, may be revealing as to the organization of the underlying neural system.

We report here measurements of the corneal blink reflex evoked by mechanical stimulation of varying intensity. Specifically, we presented an air puff stimulus to the eye at logarithmically spaced pressure levels and measured the change in lid position with high-speed infrared (IR) cameras. We approach the data within a modeling framework that extracts that amplitude and latency of the blink and characterizes the sensitivity function that relates blink response to variation in stimulus intensity. To anticipate our results, we find reliable differences

in the sensitivity functions of the ipsilateral and contralateral blink response, individual differences in the sensitivity of the corneal blink reflex, and changes in blink responses across trials as a measure of habituation.

2. Methods

2.1 Participants

We studied 17 participants recruited and tested by BlinkTBI Inc (Charleston, SC). These participants were recruited from The Citadel in Charleston, SC and from non-clinical settings in the surrounding Charleston community. Participants were at least 18 years of age, had no history of concussion within the past 5 years, and denied a history of recurrent headache. Nine of the subjects identified as women, and the mean age of all participants was 25 years (SD ± 4.0; range 20 to 32). This study was approved by The Citadel Institutional Review Board, and all participants provided written informed consent. All experiments were performed in accordance with relevant guidelines and regulations.

Our pre-registered enrollment goal was 15 subjects, and 17 were studied as the data from 2 subjects did not meet our original inclusion criteria. The analysis approach presented here departs substantially from our pre-registered plan and allowed us to retain the measurements from all subjects. The results of these planned analyses can be found with the pre-registration document: https://github.com/gkaguirrelab/preregistrations/tree/master/blink_2021.

2.2 Operation of the device

Blink responses were evoked and measured using a custom-modified, FDA cleared device (The EyeStat device, Gen3, Blink TBI Inc). The device was positioned over the eyes of the seated subject. Air puffs were produced by high-purity (“food grade”) CO_2 cannisters, minimizing the potential for introducing noxious solid particles to the cornea, and administered

at pressures below those used in ocular tonometry. During each of many ~30 second acquisitions, the device directed 8, temporally spaced air puffs (i.e., 8 “trials”) of a given pressure level to the cornea and lateral canthus. The laterality (left or right eye) of each trial was selected at random. The inter-stimulus-interval was jittered to reduce the ability of the participant to anticipate the timing of the stimulus with at least 3 seconds between trials. The eyes were illuminated with a ring of IR light emitting diodes that produced a corresponding ring of glint reflections on the tear film. A pair of high-speed IR cameras (300 Hz, 800 x 600 pixels) were used to measure the timing of obscuration of the glints by the movement of the eyelids. Recordings were made of the movement of the eyelid ipsilateral and contralateral to the side on which the stimulus was delivered. Microphones adjacent to the lateral canthus detected the arrival time of the air puff, and the timing of the pressure wave was used to synchronize recorded responses across trials.

During testing, subjects steadied themselves to receive the stimulus by holding the legs of a tripod that supported the device. Room lights were left on during the session, although the field of view of the subject was dark during data acquisition while their face was placed within the device.

The device used in this study was modified by the manufacturer to externalize pressure regulation. The CO_2 cartridge was connected by rigid tubing to an external pressure regulator (Reg3000x, Leland Gas Technologies, South Plainfield, NJ), and then returned by tubing to the device. Accuracy of specified air pressure levels was monitored with a National Institute of Standards and Technology calibrated device (PressureMon2000, RegCo, Miami Florida), which is certified to be accurate within ±0.2 pounds per square inch (PSI; 1 PSI = ~6.9 kilopascals).

2.3 Data collection

The stimulus intensity was varied in separate acquisitions between five different, log-spaced pressure values. A set of 26 acquisitions (each composed of 8 air puff trials of the same

stimulus pressure) were obtained in each of two sessions, with the order of pressure values following a pseudo-random, counterbalanced, de Bruijn sequence (Aguirre et al., 2011): [3, 3, 0, 2, 4, 4, 2, 0, 1, 3, 1, 1, 0, 4, 3, 2, 2, 3, 4, 1, 2, 1, 4, 0, 0, 3]; where 0 = 3.5 PSI, 1 = 7.5 PSI, 2 = 15 PSI, 3 = 30 PSI, and 4 = 60 PSI. We discarded the data from the entire first acquisition, as well as the first trial of each acquisition, to decrease the influence of a larger initial response exhibited by some participants. Thus, a total of 10 acquisitions were obtained at each of the five pressure levels, with each acquisition containing seven retained trials. The operator of the device attempted to achieve the desired PSI value within ±1 PSI, and the actual, achieved stimulus intensity was recorded for each acquisition. The unsigned mean deviation from nominal values was 0.31 PSI, and in all cases did not exceed 1 PSI. For one participant, 3 of the 50 acquisitions included 4 trials instead of 8 due to operator error; we elected to retain the data from this subject as this change in trial number was expected to have a negligible effect upon the data.

There was a 30 – 60 second break following each acquisition. Each session was approximately 50 minutes in duration, and the two sessions were separated by 1 to 5 days.

2.4 Data pre-processing

The raw data consisted of IR videos of the eyelids during each trial. Initial processing of these videos was conducted by Blink TBI Inc. using proprietary software. This first stage of analysis provided a measure of lid position during each trial with 3.33 ms temporal resolution, with all trials aligned to the time of arrival of the stimulus at the eye. All subsequent analyses were performed using custom MATLAB software (Mathworks, Natick, Massachusetts).

The lid position over time was obtained for each subject for each stimulus intensity level, averaging over all acquisitions and trials. The raw measurement of lid position in units of pixels was converted to a proportion of full eye closure by scaling all responses by the maximum excursion observed for that subject and session. Full lid closure was observed for all subjects at

either the 30 or 60 PSI stimulus. This normalization accounted for variation in the absolute size of the palpebral fissure across subjects and in the precise distance of the eye from the infrared cameras.

The primary analyses of the study examined the set average lid position vectors obtained from the 17 subjects at each of the 5 pressure levels, measured from the eye ipsilateral and contralateral to the stimulus, averaged across trials and acquisitions.

2.5 Modeling and summary measures of the blink response

An initial summary of the data was provided by measuring the amplitude, latency, and temporal width of the across-subject average blink response as a function of stimulus intensity. The amplitude was expressed as the proportion of lid closure. Latency was expressed as the time after stimulus arrival by which the lid had closed by 10%. The temporal width was expressed as the width (in ms) of the blink response at half of the maximum closure. The standard error of these measures was obtained by boot-strap resampling across subjects.

A model of the blink response over time was created to allow the temporal vector of lid position to be summarized with a small set of coefficients. The first component of the model was the average profile of lid position over time, combined across subjects, pressure levels, and the ipsilateral and contralateral eye. The second component was the first derivative of average lid position. This component reflects the velocity of the blink and could be used to calculate the latency of the blink response. Next, a set of residual vectors was obtained by regressing each of the 170 measures (17 subjects x 2 eyes x 5 stimulus levels) of lid position upon these first two components. The set of residuals was then subject to a principal components analysis, and the first eigenvector was retained as the third component of the model of temporal response. This third component captured variation in the temporal profile of the blink response that was neither amplitude or latency variation. Thus, these three orthogonal components account for, respectively, variation in the amplitude, velocity, and shape of the blink response.

A simple linear regression was then used to fit this three-component model to each lid-position vector, yielding three coefficients. The effect of stimulus intensity upon the coefficients was then examined, as well as the effect of other variables. This fitting approach leverages the entire profile of the blink response for estimation of amplitude and latency. Because the blink response is smooth in time, our analysis is able to estimate latency at a temporal resolution higher than the sampling rate of the (Henson et al., 2002).

2.6 Psychometric function relating blink amplitude and stimulus pressure

A Weibull cumulative distribution function (Wichmann and Hill, 2001) was used to model the effect of log-transformed stimulus pressure upon the amplitude of blink response. Two parameters controlled the shape of the fit, corresponding to the maximum slope of the function and the pressure at which 50% eye closure was predicted. This function was fit to the data from each subject using the MATLAB *fmincon* function. A comparison of the fit parameters between the ipsilateral and contralateral eye was performed with a paired t-test across subjects. Bootstrap resampling across acquisitions was used to estimate the standard error of the mean of the parameters within subject.

2.7 Examination of habituation effects

For each subject, the blink response vectors for sequential trials within each acquisition were obtained and averaged over stimulus levels. After fitting with the three-component temporal model, the coefficients were examined for an effect of trial number. For this analysis, all 8 trials in each acquisition were retained (i.e., the first trial was included).

3. Results

3.1 Blink amplitude and velocity increase with stimulus intensity

We measured the corneal blink reflex in 17 participants in response to an air puff stimulus (Figure 1a). A total of 10 acquisitions of 8 air puff trials were obtained at each of five,

log-spaced pressure intensities, with the order of acquisitions following a counter-balanced sequence (Figure 1b). IR video recordings of the eye ipsilateral and contralateral to the stimulus provided a measure of lid position over time (Figure 1c). From these recordings, the average blink response was obtained for each participant for each of the five stimulus intensities.

We first combined the responses from the eyelids ipsilateral and contralateral to the stimulus and examined the evoked blink response across participants and stimulus intensity levels. Figure 2a presents these data for each subject as a temporal raster plot. Each evoked response is in a row with the grayscale level indicating the depth of lid movement. A similar general pattern was seen across subjects (grouped blocks) and stimulus intensity levels (increasing stimulus intensity across rows within a block): Following the stimulus arrival at the cornea (vertical blue line), a blink of 100-200 msecs duration was initiated after a latency of 30-50 msecs. Examination of the average responses across subjects (Figure 2b and Table 1) demonstrates that increasing stimulus intensity evokes a blink response of larger amplitude and a shorter latency.

Our initial summary measures (Table 1) were derived from single time points in the blink response. We developed a temporal model that leverages the entire temporal profile of lid position to improve the precision and reliability of our derived measures. The model was composed of three orthogonal, smooth temporal components (Figure 3a) that describe variation in the amplitude, velocity, and shape of the evoked response. For a given blink response, we derived the three coefficients that best scale the components of the model to fit a response (Figure 3b). We fit this model to the blink response from each participant at each stimulus level and found that it provided a good description of the data, explaining over 95% of the variance.

We examined the value of the fit coefficients averaged across participants for each stimulus intensity level. Consistent with our initial summary measures, the model coefficients reflect systematic effect of air puff pressure upon blink response (Figure 4). Blink amplitude increased with stimulus intensity, with a roughly linear increase in blink depth related to log

228 changes in stimulus pressure; albeit with a plateau above 30 PSI. Blink velocity also increased
229 with stimulus intensity: log changes in stimulus intensity led to roughly linear increases in blink
230 velocity, reducing the latency of the response by about 15 msecs over the entire stimulus range.
231 By contrast, no systematic relationship between stimulus intensity and the shape component
232 was seen. This last component largely accounts for variation across participants in the position
233 of the lid in the later (>200 ms) phase of the response.

234 *3.2 The contralateral blink response is subject to an increased stimulus threshold*

235 The analyses up to this point combined the blink response measures from the eyelids
236 ipsilateral and contralateral to the stimulus. We next tested if there are consistent differences in
237 the sensitivity of the ipsilateral and contralateral response to mechanical corneal stimulation. We
238 obtained the average amplitude coefficients across subjects for each stimulus level, separately
239 for the ipsilateral and contralateral eye (Figure 5a). The measurements from each eye across
240 pressure levels was then fit with a non-linear psychometric function (the Weibull cumulative
241 distribution function). These fits provided a good account of the data and revealed that the
242 intensity response function measured from the contralateral eye was shifted to the right as
243 compared to the response from the ipsilateral eye. This property of the data indicates that
244 generally higher intensity stimuli were required to evoke the same degree of lid closure in the
245 contralateral eye as compared to the ipsilateral.

246 The Weibull function is under the control of two parameters that correspond to the
247 stimulus intensity required to produce a 50% eye closure (the “half response threshold”) and the
248 maximum slope of the change in eye closure with log changes in stimulus intensity. Figure 5b
249 presents the half-response threshold values obtained for each participant from the ipsilateral
250 and contralateral eyelid. While a wide range of values was seen, the plot points for all 17
251 participants were displaced ~0.1 log units above the unit slope line. A paired t-test across
252 participants of this measure between the contralateral and ipsilateral eye showed a significant

difference (t[16 df] = 8.29, p = 3.499e-7). Thus, there was a highly reliable, ~25% decrease in the threshold sensitivity of the response of the contralateral eyelid to corneal stimulation as compared to the ipsilateral eyelid.

Figure 5c presents the maximum slope of the psychometric function measured from the ipsilateral and contralateral eye for each subject. A wide range of values was again seen, although in this case the plot points did not systematically depart from the unit slope line, indicating a similar measurement from the two eyes. A paired t-test indicated that there was not a highly reliable difference in the slope value between the eyes (t[16 df] = 2.17, p=0.0453).

We examined if the timing and shape of the blink response of the ipsilateral and contralateral eye differed. Across subjects and averaged across pressure levels, the velocity coefficient value was larger in the response from the contralateral eye as compared to the ipsilateral eye (t[16 df] = 3.83, p = 1.475e-03), corresponding to an approximately 4 msec relative delay in the response of the contralateral eye.

3.3 There is reliable individual variation in sensitivity to corneal stimulation

We next examined individual variation in the relationship between stimulus intensity and blink amplitude. Given that the difference between the ipsilateral and contralateral blink response was both small and consistent across individuals, we considered the blink responses averaged across the two eyelids. Figure 6a presents the fit of the Weibull function to the blink response amplitudes for each participant, ordered by the half-response threshold value obtained. For all participants, the psychometric function provided a good account of the effect of stimulus intensity upon blink amplitude, although the form of this relationship varied substantially. This variability can be seen both in the half-response threshold of the function (blue dotted lines), and in the maximum slope (steepness) of the fits.

The two parameters of the Weibull fit define for an individual the sensitivity of their blink response to varying corneal stimulation. Figure 6b plots the value of these two parameters for

each participant, accompanied by the bivariate ellipse that indicates the standard error of the mean for the parameter. Differences between individuals were substantially larger than the measurement uncertainty. There was a positive correlation between half-response threshold and maximum slope across participants (r = 0.73). The underlying differences in the blink response across stimulus levels is shown for two example participants in Figure 6c.

For roughly half of the participants, a decline in the amplitude of the blink was noted between the 30 and 60 PSI stimulus levels. Post-hoc examination of the data indicated that this phenomenon resulted from some subjects narrowing their palpebral fissure (i.e., squinting) during the set of eight trials with the highest stimulus intensity. This partial closing of the eye resulted in a smaller excursion of the lid in response to the stimulus.

3.4 Blink amplitude and velocity change with repeated stimulation

Finally, we examined how the properties of the blink response changed over the 8 trials that were presented in rapid succession within each acquisition. For each participant, we fit the 3-component temporal response model to the average response across stimulus intensity, acquisitions, and sides, separately for each of the 8 trials. Figure 7 shows that across trial number, there was a decrease in the amplitude of the blink response, a slight increase in velocity, and no change in blink shape. These changes followed an exponential form, with the largest change in response coefficients being present between the first and second trial. We compared the R^2 of the exponential model fit in the data to the R^2 values obtained from fits to 10,000 permutations of the trial number order and found that the exponential form explains significant variance in the data for the amplitude (p=1.00e-4) and velocity (p=0.001) components, but not shape (p=0.235)

4. Discussion

We have developed a measure of parametric variation in the corneal blink reflex and have shown that there are substantial individual differences in the sensitivity of this response to

303 changes in stimulus intensity. There is surprisingly little prior work that has measured how the
304 blink response varies with the intensity of a somatosensory stimulus. In a review of the clinical
305 assessment of the blink reflex, Esteban observed that increases in the electrical current used to
306 stimulate the supraorbital nerve evoked larger and earlier EMG components from the orbicularis
307 oculi (which mirrors our findings) but this informal observation was not quantified (Esteban,
308 1999). Flaten and Blumenthal found that varying the intensity of an air puff (directed at the
309 temple) between 1.5 and 4.5 PSI resulted in a monotonic increase in the amplitude of the EMG
310 voltage response from the orbicularis oculi (Flaten and Blumenthal, 1998). There have been
311 studies of parametric variation in auditory (Peak, 1932) and visual stimulation (Bixler et al.,
312 1967) which generally show an increase in amplitude and a decrease in blink latency with
313 increasing stimulus intensity. Overall, however, we are unaware of prior work that has quantified
314 how the form and timing of the blink changes with stimulus intensity, or how these changes
315 covary within or across people.

316 Prior measurements of the corneal blink reflex have been conducted primarily using
317 electrical stimulation and measurement of an EMG response; here we use tactile stimulation
318 and a measure of the mechanical movement of the eyelid. We are unable to separate in our
319 measurement the individual response components observed in EMG (e.g., R1, R2, etc), but
320 suspect that our response mostly reflects R2, corresponding with the actual blink of the eyelids
321 (Rossi et al., 1989). Our measure reflects the integrated reflex arc, from sensory transduction to
322 motor output. It may therefore be more sensitive to pathologic abnormalities in the corneal blink
323 reflex, albeit with less etiologic specificity. An advantage of our measure is that it may be used
324 within the magnetic resonance imaging environment, thus supporting studies of the neural
325 correlates of trigeminal stimulation.

326 We have shown that blink amplitude is well described by a two-parameter psychometric
327 function of the log of trigeminal stimulation intensity. The psychometric function is fully described
328 by the threshold and slope parameters. We find a systematic difference between the threshold

329 parameters measured from the eyelid ipsilateral and contralateral to the stimulus. That is, a
330 higher intensity stimulus is required to evoke a given amount of lid movement in the
331 contralateral eye as compared to the ipsilateral eye. Consistent with this, prior studies have
332 found that the blink response contralateral to an air puff to be smaller and slower (VanderWerf
333 et al., 2003). A notable feature of our data is that, despite marked individual variation in overall
334 threshold and slope, the threshold difference between the ipsilateral and contralateral blink
335 response function is nearly identical across individuals (Figure 5b). This suggests that the
336 increased contralateral threshold arises from a common neural mechanism across individuals,
337 operating downstream from the source of individual variation.

338 We find that there are substantial differences amongst participants in the overall
339 sensitivity of the corneal blink reflex, as indexed both by half-response threshold and the slope
340 of the response function. There is a relatively strong correlation across individuals between
341 these two parameters, suggesting that people vary in a primary sensitivity axis that impacts both
342 of these parameters of the psychometric function. The site of this variation could be present
343 anywhere along the reflex pathway, and a goal for future work is to identify behavioral or
344 perceptual correlates of this variation and the neural source of the modulatory effect.

345 In other sensory domains, measurement of a stimulus-response function offers a
346 fundamental characterization of sensitivity that can have clinical importance (Balcer et al.,
347 2000). For the blink reflex, it is possible that measurement of the response function may reveal
348 alterations in the sensitivity of the trigeminal system in clinical disorders. An intriguing target is
349 migraine, for which potentiation of pain signals from trigeminal afferents is a cardinal feature.
350 Despite the apparent association between the trigeminal system and migraine, there is limited
351 consensus regarding what (if any) alterations of somatic sensory processing accompany
352 headache disorders (Coppola and Chen, 2021). EMG measures of the trigeminal blink response
353 have been extensively studied in migraine, but with conflicting results regarding if an alteration
354 in response is present (Vollono, 2021). It may be the case that these studies, performed at a

single stimulus intensity level, have missed differences that would be revealed in the full trigeminal sensitivity function.

Our measurement of the mechanical sensitivity of the blink reflex could be improved. First, the delivery of the air puff was accompanied by an audible hiss. An acoustic cue that precedes an air-puff stimulus (e.g., by 70 ms) inhibits the corneal blink response (Krauter et al., 1973), but can have an excitatory effect when presented simultaneously (Flaten and Blumenthal, 1998). In our study, the auditory component of our stimulus arose at the nozzle adjacent to the eye, and thus the corneal stimulus and auditory cue were essentially simultaneous. We may therefore expect an excitatory effect of the stimulus sound in our measurements, although we note that our auditory cue is weaker, and our corneal stimulus much stronger, than in these prior studies. Future studies might have participants wear noise-cancelling headphones. A second area for improvement is that every trial presented a stimulus. Participants may blink or squint in anticipation of a stimulus, and this behavior might vary across individuals. The inclusion of acquisitions that present a null (0 PSI) stimulus would allow this behavior to be detected and modeled as part of the psychometric function.

5. Conclusion

We find that parametric variation in the intensity of mechanical stimulation of the cornea produces a corresponding, graded response in the velocity and amplitude of the blink response. The function that relates stimulus intensity to blink amplitude has a common form but different sensitivity parameters across individuals. This measure is not intended to replace electrical stimulation and EMG recording for diagnostic purposes. Instead, we view this as a promising framework for investigating group and individual differences in the sensitivity of the trigeminal system.

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and D.P.G. Methodology: E.B.H. and G.K.A. Project administration: E.B.H. Resources: D.P.G. Supervision: D.P.G. and G.K.A. Visualization: E.B.H. and G.K.A. Writing - original draft: E.K., E.B.H., and G.K.A. Writing - review & editing: E.K., E.B.H., D.P.G., V.Y.B., and G.K.A.

Data availability statement: The available raw data are of the form of lid position vectors recorded for every trial. These data, and the code needed to reproduce the analysis and figures presented here, are publicly available:
https://github.com/gkaguirrelab/Kaiser_2023_ClinNeurophys

Additional Information:

Conflicts of Interest: None of the authors have potential conflicts of interest to be disclosed.

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References

Aguirre GK, Mattar MG, Magis-Weinberg L. de Bruijn cycles for neural decoding. Neuroimage 2011;56(3):1293-300.

Balcer LJ, Baier ML, Pelak VS, Fox RJ, Shuwairi S, Galetta SL, et al. New low-contrast vision charts: reliability and test characteristics in patients with multiple sclerosis. Mult Scler 2000;6(3):163-71.

Bixler EO, Bartlett NR, Lansing RW. Latency of the blink reflex and stimulus intensity. Percept Psychophys 1967;2:559-60.

Coppola G, Chen W-T. Neurophysiology of the Migraine Brain. Cham :: Springer, 2021.

Esteban A. A neurophysiological approach to brainstem reflexes. Blink reflex. Neurophysiol Clin 1999;29(1):7-38.

Flaten MA, Blumenthal TD. A parametric study of the separate contributions of the tactile and acoustic components of airpuffs to the blink reflex. Biol Psychol 1998;48(3):227-34.

Henson RN, Price CJ, Rugg MD, Turner R, Friston KJ. Detecting latency differences in event-related BOLD responses: application to words versus nonwords and initial versus repeated face presentations. Neuroimage 2002;15(1):83-97.

Krauter EE, Leonard DW, Ison JR. Inhibition of human eye blink by brief acoustic stimulus. J Comp Physiol Psychol 1973;84(2):246-51.

May PJ, Porter JD. The distribution of primary afferent terminals from the eyelids of macaque monkeys. Exp Brain Res 1998;123(4):368-81.

May PJ, Warren S. Macaque monkey trigeminal blink reflex circuits targeting orbicularis oculi motoneurons. J Comp Neurol 2021;529(11):2842-64.

Peak H. Intensity of stimulation and the amplitude and latency of the lid-reflex. The American Journal of Psychology 1932;44(4):785-8.

Rossi B, Risaliti R, Rossi A. The R3 component of the blink reflex in man: a reflex response induced by activation of high threshold cutaneous afferents. Electroencephalogr Clin Neurophysiol 1989;73(4):334-40.

VanderWerf F, Brassinga P, Reits D, Aramideh M, Ongerboer de Visser B. Eyelid movements: behavioral studies of blinking in humans under different stimulus conditions. J Neurophysiol 2003;89(5):2784-96.

Vollono C. Brainstem Reflexes. In: Coppola G, Chen W-T, editors. Neurophysiology of the Migraine Brain. Headache. Cham :: Springer; 2021.

Wichmann FA, Hill NJ. The psychometric function: I. Fitting, sampling, and goodness of fit. Percept Psychophys 2001;63(8):1293-313.

Legends

Table 1. Summary measures of average blink response
The properties of the mean (±SEM across subject) blink response in response to varying levels of corneal stimulation. The latency is the time to reach 10% eye closure. Full width at half maximum (FWHM) is the temporal width of the blink at half the maximum blink for that stimulus level.

Figure 1. Experiment overview
(a) Blink responses were measured in response to corneal stimulation. The participant placed their face within a device that positioned air delivery tubes adjacent to the lateral canthi. At unpredictable intervals an air puff was delivered to the left or right eye. A pair of high-speed infrared cameras recorded the resulting movement of the eyelids. **(b)** Counterbalanced pressure sequence. Each dash represents a single acquisition that presented a sequence of 8 air puff trials. The air pressure used for the 8 trials was varied across acquisitions as shown. The entire sequence was administered twice. **(c)** Lid position over time obtained for an example subject. The data from each acquisition is color coded to indicate stimulus intensity, following the convention shown in panel b.

Figure 2. Observed blink responses
(a) The raster plot presents the temporal profile of lid position (averaged across acquisitions and ipsilateral and contralateral eyes) on each row, with blink depth indicated by grayscale shading. The responses to each of the five stimulus intensity levels are grouped together with each block running vertically. Each block corresponds to a different participant (P1, P2, etc). The time of stimulus arrival at the cornea is indicated by a blue line. **(b)** The average (across subject) blink response evoked by the five stimulus intensity levels (color coding following the convention in Figure 1b).

Figure 3. Temporal model components
(a) Lid position vectors over time were fit using a three-component temporal model. These components corresponded to the amplitude of the blink (black), the first-derivative of lid position and thus velocity (blue), and a third component that captured residual variation in shape (gray). **(b)** Example of the fit (red line) to a blink response (gray dots). Shown *inset* is the composition of this example fit, which is defined by the three coefficient values that scale the three temporal components. The sum of these scaled components provides the red fit line.

Figure 4. Coefficient values by stimulus intensity
Each plot presents the mean (across participant) coefficients for the three temporal components (amplitude, velocity, and shape) as a function of stimulus intensity (log PSI). The shaded area is ±1 standard deviation of the mean across participants, and the error bars ±2 standard errors.

Figure 5. Ipsilateral versus contralateral blink responses.
(a) The mean (across participant) amplitude coefficients as a function of stimulus intensity, obtained separately for the eyelid ipsilateral (filled circles) and contralateral (open circles) to the stimulus. Amplitude is expressed as the proportion of a full eyelid closure. The points are fit with Weibull cumulative distribution function (red lines). **(b)** The psychometric function was fit to the amplitude data for each participant and side (ipsilateral and contralateral), yielding two parameters (half-response threshold and maximum slope). Here, each plot point indicates the half-response threshold parameters measured for a particular participant from the ipsilateral and contralateral eyelid. A linear fit to the set of points (gray line) is parallel to and shifted upwards from the unit slope (dashed line), corresponding to an ~0.1 log unit increased half-response

threshold value measured from the contralateral as compared to the ipsilateral eyelid. **(c)** Each plot point indicates the maximum slope parameter value obtained from the ipsilateral and contralateral eyelid from each participant.

Figure 6. Individual differences in psychometric properties of blink amplitude.
(a) Each sub-plot presents the amplitude coefficients for a participant as a function of stimulus intensity, averaged over acquisitions and the contralateral and ipsilateral eye. The fit of a Weibull cumulative distribution function is shown (red line), as is the half-response threshold value (dashed blue lines). Two example participants are identified with circled numbers, and these same participants are so indicated in subsequent panels. **(b)** The relationship between the half-response threshold and maximum slope parameters for each participant (red dots), surrounded by the bivariate normal distribution at one standard error of the mean obtained by bootstrap resampling across the 10 acquisitions (gray ellipses). **(c)** The average lid position plots at each stimulus intensity for two example participants (line color follows the convention of Figure 1).

Figure 7. Coefficient values by trial number
Each plot presents the mean (across participant) coefficients for the three temporal components (amplitude, velocity, and shape) as a function of trial number. The shaded area is ±1 standard deviation of the mean across participants, and the error bars ±2 standard errors. The fit of an exponential function is shown (red line).

Tables:

Table 1:

Stimulus (PSI)	Proportion blink	Blink Latency (ms)	FWHM (ms)
3.5	0.40 ± 0.1	61.1 ± 2.8	86.8 ± 23.5
7.5	0.61 ± 0.1	54.5 ± 1.8	83.8 ± 6.1
15.0	0.78 ± 0.1	49.2 ± 1.9	90.4 ± 6.2
30.0	0.90 ± 0.0	45.2 ± 1.7	96.1 ± 7.2
60.0	0.97 ± 0.0	40.2 ± 1.1	106.4 ± 7.5

Figures:

Figure 1:

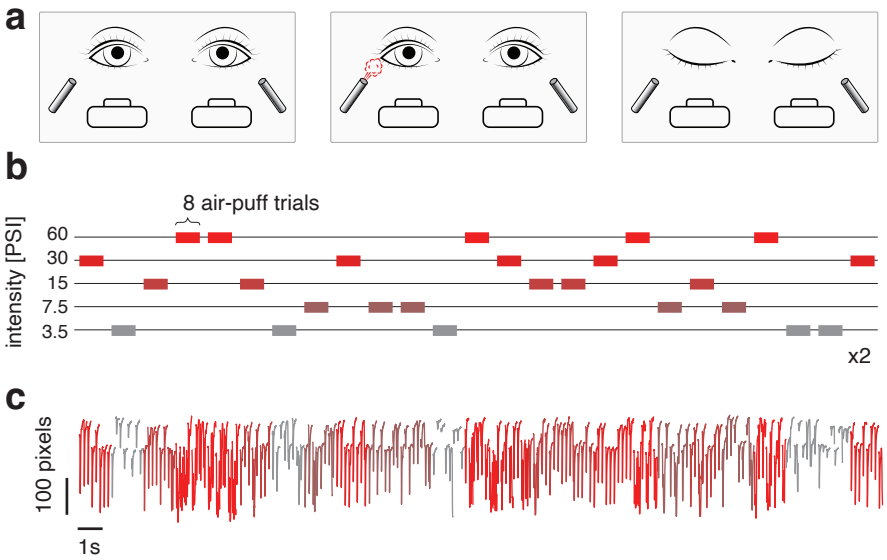

Figure 2:

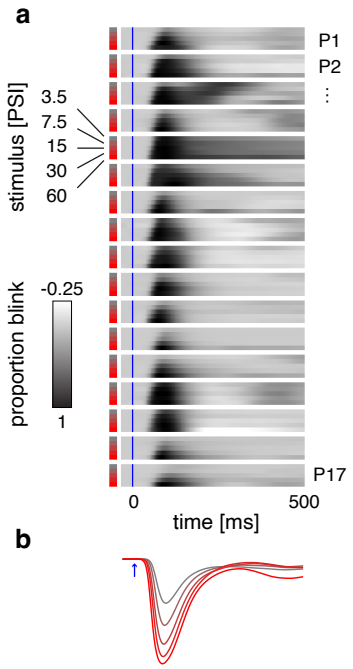

Figure 3:

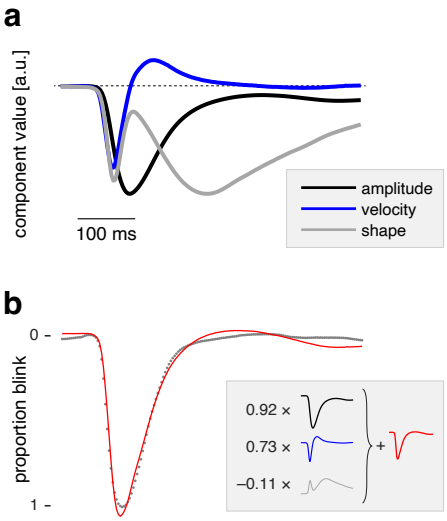

Figure 4:

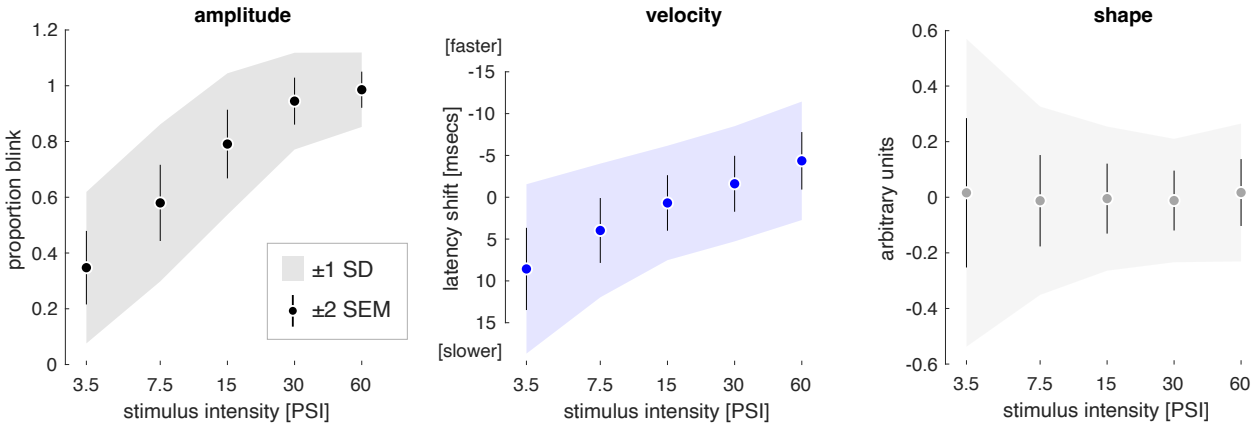

Figure 5:

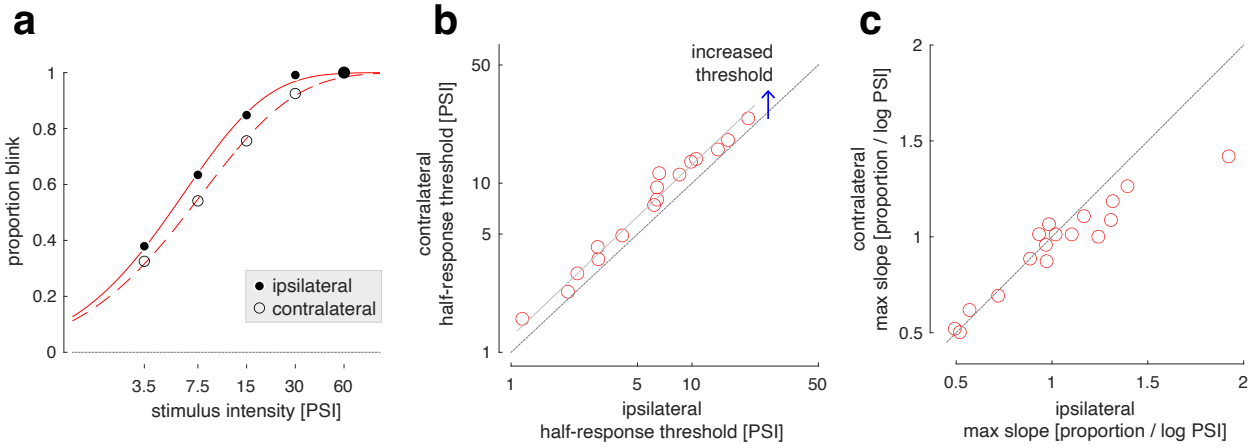

Figure 6:

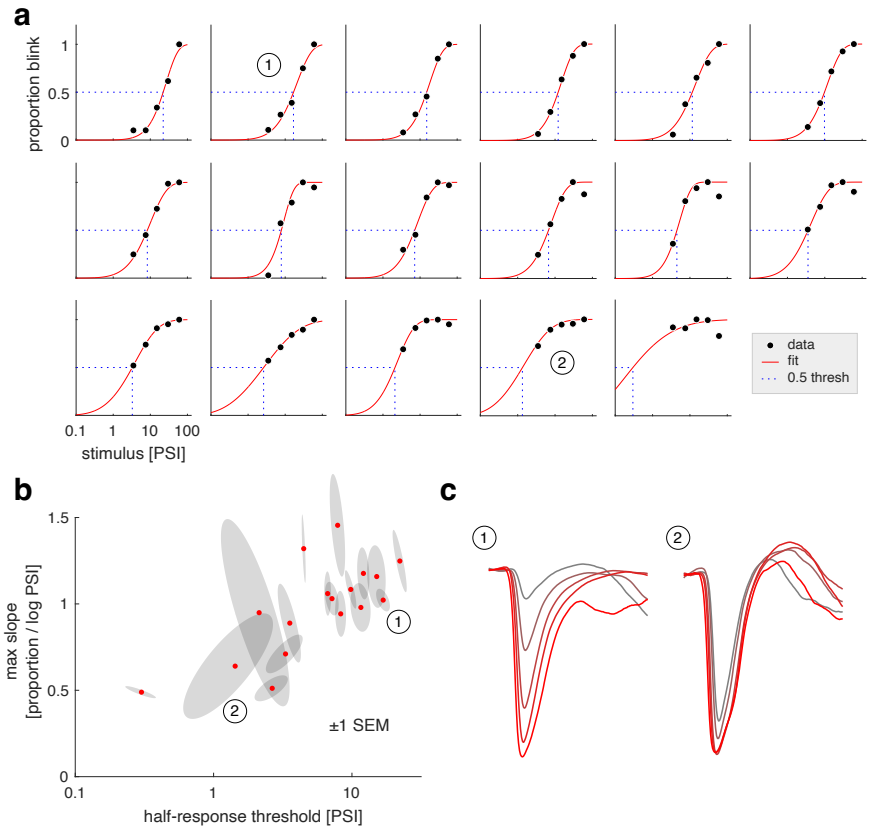
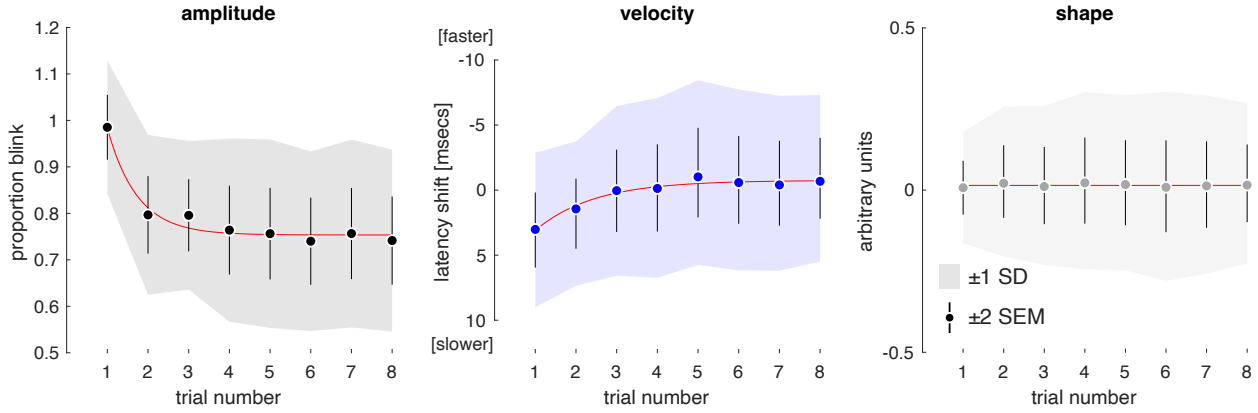
Figure 7: