1 **Title: A measure of the corneal blink reflex to parametric variation of mechanical**
2 **stimulation**
3

4 **Author(s):**
5 Eric A Kaiser[1†]; Edda B Haggery[1†], Dena P Garner[2], Vatinee Y Bunya[3], Geoffrey K Aguirre[1*]
6
7 [†]These authors contributed equally
8
9 [*]**Corresponding Author:**
10 Geoffrey K Aguirre
11 3400 Spruce Street, Philadelphia, PA 19104
12 aguirreg@upenn.edu; Telephone: +1(215) 662-3606; Fax: +1(215) 662-3907
13
**Affiliation Information for Authors**:
[1]Department of Neurology, Perelman School of Medicine, University of Pennsylvania,
Philadelphia, PA 19104, United States
[2]Department of Health and Human Performance, The Citadel, Charleston, SC 29409, United
States
[3]Scheie Eye Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia,
PA 19104, United States
21

**Abstract**
*Objective:* To measure the effect of stimulus intensity upon the corneal blink reflex, test for
differences between contralateral and ipsilateral reflex responses, and test for individual
differences in trigeminal sensitivity.
*Methods:* We measured blink responses in 17 healthy, adult participants in response to air puffs
delivered to the cornea at five different, log-spaced intensities (3.5 - 60 PSI). Lid position over
time was decomposed into amplitude, velocity, and shape components.
*Results:* We found that variation in blink amplitude was well fit with a two-parameter Weibull
cumulative density function of log stimulus intensity. There was a reliable decrease in threshold
sensitivity of the contralateral as compared to ipsilateral blink response. This decrease was
consistent across participants despite substantial individual differences in the threshold and
slope of the overall sensitivity function, suggesting that the laterality effect arises in the neural
circuit subsequent to individual differences in sensitivity.
*Conclusions:* A parameterized model of the corneal blink reflex captures the effects of laterality,
participant, and repetition upon a complex temporal response.
*Significance*: Measurement of the corneal blink sensitivity function may reveal differences
between patient populations that are not apparent for measurements made at a single stimulus
intensity level.
40
41 **Key Words**: trigeminal system; blink reflex; individual differences
42

**Highlights:**
• Variation in the corneal blink response with stimulus intensity is well described by a
parameterized model.
• Differences in model parameters capture the effects of stimulus laterality and repetition on
the evoked response.
• There are substantial individual differences in the parameters of the corneal blink response
sensitivity function.

## 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

76  in the sensitivity functions of the ipsilateral and contralateral blink response, individual

77  differences in the sensitivity of the corneal blink reflex, and changes in blink responses across

78  trials as a measure of habituation.

80  **2.  Methods**
81
*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 $\pm$

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

changes in stimulus pressure; albeit with a plateau above 30 PSI. Blink velocity also increased

with stimulus intensity: log changes in stimulus intensity led to roughly linear increases in blink

velocity, reducing the latency of the response by about 15 msecs over the entire stimulus range.

By contrast, no systematic relationship between stimulus intensity and the shape component

was seen. This last component largely accounts for variation across participants in the position

of the lid in the later (>200 ms) phase of the response.

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

The analyses up to this point combined the blink response measures from the eyelids

ipsilateral and contralateral to the stimulus. We next tested if there are consistent differences in

the sensitivity of the ipsilateral and contralateral response to mechanical corneal stimulation. We

obtained the average amplitude coefficients across subjects for each stimulus level, separately

for the ipsilateral and contralateral eye (Figure 5a). The measurements from each eye across

pressure levels was then fit with a non-linear psychometric function (the Weibull cumulative

distribution function). These fits provided a good account of the data and revealed that the

intensity response function measured from the contralateral eye was shifted to the right as

compared to the response from the ipsilateral eye. This property of the data indicates that

generally higher intensity stimuli were required to evoke the same degree of lid closure in the

contralateral eye as compared to the ipsilateral.

The Weibull function is under the control of two parameters that correspond to the

stimulus intensity required to produce a 50% eye closure (the "half response threshold") and the

maximum slope of the change in eye closure with log changes in stimulus intensity. Figure 5b

presents the half-response threshold values obtained for each participant from the ipsilateral

and contralateral eyelid. While a wide range of values was seen, the plot points for all 17

participants were displaced ~0.1 log units above the unit slope line. A paired t-test across

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

changes in stimulus intensity. There is surprisingly little prior work that has measured how the

blink response varies with the intensity of a somatosensory stimulus. In a review of the clinical

assessment of the blink reflex, Esteban observed that increases in the electrical current used to

stimulate the supraorbital nerve evoked larger and earlier EMG components from the orbicularis

oculi (which mirrors our findings) but this informal observation was not quantified (Esteban,

1999). Flaten and Blumenthal found that varying the intensity of an air puff (directed at the

temple) between 1.5 and 4.5 PSI resulted in a monotonic increase in the amplitude of the EMG

voltage response from the orbicularis oculi (Flaten and Blumenthal, 1998). There have been

studies of parametric variation in auditory (Peak, 1932) and visual stimulation (Bixler et al.,

1967) which generally show an increase in amplitude and a decrease in blink latency with

increasing stimulus intensity. Overall, however, we are unaware of prior work that has quantified

how the form and timing of the blink changes with stimulus intensity, or how these changes

covary within or across people.

Prior measurements of the corneal blink reflex have been conducted primarily using

electrical stimulation and measurement of an EMG response; here we use tactile stimulation

and a measure of the mechanical movement of the eyelid. We are unable to separate in our

measurement the individual response components observed in EMG (e.g., R1, R2, etc), but

suspect that our response mostly reflects R2, corresponding with the actual blink of the eyelids

(Rossi et al., 1989). Our measure reflects the integrated reflex arc, from sensory transduction to

motor output. It may therefore be more sensitive to pathologic abnormalities in the corneal blink

reflex, albeit with less etiologic specificity. An advantage of our measure is that it may be used

within the magnetic resonance imaging environment, thus supporting studies of the neural

correlates of trigeminal stimulation.

We have shown that blink amplitude is well described by a two-parameter psychometric

function of the log of trigeminal stimulation intensity. The psychometric function is fully described

by the threshold and slope parameters. We find a systematic difference between the threshold

parameters measured from the eyelid ipsilateral and contralateral to the stimulus. That is, a

higher intensity stimulus is required to evoke a given amount of lid movement in the

contralateral eye as compared to the ipsilateral eye. Consistent with this, prior studies have

found that the blink response contralateral to an air puff to be smaller and slower (VanderWerf

et al., 2003). A notable feature of our data is that, despite marked individual variation in overall

threshold and slope, the threshold difference between the ipsilateral and contralateral blink

response function is nearly identical across individuals (Figure 5b). This suggests that the

increased contralateral threshold arises from a common neural mechanism across individuals,

operating downstream from the source of individual variation.

We find that there are substantial differences amongst participants in the overall

sensitivity of the corneal blink reflex, as indexed both by half-response threshold and the slope

of the response function. There is a relatively strong correlation across individuals between

these two parameters, suggesting that people vary in a primary sensitivity axis that impacts both

of these parameters of the psychometric function. The site of this variation could be present

anywhere along the reflex pathway, and a goal for future work is to identify behavioral or

perceptual correlates of this variation and the neural source of the modulatory effect.

In other sensory domains, measurement of a stimulus-response function offers a

fundamental characterization of sensitivity that can have clinical importance (Balcer et al.,

2000). For the blink reflex, it is possible that measurement of the response function may reveal

alterations in the sensitivity of the trigeminal system in clinical disorders. An intriguing target is

migraine, for which potentiation of pain signals from trigeminal afferents is a cardinal feature.

Despite the apparent association between the trigeminal system and migraine, there is limited

consensus regarding what (if any) alterations of somatic sensory processing accompany

headache disorders (Coppola and Chen, 2021). EMG measures of the trigeminal blink response

have been extensively studied in migraine, but with conflicting results regarding if an alteration

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.

**Acknowledgements:** none

**Author Contributions:** Conceptualization: E.K., V.Y.B., and G.K.A. Data curation: G.K.A.
Formal analysis: E.B.H. and G.K.A. Funding acquisition: V.Y.B. and G.K.A. Investigation: E.B.H.

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.
386

**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.

**Funding Sources**: This work was supported by the National Institutes of Health [R21
NS130565 (to GKA); P30 EY001583], who had no involvement in the collection, analysis, or
interpretation of data, or in the writing of the manuscript. In kind support provided by BlinkTBI
Inc., including hardware, initial video processing, and engineering expertise.

397
398

**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

486    threshold value measured from the contralateral as compared to the ipsilateral eyelid. **(c)** Each
487    plot point indicates the maximum slope parameter value obtained from the ipsilateral and
488    contralateral eyelid from each participant.
489
**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).
500
501    **Figure 7. Coefficient values by trial number**
502    Each plot presents the mean (across participant) coefficients for the three temporal components
503    (amplitude, velocity, and shape) as a function of trial number. The shaded area is ±1 standard
504    deviation of the mean across participants, and the error bars ±2 standard errors. The fit of an
505    exponential function is shown (red line).
506

**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:**

517   **Figure 2:**

**a**

**b**

518
519

520   **Figure 3:**
521

**a**

**b**

522
523

524  **Figure 4:**
525
526

527
528
529
530
531  **Figure 5:**
532

533
534

535 **Figure 6:**
536

537
538
539
540 **Figure 7:**
541

542
543