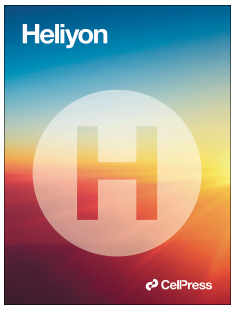

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Enhanced attention in rats following blast-induced traumatic brain injury

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Running Title: Cognitive effects of blast TBI

HIGHLIGHTS

- We studied the cognitive effects of blast-mediated traumatic brain injury in rats.
- Rats completed increasingly difficult visual learning tasks using touchscreens.
- Complex tasks showed increased attention in blasted subjects relative to controls.
- Post-task assessments failed to disclose loss of visual function due to blast.

ABSTRACT

Purpose: To evaluate visuo-cognitive sequelae following blast-induced traumatic brain injury in a rat model.

Methods: Rats were randomly assigned to one of four groups depending on the intensity/quantity of a blast received in a blast chamber**:** sham (no blast), low intensity (22 psi), medium intensity (26 psi), or three medium intensity blasts (26 psi $\times$ 3). After recovery, all subjects were given visual discrimination tasks of increasing complexity, until mastery. After behavioral training, visual function was assessed via spectral-domain optical coherence tomography and pattern electroretinogram, and the extent of retinal damage was quantified via immunohistochemistry of retinal ganglion cells.

Results:

None of the measures assessing visual function revealed significant differences as a function of blast intensity/quantity. Behavioral training did not disclose short-term effects of blast in general motivation or the development of anticipatory responding. No differences in general learning ability and the number of perseverative errors were observed. However, behavioral training found effects of blast in attentional function; relative to controls, subjects that received blasts were faster in learning to attend to informative (over non-informative) cues in the most difficult visual discrimination task.

Conclusion:

Blast exposure in rats resulted in increased attention following blast, with no appreciable deficits in visual function. These results are contrary to what is often reported for human clinical populations; as such, more research bridging methodological differences is necessary.

INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of death, which accounts for nearly 30% of all injury deaths in America(1). Each year over 2 million Americans are reported to suffer from TBI, but this figure is likely to be underestimated as many patients never seek medical attention(2-4). In addition to civilians, military personnel are particularly prone to suffer TBI. Since 2000, there have been over 450,000 reported cases of TBI amongst members of the military. It has been estimated that 50% of all cases of TBI affecting military personnel have been blast-mediated (bTBI)--caused by blast waves generated during military combat or by improvised explosive devices(5). The effects of bTBI have been reported to be heterogeneous. This heterogeneity may be a function of the energy delivered to the tissue, genetic susceptibility(6), or other factors that have not yet been elucidated. The immediate effects of bTBI can be mild and dissipate within a few months after injury in a proportion of affected individuals. However, the long-term consequences of bTBI are insidious; some individuals slowly develop perceptual and cognitive impairments such as reduced visual function(7, 8), increased incidence of affective disorders(9, 10), and impairments in memory and executive function(11), among many others(12).

Given the prevalence and heterogeneity of bTBI's cognitive symptomatology, the development of animal models that can be studied under tightly controlled conditions is a critical necessity. However, the development of animal models for bTBI does not come without challenges. Most animal models of bTBI address a fraction of the consequences of bTBI. In a recent survey, Aravind et al. (13) found that roughly 45% of the preclinical animal studies examined memory (with nearly half of those studies

evaluating spatial memory), another 45% evaluated behavior related to anxiety disorders, but only 10% of studies evaluated more complex forms of learning. Furthermore, current rodent models of bTBI are not only limited in terms of the complexity of the behaviors studied, but also are only partially successful in detecting effects following bTBI. Aravind et al. found that nearly one-third of the rat studies reviewed failed to find any evidence of impairments following bTBI, and many of the studies showing decrements found effects that were either transient or sporadic in time.

The gap between the actual symptomatology of patients suffering from bTBI and the cognitive constructs assessed by animal models of bTBI is worrisome. Animal studies are often designed with many assays in mind (e.g., behavioral, neurophysiological, genetic, etc.), and thus tend to use quick and simple behavioral tasks to assess the constructs under study. Comprehensive studies are rare; but recently, Muelbl et al.(14) tested sham and bTBI rats using a wide range of behavioral tasks, including drug self-administration, cue-based discriminations, location-based discriminations, discrimination reversals, and even delayed matching-to-sample tasks. Yet, this study found significant group differences only on cue-based discriminations, with bTBI rats making more errors before attaining a learning criterion (and making more perseverative errors in doing so) relative to their sham counterparts.

In our present study, we develop a comprehensive rodent model of learning following bTBI, by giving rats a series of increasingly difficult visual discrimination tasks that recruit increasingly complex cognitive functions: from motivation (the overall level of engagement in the task at hand) to selective visual attention(15) (the ability to prioritize the processing of relevant over irrelevant information). Two days after bTBI, rats

received an introductory, response chaining task; this task allowed measurement of short-term changes in overall motivation and overall ability to engage in anticipatory learning(16). Then, rats received a conditional discrimination task, in which the value of two choices depended upon the identity of another visual stimulus; this task allowed for the measurement of changes in strongly supervised learning and the incidence of perseverative errors. Finally, rats received a conditional discrimination task in which the value of two choices depended on one of two simultaneously presented stimuli; this task allowed measurement of changes in selective attention, as indexed by our subjects' contact with informative portions of the visual display. Blast exposure has been associated with visual deficits in rodent models(17), so, after the behavioral tasks were completed, we performed assays of retinal function and structural organization to corroborate the extent to which group differences in learning (if any) were due to failures in visual processing.

METHODS

Subjects

Forty-eight adult, male, wild-type Long-Evans rats were used in this experiment (292-589 g in weight). The rats were randomly assigned to Sham (SHA), Low-intensity blast (LOW), Medium-intensity blast (MED), and Medium-intensity blast repeated three times (MED3) groups (n = 12 per group). The animals were housed individually, with *ad libitum* access to water, but food-restricted to maintain 85% of their free-feeding weight. All housing and experimental procedures were approved by the Iowa City Veterans Affairs Institutional Animal Care and Use Committee (Animal Welfare Assurance Number: D16-00443).

Pre-Training Procedure

The visuo-cognitive tasks were carried out in two rat operant chambers with touchscreen capabilities (Campden Instruments Ltd.). Each chamber was individually controlled and located in noise-attenuation boxes. The routines controlling the experimental events were programmed using ABET II Software (Lafayette Instrument Company, Inc.) and managed using Whisker(18). Visual stimuli were displayed in 4 different 6.6 × 6.6 cm areas. Two, vertically aligned locations were used to present sample stimuli, and the two remaining horizontally aligned locations were used to present response stimuli. A pellet-dispenser delivered sucrose pellets (5TUL; TestDiet) into a food cup located on the wall opposite to the touchscreen.

Following a reduction to 85% of their free-feeding weights, rats received hand-shaping to operate the touchscreen. After touchscreen performance was satisfactory, each subject received a pretraining session containing 100 trials. On each trial, an image appeared randomly in any of the four possible locations (top, bottom, left, or right). After the subject touched the image, a set of simultaneous events associated with the delivery of the reward ensued: the image disappeared from the screen, a pure tone (1 kHz) was played inside the chamber for 1 s, and 2 food pellets were delivered into the food cup. The interval between trials varied randomly between 6 to 10 seconds.

Blast Injury

After pretraining, subjects were randomly assigned to each group and subjected to blast injury (LOW, MED, and MED3 groups) or a sham procedure (SHA). Blast injury was induced in rats using an advanced blast simulator (ABS, Stumptown Research and Development, Black Mountain, NC) that generates a blast wave using compressed gas, and is similar in geometry to advanced blast simulators currently in use(19). The ABS

has a 30 cm X 30 cm test area, and the test is 1.93m from the driver portion of the ABS. The blast wave was generated by the rupture of a membrane fitted between the driver and expansion portion of the ABS. For LOW blasts 18 oz coated fabric was used (Naizil Coated Fabrics), and 26.5 oz coated fabric (Mehler Texnologies) was used for MED blast intensities. The overall length of the ABS from the membrane separating the driver from the expansion tube to the end of the blast wave eliminator is 4.11m. All rats were anesthetized with an intraperitoneal (i.p.) injection of ketamine (50 mg/kg) and xylazine (3 mg/kg), secured within a padded, protective restraint, and placed inside the ABS with their heads oriented in the direction of the blast source. The blast wave was primarily a head only blast, with the rest of the body secured in the animal holder. The pressure measured at the wall perpendicular to the subject was 21.9 $\pm$ 0.14 PSI for LOW, 25.8 $\pm$ 0.18 PSI for MED, and 25.9 $\pm$ 0.11 PSI for group MED3. Blasts were carried out on consecutive days for subjects in the MED3 group. For subjects in the Sham group, compressed air was briefly pumped into the ABS with no membrane in place. Rats were subsequently removed from the chamber and anesthesia was reversed with an i.p. injection of atipamezole hydrochloride (4 mg/kg). Rats were given one i.p. dose of buprenorphine (0.05 mg/kg). Rats did not display any signs of overt injury or distress following blast exposure. The day after the blasting procedure, all subjects completed a single pretraining session as described above.

Task 1: Response Chaining

Training in the visuo-cognitive tasks began two days after the blast injury. In Task 1 (Figure 1A), subjects received daily training sessions until they completed 100 trials within a 1-hour session. On each trial, one of the sample stimuli was randomly presented in its corresponding location (top or bottom). After the subject touched the

sample stimulus, a response stimulus appeared in a fixed location (left for top, and right for bottom). A final touch to the response stimulus ended the trial, and all the events associated with the delivery of reward occurred, as described for the pretraining phase.

Task 2: Conditional Discrimination

For Task 2 (Figure 1B) subjects received daily training sessions containing 100 trials until their overall percentage of correct responses was 85% or higher. On each trial, one of the sample stimuli (top or bottom) was randomly presented in its corresponding location. After the rat touched the sample stimulus, two response stimuli (left and right) appeared in their corresponding locations. Touching the correct response stimulus for the sample stimulus (left for top and right for bottom) was rewarded; touching the incorrect response stimulus for the sample stimulus (right for top and left for bottom) resulted in no food or tone delivery and the subject was given a correction trial with the same stimuli after the intertrial interval. Correction trials were given until a correct response was made. Only first-attempt responses were used in the calculation of overall accuracy.

Task 3: Relevant/Irrelevant Conditional Discrimination

For Task 3 (Figure 1C) subjects received daily training sessions until their overall percentage of correct responses was 85% or higher. In each trial, two sample stimuli were presented in their corresponding locations. One of the samples (the relevant sample) determined the correct response stimulus (left for top relevant and right for bottom relevant). The other sample stimulus (irrelevant sample) was sampled at random and thus conveyed no useful information regarding the correct response stimulus (i.e., each irrelevant sample was equally likely to appear alongside the left and right stimulus responses). After the samples were presented, subjects had to touch any of the

samples 1, 3, or 5 times (sessions 1 to 2, 3 to 4, and 5 onwards, respectively). After this observing requirement was met, the response stimuli appeared and a touch to either of them ended the trial as previously described. All other trial parameters were identical to those used in Task 2. Within 1-13 days after the completion of this task (mean = 6.2 days), subjects were subjected to two forms of visual testing, both under anesthesia.

Pattern-Evoked Electroretinography (PERG)

Subjects received PERG of both eyes to assess the overall electrophysiological function of the RGCs. Under anesthesia, subjects were put on a heated animal holder, approximately 10 cm from the stimulus monitor. Finally, responses were evoked using alternating, reversing black and white vertical stimuli presented on an LED monitor (Jorvec, Miami, FL, USA). Subdermal recording electrodes were placed mediodorsally, in the neck area (reference needle), and at the base of the tail (ground needle). Additionally, a gold-plated wire recording electrode was shaped into a semicircle (2 mm diameter) and positioned coronally, encircling the scleral ring around the eye's equator. The stimuli (18° radius visual angle subtended on full field pattern, 1.5-cm-high x 14-cm-wide bars, 2 reversals per second, 150 averaged signals with cutoff filter frequencies of 1–30 Hz, 98% contrast, 80 cd/m2 average monitor illumination intensity using luminance-matched pattern reversals to exclude outer retinal contributions) were presented under mesopic conditions (8.5-lux room luminance) without dark adaptation. The recording was carried out for both eyes separately.

Spectral-Domain Optical Coherence Tomography (SD-OCT)

Subjects received SD-OCT of both eyes using a Spectralis SD-OCT (Heidelberg Engineering, Vista, CA, USA) imaging system (Heidelberg Engineering). Rats were anesthetized (as described above), pupils were dilated using a 1% tropicamide solution,

and the cornea was moisturized with a saline solution. Volume scans (49-line dense array, 15 A-scans per B-scan, 20° scan angle, 20° × 25° scan area) positioned directly over the optic nerve head were taken for each eye. The retinal ganglion cell complex (RGCC) thickness + the retinal nerve fiber layer (RNFL) was quantified as the sum of the thickness of the retinal nerve fiber, ganglion cell, and inner plexiform layers. Using unlabeled data, two B-scans per eye were analyzed by two experimenters by measuring the overall thickness at five equidistant points along the scan and excluding blood vessels from the calculation.

Immunohistochemical-based RGC quantification

After euthanasia, whole eyes were enucleated and the posterior cups were dissected and fixed for 4 hours in 4% paraformaldehyde, and stored in sterile 1X DPBS prior to staining. The immunohistochemical labeling of RGCs via RNA binding protein with multiple splicing (RBPMS)(20) was performed approximately 2 weeks after fixation. Briefly, the posterior cups were incubated in a 0.3% Triton X-100 solution in phosphate-buffered saline (PBST) overnight at 37°C; retinas were dissected and bleached in a 3% hydrogen peroxide solution in 1% sodium phosphate buffer for 3 hours at room temperature. Retinas were permeabilized for 15 minutes at -80°C in PBST, blocked in a 2% normal goat serum in PBST overnight at 4°C, and immunohistochemically labeled using an anti-RBPMS antibody (1:500; guinea pig polyclonal antibody; Santa Cruz Biotechnology, Dallas, TX, USA) in 2% normal goat serum, 1% Triton X-100, and 1% dimethyl sulfoxide (DMSO) at 4°C for five nights. All reagents were sterile upon receipt, were prepared in a sterile manner, and were incubated in covered containers to prevent contamination. The retinas were then washed in PBS with 2% Triton X-100 for 5 minutes at room temperature, washed with PBST four times (10 min each), and

incubated with a secondary antibody (1:200; Alexa Fluor 488 donkey anti-guinea pig; Invitrogen, Waltham, MA, USA) in darkness overnight at 4°C. Finally, retinas were counterstained with TO-PRO-3 Iodide (1:1000; Molecular Probes, Eugene, OR, USA), transferred to glass microscopy slides, and flat-mounted using ProLong Diamond Antifade Mountant (Fisher Scientific, Hampton, NH, USA), and coverslipped. Flat-mounted retinas were imaged by confocal microscopy (Zeiss LSM 710, White Plains, NY, USA) at a total magnification of 3400. For each retina, 12 confocal images were collected (1024 3 1024 px, 0.18-mm2 image area) from nonoverlapping in the mid-peripheral region with z stacks of three to five images collected for each image as previously described(21). Images of BRN3A-labeled nuclei were processed in ImageJ (National Institutes of Health, Bethesda, MD, USA), by first Z-projecting at maximum intensity, followed by the Subtract Background tool with rolling ball radius set to 35 pixels, followed by the Smooth tool. The RBPMS channel was converted to grayscale, and RGCs were automatically counted using RGCODE(22), to be visually checked later and manually-corrected (if necessary).

Statistical Analysis

Because all behavioral tasks were given for a short period (Task 1) or until the subjects met a criterion (Tasks 2 and 3), the longitudinal effect of training was analyzed by binning the relevant data into “relative” blocks on a subject-by-subject basis(23) (i.e., data were aggregated on blocks of different size such that all subjects had the same number of blocks). All analyses were performed using R(24) (version 4.1.3) along the packages *brms(25)* (version 2.17.0), *tidybayes(26)* (version 3.0.2), *bayestestR(27)*

(version 0.11.5), and *performance(28)* (version 0.9.0) as well as packages for data analysis and visualization contained in the *tidyverse(29)* (version 1.3.1) package. The data were analyzed via mixed-effects models, estimated under a Bayesian framework (see Supplemental information for the specification of each model). We performed statistical inference based on the posterior distributions of group-level parameters. In addition to reporting the posterior mean and 95% Credible intervals for each parameter, we report a pointwise Bayes factor representing the evidence supporting an effect (i.e., $b \neq 0$) versus the evidence supporting no effect (i.e., $b = 0$), adopting a weak prior centered around 0 (Student's t distribution with 1 degree of freedom and a standard deviation of 1). In this case, Bayes factors above 1 denote support for the existence of an effect, with values larger than 3, 10, 30, and 100 representing substantial, strong, very strong, and decisive evidence, respectively(30). The reciprocal of those quantities denotes the same degrees of evidence against the existence of an effect. Data in the figures are presented as Mean $\pm$ the Standard Error of the Mean (SEM). See Table 2 for means and standard errors for each assessment of visual function. See Table 1 for a summary of the main behavioral findings. See Supplemental Table 1 for a summary of commonly used abbreviations in this manuscript.

RESULTS

We analyzed all data using mixed-effects models estimated using a Bayesian framework. We used a mixed-effects approach because it allows for the estimation of random subject variability, resulting in parameter shrinkage at the group level. We adopted a Bayesian parameter estimation because it naturally captures the uncertainty

about both fixed and random effects (allowing for conservative inference) and its wide distributional family support.

For each measure, we first selected an appropriate representation of the random-effects structure supported by the data, by exhaustively comparing models of increasing complexity. At each step, we used leave-one-out (LOO) cross-validation to compare the expected log pointwise predictive density among models and retained the model with the highest value(41). See Supplemental Table 2 for the specification of each resulting model.

Task 1: Response Chaining

Subjects did not have much to learn in Task 1, as this task had an introductory character. All but three subjects (1 in group SHA and 2 in group LOW) completed this task in one session. Yet, there were two behavioral indexes with the potential to disclose group differences: 1) overall motivation to respond during the task (as indexed by response reaction times) and 2) overall learning ability (as indexed by anticipatory responding).

The log choice reaction time for all groups, across relative blocks of trials is shown in Figure 2A. We defined choice reaction times as the time elapsed between the presentation of the response stimulus and the response stimulus being touched by the subject. Reaction times that were 2.5 standard deviations away from the mean, in any direction, were excluded from the analysis on a subject-to-subject basis. The remaining data were analyzed using a generalized linear model with a Gamma distribution and a log link function, including log relative block (0 to 9) and group (reference coded using SHA as the reference group) as fixed effects. As it can be inferred from Figure 2A, the reaction times of the SHA group became shorter with continued training (Table 1, b = -

0.25, 95% CI [-0.41, -0.09], BF_{10} = 5.43) and the rate at which reaction times shortened in blast groups was not reliably different for any of them (maximum BF_{10} = 0.42).

The percentage of anticipatory touches for all groups, as a function of relative blocks is shown in Figure 2B. The relations between sample and response stimuli allowed for subjects to learn the location of the upcoming response stimulus and thus develop anticipatory responses. Specifically, whenever the S1 sample stimulus was given on a trial, its corresponding response stimulus (R1) always appeared on the left side of the touchscreen. Similarly, whenever the S2 sample stimulus was given on a trial, its corresponding response stimulus (R2) always appeared on the right side of the touchscreen. We classified sample touches as anticipatory if their x coordinate was in the half closer to the location of the upcoming response stimulus. These data were analyzed using a generalized linear model with a binomial distribution and a logit link function, including the same factors mentioned above. The model revealed that SHA subjects did not develop anticipatory responding across relative blocks (*b* = -0.02, 95% CI [-0.17, 0.14], BF_{10} = 0.06), and there were no reliable differences in this regard for any of the blast groups (maximum BF_{10} = 0.19).

Overall, Task 1 suggests that the bTBI had no short-term effects (i.e., 2 days after injury) at the motivational level and no short-term effects in the development of anticipatory responding.

Task 2: Conditional Discrimination

Relative to sham subjects, blasted subjects were neither faster nor slower in completing Task 2. On average, group SHA reached the learning criterion in 2.92 $\pm$ 0.50 sessions, group LOW did so in 3.08 $\pm$ 0.56 sessions, group MED did so in 2.25 $\pm$ 0.13 sessions, and group MED3 did so 2.17 $\pm$ 0.11 sessions. A Gaussian model on the

logarithm of the sessions required to meet the learning criterion revealed no group differences (maximum BF_{10} = 0.28, Table 1).

Task 2 was the first instance in which our subjects could make correct or incorrect responses. Therefore, any potential differences between groups can be evaluated with two additional metrics. Figure 3A shows one of these metrics, accuracy, as indexed by the percentage of correct choices across relative blocks of training, for each group. A logistic model as described above revealed an overall increase in accuracy across relative blocks for group SHA (*b* = 0.88, 95% CI [0.66, 1.10], BF_{10} > 100), but no reliable differences for any of the blast groups (maximum BF_{10} = 0.18).

Figure 3B shows the second of these metrics, perseveration, as indexed by the log mean number of corrections per trial as a function of relative blocks of training, for each group. A Gaussian model disclosed an overall reduction in the number of correction trials across relative blocks for group SHA (*b* = -0.67, 95% CI [-0.85, -0.49], BF_{10} > 100), but no reliable differences for any of the blast groups (Table 1, maximum BF_{10} = 0.36).

Figure 3C shows the log reaction times in this task, now defined as the time elapsed between the presentation of the response stimuli, and a touch to any of them. Again, we observed a decrease in reaction times as training ensued for group SHA (*b* = -0.14, 95% CI [-0.20, -0.08], BF_{10} > 100), but no reliable differences for any of the blast groups (maximum BF_{10} = 0.42).

Finally, Figure 3D shows the percentage of anticipatory touches across relative blocks. A model revealed an overall increase in anticipatory responding across blocks for group SHA (*b* = 0.37, 95% CI [0.20, 0.55], BF_{10} > 100), but no differences for any of the blast

groups (maximum BF_{10} = 0.38). There was, however, weak support for increased anticipatory responding in group MED3 relative to group SHA, during the first relative block of training (*b* = 0.48, 95% CI [0.10, 0.86], BF_{10} = 2.56).

Overall, the results of Task 2 showed that bTBI did not impair learning of simple visual discriminations and did not increase perseveration errors. Response speed was equivalent among groups, and although subjects developed anticipatory responding, blast groups did not do so at different rates relative to the sham group.

Task 3: Relevant/Irrelevant Conditional Discrimination

Relative to sham subjects, blasted subjects were faster in completing Task 3 (Table 1). On average, group SHA reached the learning criterion in 57.1 ± 13.9 sessions, group LOW did so in 32 ± 7.91 sessions, group MED did so in 23.9 ± 4.91 sessions, and group MED3 did so 19.4 ± 5.28 sessions. The apparent monotonicity of this effect was partially supported by a Gaussian model on the logarithm of the sessions required to meet the learning criterion. Specifically, the model showed very strong evidence supporting a difference for group MED3 (*b* = -0.90, 95% CI [-1.44, -0.33], BF_{10} = 16.53), anecdotal evidence for group MED (*b* = -0.60, 95% CI [-1.16, -0.05], BF_{10} = 2.56), and no evidence supporting a difference when it came to group LOW (*b* = -0.39, 95% CI [-0.94, 0.16], BF_{10} = 0.62).

Figure 4A shows the percentage of correct choices across relative blocks of training, for each group. A logistic model as described above revealed an overall increase in accuracy across relative blocks for group SHA (*b* = 0.46, 95% CI [0.44, 0.49], BF_{10} > 100), but more importantly, some group differences relative to them. Specifically, both group MED and MED3 were faster in learning the task relative to group SHA (*b* = 0.11, 95% CI [0.07, 0.15], BF_{10} > 100, and *b* = 0.17, 95% CI [0.12, 0.22], BF_{10} > 100,

respectively). Group LOW received only anecdotal evidence in this regard (b = 0.06, 95% CI [0.02, 0.10], BF_{10} = 1.58).

Perseverative errors (Figure 4B) decreased across training for group SHA (b = -0.60, 95% CI [-0.68, -0.53], BF_{10} > 100), and this decrement was significantly larger for group MED3 (b = -0.17, 95% CI [-0.28, -0.06], BF_{10} = 6.13), but the same was not true for the other two blast groups (maximum BF_{10} = 0.14). Reaction times (Figure 4C) decreased across training for group SHA (b = -0.14, 95% CI [-0.20, -0.08], BF_{10} = 90.35), with no differences for any of the blast groups (maximum BF_{10} = 0.10). Overall anticipatory responses (Figure 4D) increased as a function of training (b = 0.37, 95% CI [0.28, 0.47], BF_{10} > 100) for group SHA, and there was anecdotal evidence suggesting this increase even larger for the MED3 group (b = 0.17, 95% CI [0.04, 0.29], BF_{10} = 1.74).

Task 3 was designed to examine whether bTBI impaired attention. As the conditional discriminations in Task 3 included both informative and non-informative sample stimuli on each trial, this task measured the subjects' ability to attend to relevant information, and/or to ignore irrelevant information. Hence, we examined whether subjects differentially allocated their touches toward relevant samples instead of the irrelevant ones. Figure 4E displays the percentage of touches on the relevant sample across relative training blocks for each group. A logistic model as described above showed that there was no overall increase in the percentage of relevant touches as a function of training for group SHAM (b = 0.07, 95% CI [-0.06, 0.20], BF_{10} = 0.10), and that only group MED3 reliably increased their percentage of relevant touches as a function of training (b = 0.31, 95% CI [0.12, 0.49], BF_{10} = 5.69).

Past research has found that attending to relevant aspects of a task closely follows mastery of the task itself(31). Thus, we next assessed whether the degree of attention paid to the relevant sample (as indexed by relevant sample touches) was predictive of choice accuracy in each group (Figure 4F). A binomial model of choice accuracy at each relative block and their corresponding relevant touch probabilities (centered) disclosed that accuracy was positively correlated with touches to the relevant sample for group SHA (b = 2.97, 95% CI [2.45, 3.46], BF_{10} > 100). More importantly, however, this relation was heightened in all three blast groups (b = 1.88, 95% CI [1.22, 2.58], BF_{10} > 100, b = 3.41, 95% CI [2.68, 4.15], BF_{10} > 100, b = 3.38, 95% CI [2.71, 4.09], BF_{10} > 100, for group LOW, MED, and MED3, respectively).

Task 3 showed that bTBI affected performance in a somewhat monotonic way, although we only managed to detect reliable differences when the group that received the greatest level of TBI (MED3) was compared against the SHA group. Still, the effects were contrary to what we had expected. We found faster learning, more anticipatory responding, and better selective attention after bTBI. The stark difference between sham and blast groups across these three metrics suggests that the bTBI groups solved the task in substantially different ways relative to the sham group. Although subjects from all groups could use the same response cues to aid their choice behavior, bTBI groups managed to do so more effectively, as indicated by increased anticipation of the location of the correct response stimulus and increased contact with the relevant sample.

PERG

An analysis of PERG data revealed no major differences across three different metrics between the sham and any of the three blast groups. The groups did not differ

in the latency of the PERG (Table 2, Figure 5A; maximum BF_{10} = 0.37) with group latencies of 77.70 ± 12.00 ms (SHA), 88.40 ± 17.90 ms (LOW), 82.30 ± 24.90 ms (MED), and 85.80 ± 18.90 ms (MED3). The groups also did not differ in the PERG amplitude (Figure 5B; maximum BF_{10} = 0.15), with group amplitudes of 18.80 ± 1.87 µV (SHA), 17.30 ± 1.26 µV (LOW), 17.00 ± 1.38 µV (MED), and 17.7 ± 2.27 µV (MED3). Finally, the groups did not differ in the ratio between positive and negative deflections of the evoked potential (Figure 5C; maximum BF_{10} = 0.40): 18.80 ± 2.00 (SHA), 16.30 ± 1.23 (LOW), 14.40 ± 0.85 (MED), and 14.80 ± 1.34 (MED3), even though there was a monotonic, negative trend as a function of blast frequency/intensity.

SD-OCT and RGC quantification

The indexes provided by PERG correlated with findings of the relative thickness of the RGC complex in sham and blast groups (Table 2, Figure 5D). Figure 6 shows representative examples of stained and counted retinal slides across groups. Again, we found a negatively monotonic trend as a function of blast frequency/intensity, but no significant differences between the sham and any of the blast groups (maximum BF_{10} = 0.20) with RGC complex + RNFL thickness of 76.90 ± 0.94 µm (SHA), 75.40 ± 1.06 µm (LOW), 75.10 ± 1.24 µm (MED), and 74.90 ± 1.16 µm (MED3). Like our findings with SD-OCT, we found no differences between the sham and any of the blast groups regarding overall RGC density (Figure 5E; maximum BF_{10} = 0.40) with 1603 ± 116.00 $RGCmm^2$ (SHA), 1618 ± 134.00 $RGCmm^2$ (LOW), 1862 ± 52.20 $RGCmm^2$ (MED), and 1780 ± 40.30 (MED3) $RGCmm^2$.

DISCUSSION

In the current study we examined the effects of bTBI in a rat model. Our blast procedure did not elicit impairments in retinal organization and function (Figure 5), but they did suggest impairments that were monotonically related to the intensity/frequency of the blast. Although mild, the intensity of the blasts our subjects received was well within the range of parameters reported in the literature(13). Due to the overall difficulty of our operant tasks, visual assays were carried out 160 days since blast, a period that is well above the duration of most studies in the literature(13).

Our analysis of visual structure and function did not detect major visual impairments; blast subjects were clearly able to discriminate the visual stimuli. However, our blast procedure led to fine-grained differences at the behavioral level, which were more clearly revealed in a task that required the deployment of selective attention to be mastered (Figure 1C). In these tasks bTBI was associated with faster learning, decreased errors, and most strikingly – increased attention to informative cues (Figure 4). These measures are related to each other and therefore, causality is difficult to establish(31), however, it is possible that blast injury caused subjects to rely more strongly on interoceptive response cues and develop stimulus-response strategies early in training (i.e., “top then left”, “bottom then right”, see Figure 1) that would lead to the behaviors observed in task 3. Future studies should closely assess candidate brain circuitry whose disruption might affect performance in this type of task, such as the hippocampus involvement in memory(32) or the prefrontal cortex involvement in executive function(33).

Our behavioral results somewhat diverge from those by Muelbl et al.(14), who reported slower learning and an increase in perseverative errors in bTBI rats relative to shams, in a task that most resembled the current Task 2 (Figure 1B). In the present study, we did not identify reliable differences between any of the blast groups and the sham group, but the overall number of sessions that each group required to meet the learning criterion suggested that bTBI instead sped up learning, instead of slowing it down. Many methodological differences could explain these contrary observations, ranging from the difference in rat strains to the characteristics of the blast chamber itself, but a difference in overall task difficulty is a likely candidate. Muelbl et al.'s task was a feature positive discrimination between a reinforced lever plus a visual cue and a non-reinforced lever. In contrast, Task 2 can be construed as two feature positive discriminations, in which two response stimuli were equally reinforced conditional on two different cues. Such an added difficulty might have masked small group differences. Regardless, we are not the first to report faster learning after bTBI in a rodent model. Recently, Baskin et al.(34) found better discrimination between reinforced and nonreinforced levers in mice that had been repeatedly blasted, relative to sham subjects. Most notably, Baskin et al. used the same feature-positive discrimination paradigm used by Muelbl et al.

Our study did not identify significant changes in the RGC function, structure, or remaining RGCs observed with BRN3A staining. We did observe non-significant changes in retinal function and structure that are likely due to the blast injury, with decreases in the RGC Complex + RNFL and the PERG amplitude. This observation is in contrast to previous reports that show decrements in visual function that are often accompanied by the death of retinal neurons following TBI(6, 17, 35-40). The lack of

significant differences observed in this study may be due the different blast model that was used in these studies, which may impart less loading pressure on neurons than systems utilized in previous studies. It will be important in future studies to examine higher blast pressures and sample visual responses at different times after injury.

In conclusion, our rodent model resulted in increased attention following bTBI, but this result is contrary to the deficits often reported in the clinical population(12), which will require further research to accurately understand.

Declarations Statement

This study was approved by the Iowa City Veterans Affairs Institutional Animal Care and Use Committee, Protocol 2090201. The authors have no competing interests to declare.

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Data availability statement

All the data and analysis scripts used to prepare this manuscript are available at https://osf.io/d8hqr/?view_only=ff1f2710ed43485794b521082d93144d.

ABBREVIATIONS

Abbreviation	Definition
ABS	advanced blast simulator
bTBI	blast-mediated traumatic brain injury
LOW	low-intensity blast injury
MED	medium-intensity blast injury
MED3	triple blast injury using medium blast intensity
PERG	pattern electroretinogram
RGC	retinal ganglion cell
RNFL	retinal nerve fiber layer
SD-OCT	spectral domain optical coherence tomography
SHA	sham-blast injury
TBI	Traumatic Brain Injury

TABLES

Task	Behavioral index	Results	Group differences relative to SHA?
Task 1	Reaction times	Overall reduction in reaction times.	No
	Anticipation	No development of anticipatory responding.	No
Task 2	Sessions to criterion	Task completed in a few sessions.	No
	Response accuracy	Overall increase in accuracy.	No
	Perseverative errors	Overall decrease in perseveration.	No
	Reaction times	Overall reduction in reaction times.	No
	Anticipation	Overall increase in anticipatory responding.	Weak support for more anticipation in group MED3 early in training.
Task 3	Sessions to criterion	Task completed in many sessions.	Very strong support for faster learning in group MED3, and anecdotal support for faster learning in group MED.

	Response accuracy	Overall increase in accuracy.	Very strong support for faster learning in groups MED3 and MED. Anecdotal support for faster learning in group LOW.
	Perseverative errors	Overall decrease in perseveration.	Substantial support for faster decrease in group MED3.
	Reaction times	Overall decrease in reaction times.	No
	Anticipation	Overall increase in anticipatory responding.	Anecdotal support for faster anticipation in group MED3.
	Attention	No overall increase in relevant touches.	Substantial support for increase in group MED3.
	Accuracy/Attention	Positive correlation between relevant touches and accuracy.	Very strong support for stronger correlations in groups LOW, MED, and MED3.

Table 1. Summary of results from visual-cognitive studies of rats exposed to sham (SHA), Low-intensity blast injury (LOW), Medium-intensity blast injury (MED), or repetitive medium intensity blast injury (MED).

Parameter	SHA	LOW	MED	MED3
PERG Amplitude (µV)	18.80 ± 1.87	17.30 ± 1.26	17.00 ± 1.38	17.7 ±2.27
PERG latency (ms)	77.70 ± 12.00	88.40 ± 17.90	82.30 ± 24.90	85.80 ± 18.90
PERG Ratio	18.80 ± 2.00	16.30 ± 1.23	14.40 ± 0.85	14.80 ± 1.34
SD-OCT RGC Complex +RNFL thickness (µm)	76.90 ± 0.94	75.40 ± 1.06	75.10 ± 1.24	74.90 ± 1.16
RGC per mm2	1603 ± 116.00	1618 ± 134.00	1862 ± 52.20	1780 ± 40.30

Table 2. Summary of visual parameters collected from rats exposed to sham (SHA), Low-intensity blast injury (LOW), Medium-intensity blast injury (MED), or repetitive medium intensity blast injury (MED).

FIGURES

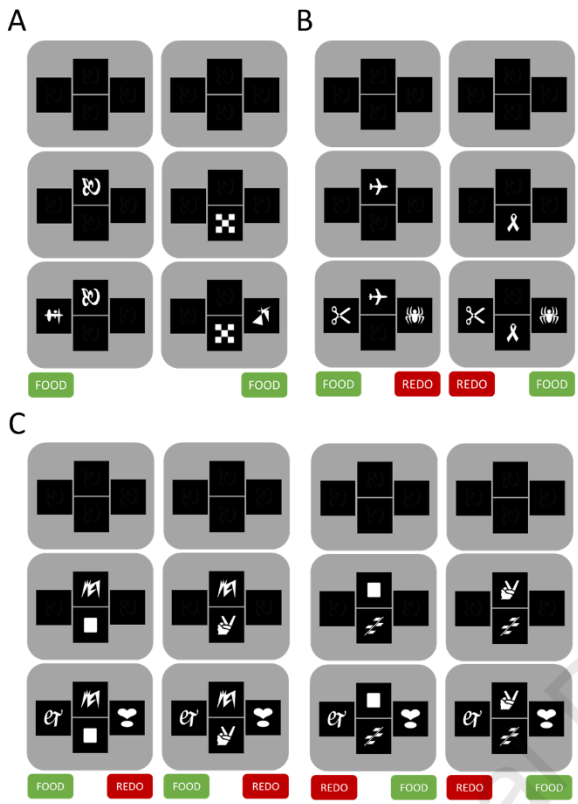

Figure 1. Behavioral tasks used in this study. Each gray square represents the state of the display during a trial, going from top to bottom. The consequence of touching each of the response stimuli (left or right) is shown at the bottom of each square (FOOD = delivery of food pellets; REDO = no delivery of food pellets and a correction trial after an interval). A. Task 1: response chaining. B. Task 2: Conditional discrimination. C. Task 3: Relevant/Irrelevant conditional discrimination.

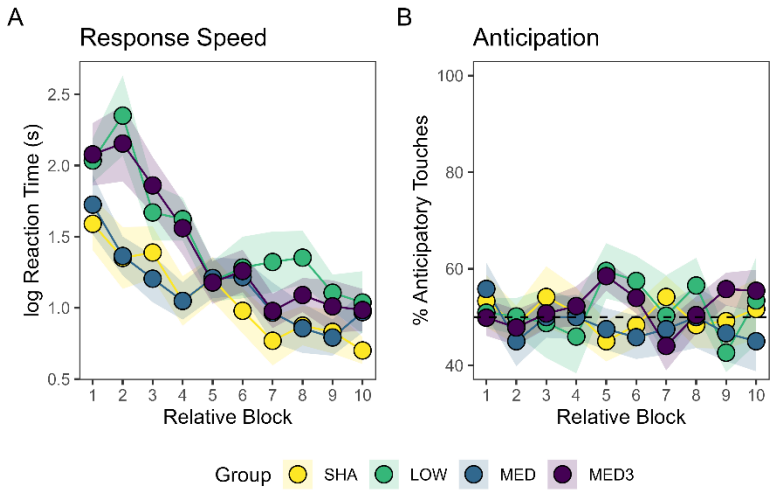

Figure 2. Task 1 results. None of the blast groups differed from the sham group in either response speed or the development of anticipatory responding. A. Log mean choice reaction times (in log seconds) as a function of relative block. B. Mean percentage of anticipatory touches made to the sample stimulus as a function of relative block. The shaded areas represent the standard error of the mean. SHA = No blast, sham control group; LOW = Low intensity blast group; MED = Medium intensity blast group; MED3 = Three medium intensity blasts group.

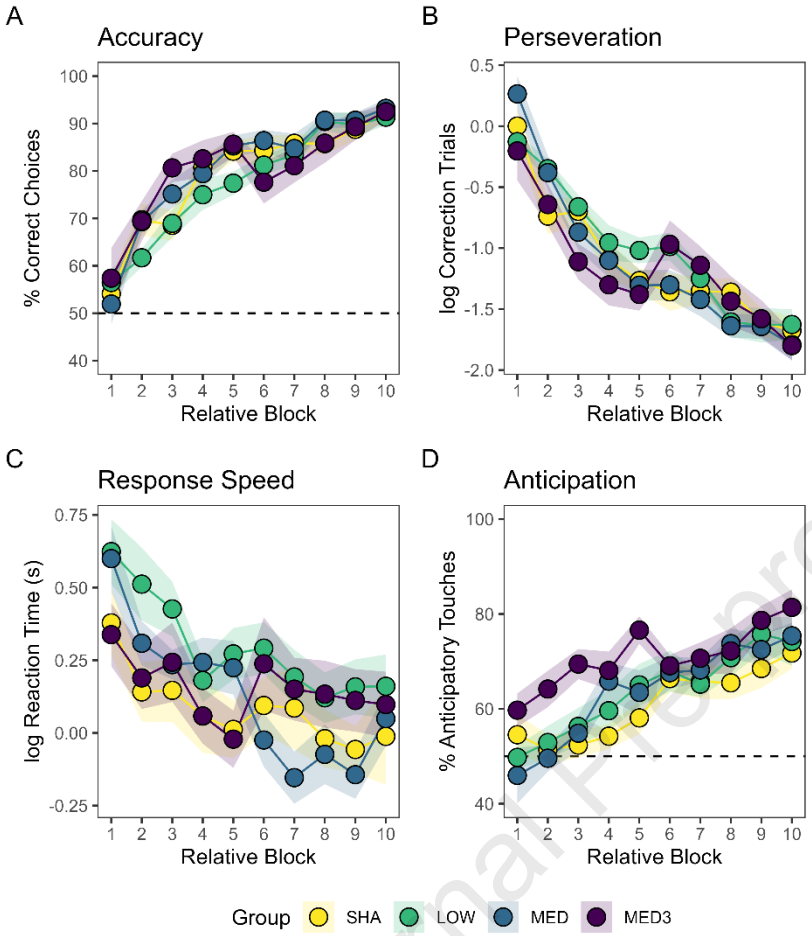

Figure 3. Task 2 results. None of the blast groups significantly differed from the sham groups in task accuracy, frequency of perseverative errors, response speed or anticipatory responding. A. Log mean choice reaction times (in log seconds) as a function of relative block. B. Mean percentage of anticipatory touches made to the sample stimulus as a function of relative block. C. Mean percentage of correct choices as a function of relative block. D. Log mean number of correction trials as a function of relative block. SHA = No blast, sham control group; LOW = Low intensity blast group; MED = Medium intensity blast group; MED3 = Three medium intensity blasts group.

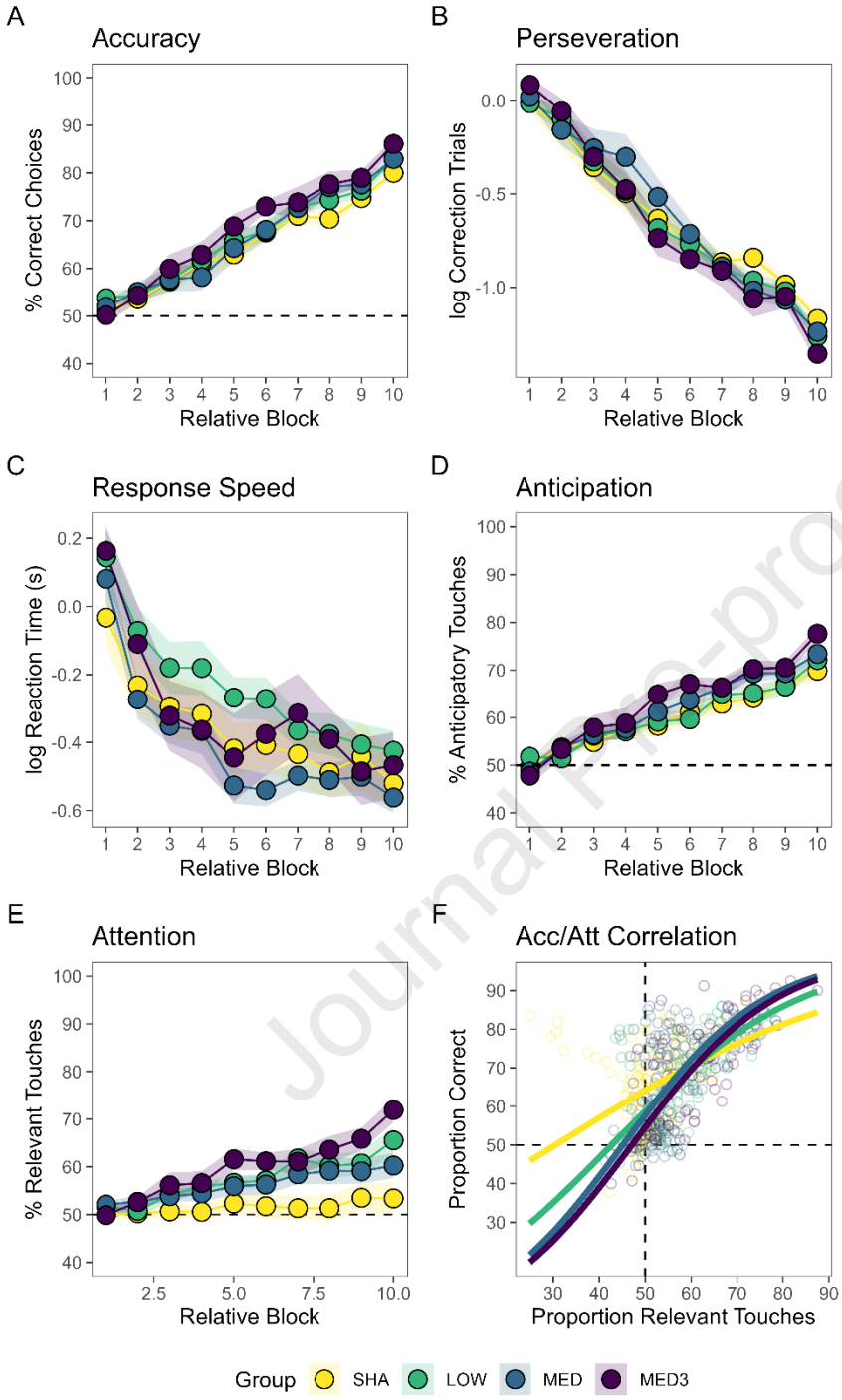

Figure 4. Task 3 results. Relative to the sham group, blast groups were significantly faster in learning the task, leading to faster learning, higher task accuracy, faster reduction of perseverative errors, and greater attention to relevant stimuli. Additionally,

the relation between attention and accuracy was stronger in all blast groups relative to the sham group. A. Log mean choice reaction times (in log seconds) as a function of relative block. B. Mean percentage of anticipatory touches made to the sample stimulus as a function of relative block. C. Mean percentage of correct choices as a function of relative block. D. Log mean number of correction trials as a function of relative block. E. Mean percentage of touches to the relevant sample as a function of relative block. F. Mean percentage of correct choices as a function of the mean percentage of touches to the relevant sample. The lines drawn represent the strength of the relation between the two measures. SHA = No blast, sham control group; LOW = Low intensity blast group; MED = Medium intensity blast group; MED3 = Three medium intensity blasts group.

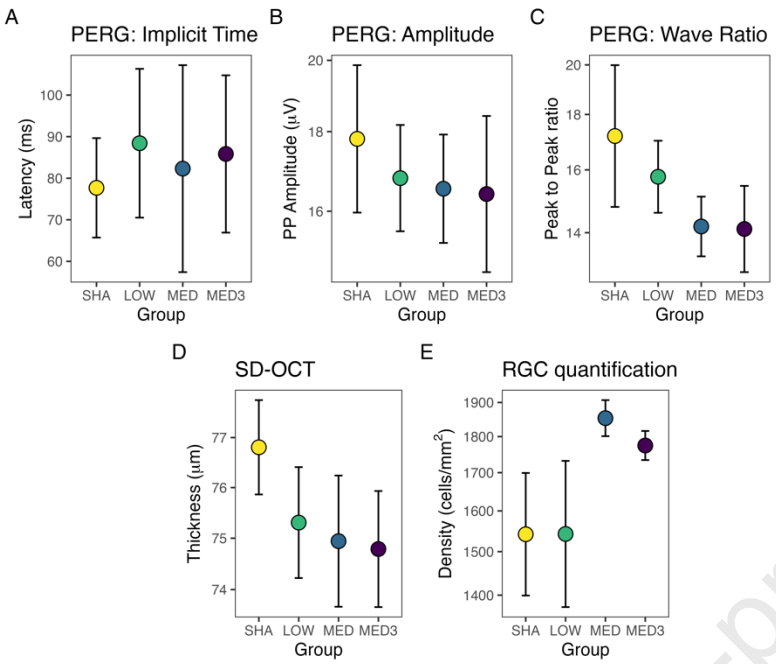

Figure 5. Functional and structural indexes of visual function. There were no significant differences between any of the blast groups (LOW, MED, MED3) and the sham group (SHA), although there were some monotonic trends. A) Latency (in ms) of the evoked potential, B) Peak to peak amplitude (µV, C) Peak to peak ratio, D) RGC complex thickness (µm), E) RGC density (cells per mm^2). Error bars represent the standard error of the mean (SEM). The scales in each panel are logarithmic, with the exception of A (linear). SHA = No blast, sham control group; LOW = Low intensity blast group; MED = Medium intensity blast group; MED3 = Three medium intensity blasts group.

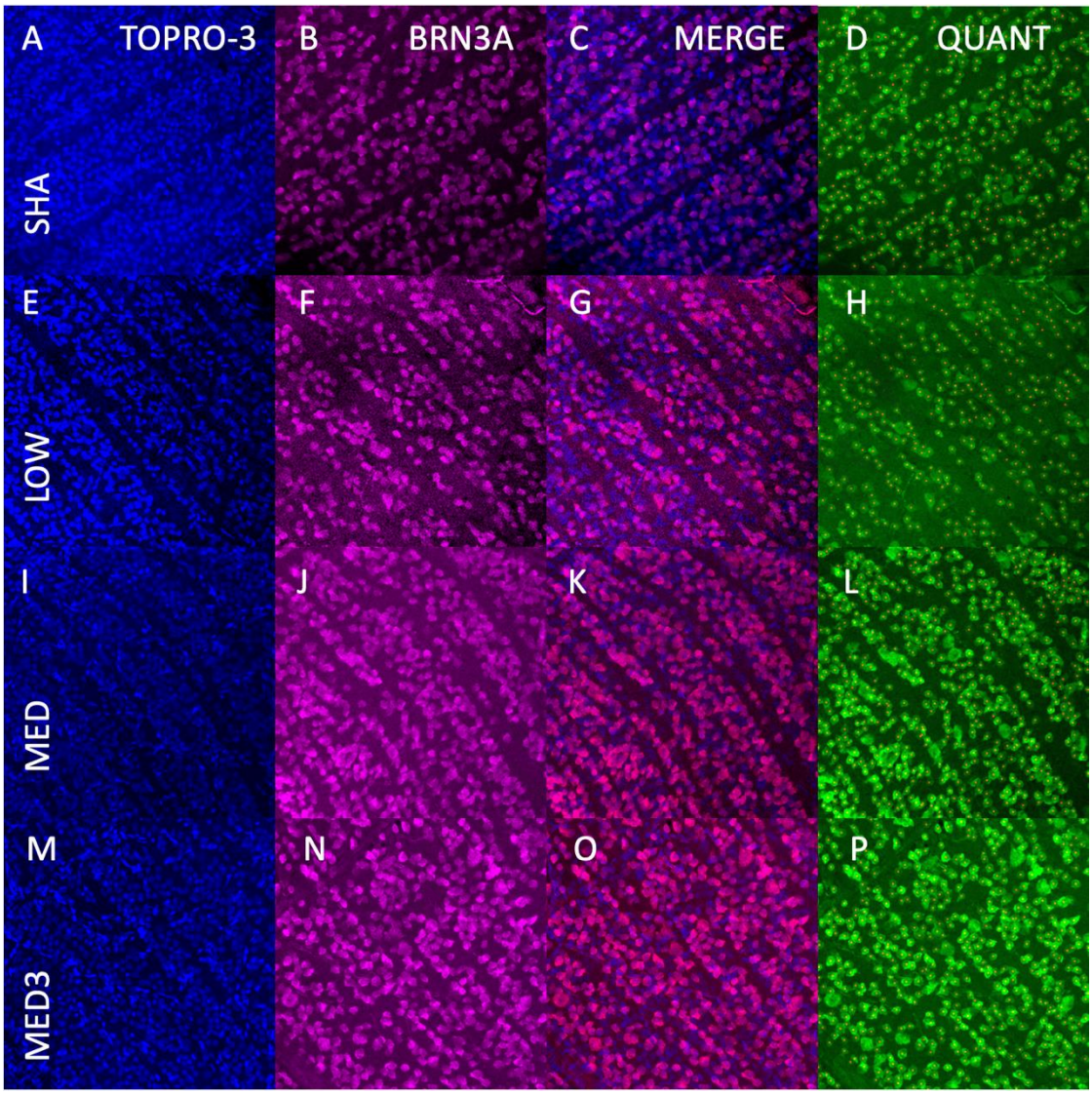

Figure 6. Sample central retina slides for SHA (A-D), LOW (E-H), MED (I-L), and MED3 (M-P) groups. Retinas were stained with TOPRO-3 counterstain (A,E,I,M), BRN3A stain identifying RGCs (B,F,J,N), a merge of the first two (C,G,K,O), and the quantification of RGCs returned by RGCODE (D,H,L,P; orange dots denote cell centroids identified by the program). SHA = No blast, sham control group; LOW = Low intensity blast group; MED = Medium intensity blast group; MED3 = Three medium intensity blasts group. Scale bar 50 µm.

SUPPLEMENTAL INFORMATION

Supplemental tables

Method	Measure	Distribution	Fixed effects	Random subject effects
PERG	Latency	Gamma	Group	None
	Log peak to peak amplitude	Gaussian	Group	None
	Log peak to peak ratio	Gaussian	Group	None
OCT	Log thickness	Gaussian	Group	None
RGC	Log cell density	Gaussian	Group	None
Task 1	Reaction times	Gamma	Log relative block	Intercept
			Group	Log relative block
	Anticipatory responses	Binomial	Log relative block	Intercept
			Group	
Task 2	Log sessions to criterion	Gaussian	Group	None
	Correct responses	Binomial	Log relative block	Intercept
			Group	Log relative block

	Log perseverative errors	Gaussian	Log relative block	Intercept
			Group	Log relative block
	Reaction times	Gamma	Log relative block	Intercept
			Group	
	Anticipatory responses	Binomial	Log relative block	Intercept
			Group	Log relative block
Task 3	Log sessions to criterion	Gaussian	Group	None
	Correct responses	Binomial	Log relative block	Intercept
			Group	
	Log perseverative errors	Gaussian	Log relative block	Intercept
			Group	
	Reaction times	Gamma	Log relative block	Intercept
			Group	Log relative block
	Anticipatory responses	Binomial	Log relative block	Intercept
			Group	Log relative block

	Relevant touches	Binomial	Log relative block	Intercept
			Group	Log relative block
	Accuracy/Attention	Binomial	Log relative block	Intercept
			Group	

Supplemental Table 1. Models used for statistical analysis.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: