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ORIGINAL ARTICLE

Simple tone discriminations are disrupted following experimental frontal traumatic brain injury in rats

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Abstract

Primary objective: To assess cognitive deficits in a rat model of brain injury.
Research design: Cognitive deficits are some of the most pervasive and enduring symptoms of frontal traumatic brain injury (TBI) in human patients. In animal models, the assessment of cognitive deficits from TBI has primarily been limited to tests of spatial learning. Recently, simple discrimination performance has been shown to be sensitive to frontal brain damage. The current study provides a detailed characterization of deficits in a two-choice tone discrimination following a bilateral frontal controlled cortical impact injury.
Methods and procedures: Rats were trained on a two-tone discrimination task in a standard operant chamber, then either a frontal brain injury was delivered or sham procedures performed. Following recovery, they were re-tested on the discrimination task and then tested on a reversal of the discrimination.
Main outcomes and results: Frontal injury caused substantial deficits in responding and discrimination accuracy as well as an increase in side bias.
Conclusions: Based on the outcomes seen in this study, discrimination and other operant tasks may provide a sensitive tool to assess the effect of therapeutic agents on cognitive deficits in animal models, which could lead to improved characterization of deficits and yield an improved assessment tool to aid in drug discovery.

Keywords

Animal models, controlled cortical impact, operant learning

History

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Introduction

It has been estimated that 10 million people suffer a traumatic brain injury (TBI) each year worldwide [1]. TBI is a major problem, especially since there are currently no approved pharmacological treatments. In particular, frontal brain injuries have been shown to have significant detrimental consequences for a variety of day-to-day behaviours and can result in a wide range of symptoms, including increased impulsivity, increased aggression, impaired response inhibition, decreased motivation and poor decision-making [2–6]. These cognitive consequences are frequently considered to be the most difficult to recover from following a brain injury and a person with a frontal brain injury may not even be aware of the extent of the deficits [7].

The physical and pathophysiological characteristics of TBIs are often unique, making treatment options more difficult. A frontal TBI can affect multiple brain regions, each responsible for the control of unique behavioural functions. Because of the heterogeneous nature of human TBI, it is very important to study experimental TBI within animal models that replicate physiological and behavioural consequences seen in humans. To this end, several animal models of TBI have been developed that cause considerable deficits and replicate the pathophysiological consequences of human brain injury. This includes processes such as excitotoxicity, oedema, increased free radical production and the immune response (for review, see Werner and Engelhard [8]). The primary result of this is the development of a lesion cavity, an area where cells have undergone apoptotic or necrotic death, but cell death also occurs in areas adjacent and even distal from the lesion cavity.

In rodent models, this cell death can damage several key structures in the brain and underlies many of the behavioural deficits observed after TBI. The frontal lobe of the rat has been proposed to be homologous to the human frontal lobe in terms of behavioural functions [9]. In the case of targeted excitotoxic or electrolytic frontal brain lesions in rodents, these deficits can range across the spectrum of human consequences described above [10–12]. However, in the field of experimental TBI, very few tests are performed to fully assess frontal cognitive functioning following TBI. The majority of tasks rely on maze performance to gauge acquisition of spatial learning as the sole measure of cognition. In a review of tasks used to test function following TBI, a 2004 paper identifies multiple types of spatial mazes and only two other tasks, passive avoidance and the gustatory neophobia task, for assessing cognition [13].

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This demonstrates the relatively limited scope of cognitive assessment in the experimental TBI field compared to other areas such as lesion studies.

Despite the considerable lack of cognitive tests in experimental TBI, there is some interest in bridging the gap between deficits seen in humans with TBI and those seen in animal models of TBI. This is especially important considering the number of pharmaceutical agents which have shown success in animal models, yet failed in humans [14]. Operant conditioning procedures have been developed that are specialized in the assessment of cognitive functions in humans and animals. In the literature on operant conditioning, there is a wide variety of tasks that are dependent on frontal brain functioning, such as decision-making, impulsivity and working memory tasks [10–12]. Cognitive deficits observed in humans with damage to similar brain structures are very similar to those seen in animals following lesions of analogous areas [5, 15, 16]. Decision-making has been studied in a large number of paradigms under a variety of different conditions, such as interfering/confounding stimuli (i.e. Stroop effect), poor stimulus discriminability and brain lesions [17–19].

Of particular interest for animal modelling in the field of TBI are simpler tasks that may reveal deficits following a frontal brain injury, such as the capacity to make accurate discriminations. Basic discrimination performance, while seemingly simple, is foundational to many more complex cognitive processes of decision-making, memory and sensitivity to external contingencies. For a person, simple discriminations are performed thousands of times during a given day and, thus, may be especially relevant to people who have suffered a TBI. Recently, the laboratory has begun to investigate how rats with different brain injuries respond on a simple discrimination task. It was found that frontally brain-injured rats showed strong deficits in remembering, acquisition of novel discriminations and reversals of discrimination contingencies under a simplified scent-discrimination paradigm. In contrast, rats with unilateral parietal injuries (a very common experimental injury model) showed no deficits in those functions, suggesting that these abilities are strongly mediated by the frontal cortex [20].

This paper describes an experiment that investigated the relationship between frontal TBI and simple conditional discriminations of high vs low tones using a standard automated operant chamber. A single subject design was adopted in order to focus the evaluation of the effects of TBI on the nuances of discrimination performance rather than a gross comparison of group differences. Based upon a previous study, injured rats were expected to show strong deficits in both the original discrimination as well as a reversal.

Methods

Subjects

The subjects were five male Sprague-Dawley rats (E01, E02, E08, E09, E10), ~3 months of age and experimentally naïve when training began. All procedures described in this study were approved in advance by the Institutional Animal Care and Use Committee and the study was conducted in laboratory facilities certified by the American Association for the Accreditation of Laboratory Animal Care. Rats received 15 grams of chow 1 hour after experimental sessions to maintain a weight of 350 grams. Rats were housed on a 12:12 hour light:dark cycle and water was available *ad libitum*. Testing was conducted daily during the light cycle.

Apparatus

The apparatus was a standard two-lever operant chamber (30 cm × 24 cm × 29 cm; Coulbourn Instruments, Allentown, PA), enclosed in a sound-attenuated box. A centrally located houselight, 1 cm from the ceiling, provided general chamber illumination. A liquid dipper, 1 cm off of the grid floor, was equipped to deliver 0.06 ml presentations of sweetened condensed milk (dilution 1:3, milk:water) and was centred between two response levers which were located 2 cm off the grid floor and 13 cm apart. Stimulus lamps, enclosed in white jewel casings, were located 3.5 cm above both levers and the dipper. A computer adjacent to the operant chamber provided tone presentations and control of stimuli and recording of responses using a PDISO-16 card interface (Measurement Computing, Norton, MA). Experimental events were controlled and data were collected using custom software written and compiled in QuickBasic 4.5.

Training

The first four sessions served to habituate rats to the operant chamber. Reinforcers were delivered independent of responses in ~30 second intervals. During reinforcer presentation, everything in the chamber turned off with the exception of an illuminated lamp in the dipper receptacle, which allowed 3 seconds of access to 0.06 ml of reinforcer. Once the rats reliably approached and consumed the reinforcer, lever pressing was established by the method of reinforcement of successive approximations independently for the left and right levers. The final training procedure involved 50 trials of randomly assigning either the left or the right lever ($p = 0.5$) to deliver a reinforcer following a single press. Once pressing occurred reliably, discrimination training began.

During discrimination training, each session started with a 5 minute blackout period, where the chamber was dark and lever presses produced no consequences. After the blackout period, the session began with discrete discrimination trials lasting for 10 seconds and separated by a 25-second inter-trial interval (ITI). During the ITI all stimuli in the chamber were extinguished and responding reset the interval, such that each response would postpone the start of the next trial by 25 seconds. Trials started with the illumination of the houselight, illumination of the three lamps and presentation of either a low pitch tone (600 Hz) or a high pitch tone (2000 Hz). Following the steps below, rats were trained to respond on the left lever to the low tone and on the right lever to the high tone. Correct responses resulted in reinforcer delivery, followed by a 22 s ITI, while incorrect responses led directly to a 25 s ITI. If the subject did not respond during the 10 second trial, a non-response was recorded and the trial transitioned to a 25 second ITI. Sessions lasted until 200 trials were completed or 60 minutes elapsed.

To facilitate learning of the tone discrimination, a series of phases were presented which progressively established discrimination of the two tones. Phase 1 of the tone discrimination training lasted for 12 days and sessions were divided into four alternating blocks of 50 consecutive trials of one trial type (i.e. high pitch with right responses reinforced). As training continued, the number of trials per block was systematically decreased into smaller alternating blocks. First, eight blocks of 25 trials were presented, then 20 blocks of 10 trials and, finally, 40 blocks of five trials. Each of these presentations lasted for three sessions. During phase 2 of tone discrimination, each session started with the first 100 trials divided into 20 alternating blocks of five trials of one type and then presented the last 100 trials randomly assigned to left or right ($p = 0.5$). Once rats were successfully completing these sessions and showing sensitivity to the discrimination, rats were advanced to the final phase. In Phase 3 every trial type was randomly determined. On this phase, once rats reached an 80% accuracy criterion for at least 3 consecutive days they were scheduled to undergo surgery.

Surgery

Surgical procedures were performed under aseptic conditions according to previous studies [20, 21]. Rats were anaesthetized under a combination of isoflurane (2–4%) and oxygen (0.8 L/min) and placed in a stereotaxic device. Body temperature was monitored and maintained at 37 °C. Rats were randomly assigned to either injury or sham procedures. For the injury procedure, a controlled cortical impact injury was delivered. An incision was made along the midline of the rat skull and the fascia retracted. A 6.0 mm craniotomy was made centred on the midline at +3.0 mm from bregma using a surgical microdrill. Care was taken to avoid damage to the meninges and dura. A 5.0 mm diameter stainless steel impactor tip was attached to an electromagnetic impactor (myneurolab.com) and centred within the craniotomy. The impactor was retracted, lowered to a depth of 2.5 mm and then the cortex was impacted at a rate of 3.0 m/s with a contact time of 0.5 second. After the injury, bleeding was stopped using sterile gauze, the incision was sutured and the animal was placed in a heated recovery chamber. The sham procedure followed an 'intact sham' process; an incision was made and then sutured under anaesthesia. No craniotomy was performed. Animals were allowed to recover for 5 days before returning to testing. Food was available *ad libitum* for the first 3 days of recovery and then returned to the 15 gram per day limit.

Testing

Assessment began according to a pre-determined schedule. Rats resumed daily testing on the tone discrimination task until they recovered to close to baseline performance (minimum 12 days). In the case of one injured rat, an intervention was done after 15 days of non-responding. The intervention was one session of simple re-shaping of responses to the lever for ~30 minutes. Following discrimination assessment, rats were given a reversal of the discrimination, in which responses to the right lever were correct for the low tone and responses to the left lever were correct for the high-pitched tone. Rats were given a maximum of 20 sessions to learn the reversal before being sacrificed to examine brain tissue loss.

Histology

On post-surgery day 45, animals were anaesthetized with a lethal dose of sodium pentobarbital (Euthasol, Virbac Animal Health; 0.3 mL i.p.) and then transcardially perfused with ice-cold 0.9% phosphate buffered saline, followed by 10% phosphate buffered formalin (PBF). The brain was then removed from the skull and post-fixed in PBF for 24 hours. After post-fixing, brains were placed in a 30% sucrose solution for 3 days. Following saturation, they were blocked and then sliced frozen on a sliding microtome at 40 μm. A series of brains slices transversing the lesion cavity were then mounted on gelatine-subbed microscope slides for staining. Slides were stained with cresyl-violet according to previously published protocols and coverslipped for examination by light microscopy [20].

To examine the extent of the lesion, five sections were selected (+5.0, +4.0, +3.0, +2.0, +1.0 from bregma). These sections were photographed under a camera (Olympus DP-70, Center Valley, PA, USA) attached to a microscope (Olympus BX-51, Bethesda, MD, USA). The areas for each section were calculated using imaging software (ImageJ, NIH). The volume was then estimated using the Cavalieri method as described in previous studies [20], the mean area from the sections was multiplied by the thickness of the sections (40 μm) and the total number of sections (five). The resulting volumes were then compared.

Data analysis

The data were analysed using an interrupted time series (ITS) analysis [22]. Each subject was analysed independently. Independent ITS models were fit for each subject with parameters assigned for the overall effect of time, the effect of surgery on discrimination, change in slope of the data after surgery, the effect of reversal and the change in slope of the data after the reversal. Whether or not a parameter was a significant contributor to the model determined whether there was a significant effect. The overall model fit was also assessed in terms of adjusted R^2 to help determine how well the pre-determined model fit the data.

The analysis of discrimination performance was broken out into several relevant parameters for assessment at the individual subject level. Specifically, this study analysed three different components of performance: completed trials, accuracy and bias. Completed trials were measured in percentage completed trials per session, the accuracy was analysed in Log D values and the bias was analysed in Log B values. Log D and Log B are parameters of a model that is functionally equivalent to the signal detection theory parameters (d' and C, respectively) which estimates the accuracy of discrimination performance and bias as independent terms. These log value parameters are especially useful for analysing choice data that is constrained by a floor or ceiling (i.e. 0% or 100%; for details on Log D see [23], for details on signal detection theory see [24]). Log D was computed by the following formula of left (L) and right (R) correct (C) and incorrect (I) responses: [0.5 * Log((L_C/R_I) *

$(R_C/L_I))$]. Log B was calculated by the following formula: [0.5 * Log((L_C/L_I) * (R_I/R_C))]. For both Log D and Log B, non-responses were not taken into account since they are analysed separately in the measure of completed trials.

Results

Overall performance

A high pre-surgery accuracy was established and maintained in both the sham ($M = 85.36$, slope = 0.22) and TBI groups ($M = 86.53$, slope = 0.10). Following surgery, the sham group maintained high levels of accuracy with little change ($M = 86.88$, slope = 0.29). Post-injury, the performance in the TBI group dropped off substantially ($M = 38.58$), but improved over time (slope = 3.70). Following a reversal, the sham accuracy dropped considerably ($M = 54.43$), but they began to improve (slope = 1.39). The TBI group also had low accuracy ($M = 47.57$), but their trend actually suggested a worsening of performance (slope = −0.44). One rat in the TBI group required intervention due to complete non-responding and, thus, did not receive the reversal. The intervention consisted of a simple hand-shaping procedure to reinforce lever pressing again. Once the rat began pressing again, he followed a similar pattern of recovery to the other two rats. See Figure 1 for a summary of performance.

Trials completed

The percentage of completed trials was computed for each session and put into a separate ITS model for each subject. The fit of the model ranged from an adjusted R^2 of 0.263–0.797 in the injured animals and −0.058–0.271 for sham animals, showing that the model more accurately predicted change as a result of injury. Specifically, all three injured animals had a significant effect of brain injury on completed trials during the discrimination phase and two of three had a significant positive effect of slope, suggesting recovery of responding. There was no effect of reversal phase on mean completed trials for injured animals, but there was a significant effect of slope during the reversal for the two injured animals. Specifically, the slope for both injured animals was negative, suggesting a decrease in number of completed trials during the reversal. One sham animal showed a change in slope after surgery and a significant change in both mean trials completed during the reversal as well as slope. This was largely due to an extremely flat baseline, which leads to a poor fit for this model since it predicts changes. See Figure 2 for details for each subject. Specific model parameters can be found in the Appendix.

Accuracy

The Log D values were computed for each session and put into a separate ITS model for each subject. The fit of the model ranged from an adjusted R^2 of 0.784–0.929 in the injured animals and 0.861–0.873 for sham animals, showing very good predictive value of all of the models for predicting accuracy. The injured animals showed specific effects of brain injury on mean discrimination accuracy in all three injured animals and two of them had significant positive changes in slope, suggesting recovery of performance.

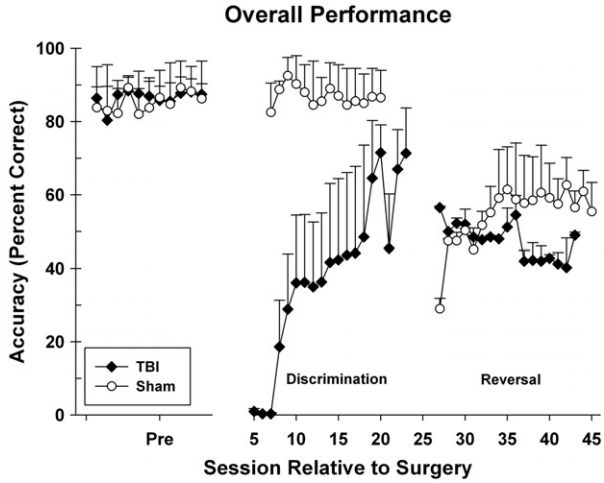

Figure 1. Overall accuracy across sessions. Injured animals show a severe drop off in performance after frontal TBI, while shams remain stable. Following a reversal of the discrimination, injured animals show slightly less sensitivity to the change.

Following the reversal, both injured animals had significant changes in accuracy and a significant effect of slope. It should also be noted that one of the injured rats had a negative slope, indicating a trend towards decreasing accuracy. Neither sham animal showed any change on discrimination accuracy post-surgery. Both shams showed a significant effect of the reversal, with both having decreased accuracy. One sham animal had a significant positive slope, showing some recovery of performance. See Figure 3 for details on each subject. Specific model parameters can be found in the Appendix.

Bias

The Log B values were computed for each session and put into a separate ITS model for each subject. The fit of the model ranged from an adjusted R^2 of 0.147–0.756 in the injured animals and 0.533–0.602 for sham animals, showing reasonable predictive value for most subjects in evaluating bias. Two of the three injured animals showed an effect of injury on bias on the discrimination, but only one had a significant slope due to recovery of extreme bias. Both injured animals showed a significant effect of bias due to the reversal, but again only one had a significant slope, suggesting attenuation of the bias. The bias for the sham animals was unaffected on the discrimination by surgery. However, on the reversal, they both showed significant changes in bias, but also significant slopes, showing a recovery to baseline bias levels. See Figure 4 for the sensitivity of each subject. Specific model parameters can be found in the Appendix.

Lesion analysis

The brain volumes were measured for each subject. The injured animals ($M = 46.29$) had reduced brain volumes compared to the sham animals ($M = 58.67$). A one-way ANOVA showed that this difference was significant, $F(1, 3) = 14.92$, $p = 0.031$. See Figure 5 for the brain volume of each subject.

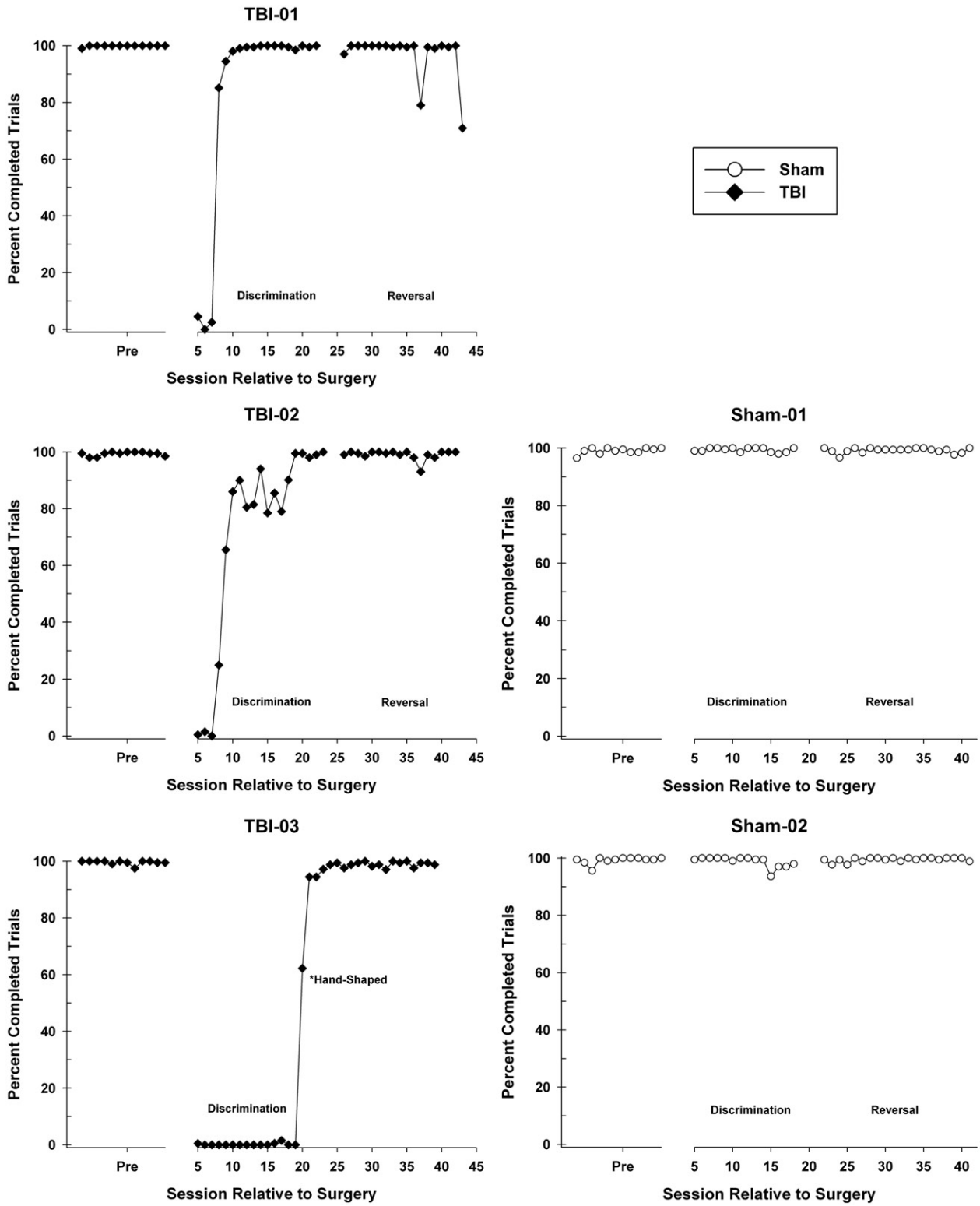

Figure 2. Completed trials across sessions. The percentage of completed trials for injured rats dropped off severely after frontal TBI, but recovered with time and was mostly unaffected by a reversal of discrimination.

Discussion

This paper showed that frontal TBI decreased accuracy on a two-choice operant tone discrimination task. Additionally, this decrease in accuracy was mediated by transient decreases in responses, impaired discrimination accuracy and increased bias towards one side. This pattern was observed across each of the subjects. The data from each outcome measure in injured animals was well described by the ITS models and revealed significant deficits that were consistent across subjects. In contrast, the sham models revealed significant changes in discrimination accuracy (Log D) only following the contingency reversal.

The deficits in injured animals seen on this task map on to many of the cognitive deficits reported in humans following TBI. The impairments in responding suggest possible ties

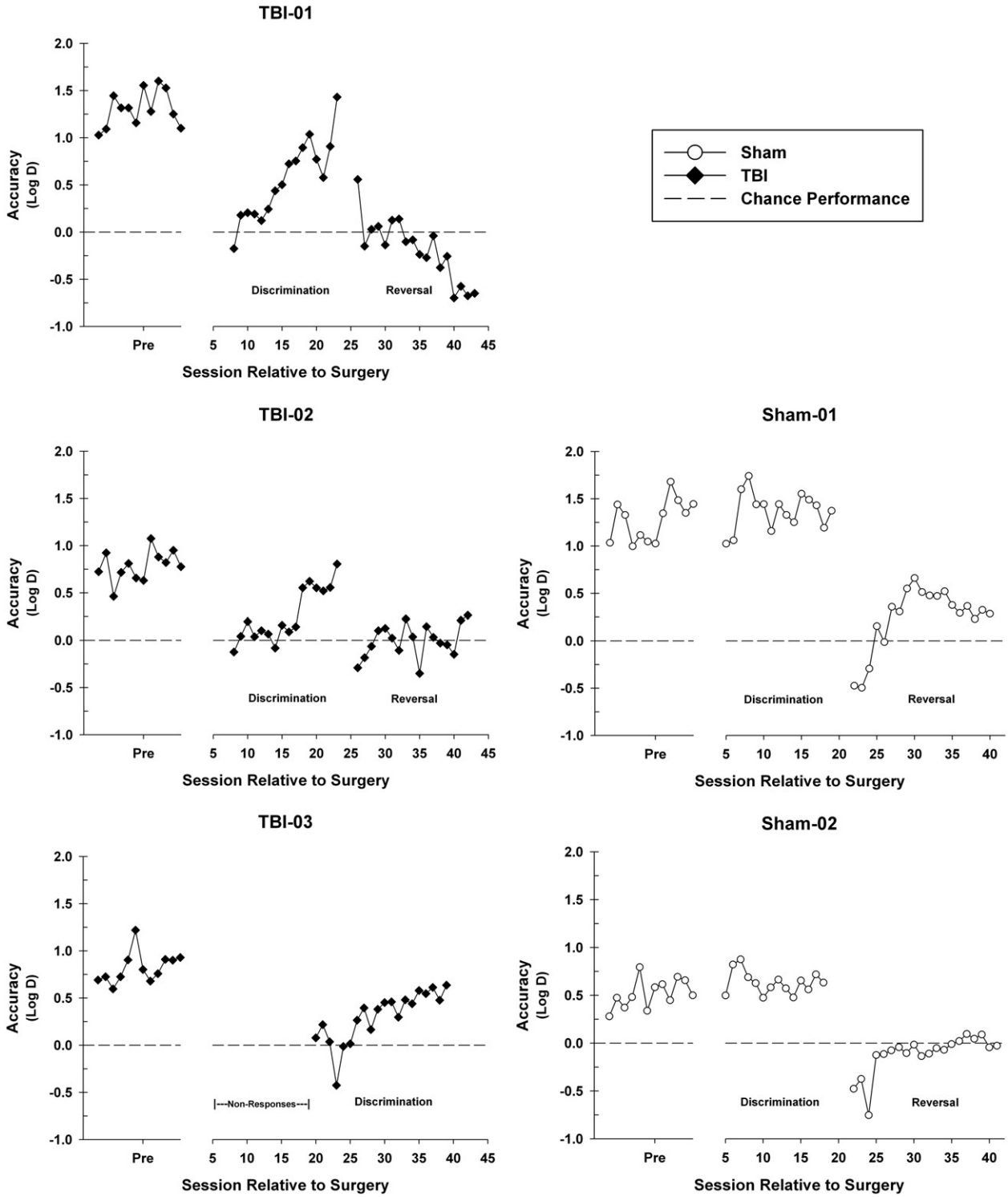

Figure 3. Discrimination performance across sessions. Injury causes a severe drop off in accuracy, which recovers with time. A reversal of the discrimination causes lower discrimination accuracy in both injured and sham rats.

to motivational deficits after the injury event. Apathy, anhedonia and depression have been widely reported in human cases of TBI [2, 6]. These can have a major impact on life quality for patients suffering from TBI and affect the ability to perform everyday tasks. The impairments in discrimination as well as the tendency to develop biased responding in the frontally-injured rats directly relate to insensitivity to changes in contingencies, seen in human patients on the Wisconsin Card Sorting Task [25] and other operant measures [5, 26]. In fact, such insensitivity to external contingencies has been advanced as a major factor in impaired decision-making that is seen in patients with TBI [16]. These impaired decisions, based on an inability to discriminate accurately between options can lead to detrimental consequences in everything from financial decisions to appropriately evaluating social situations.

Based on these comparisons to human brain injury, the bilateral frontal model of injury in the rat appears to generate behavioural consequences very similar to human TBI. Furthermore, discrimination tasks such as the one used in

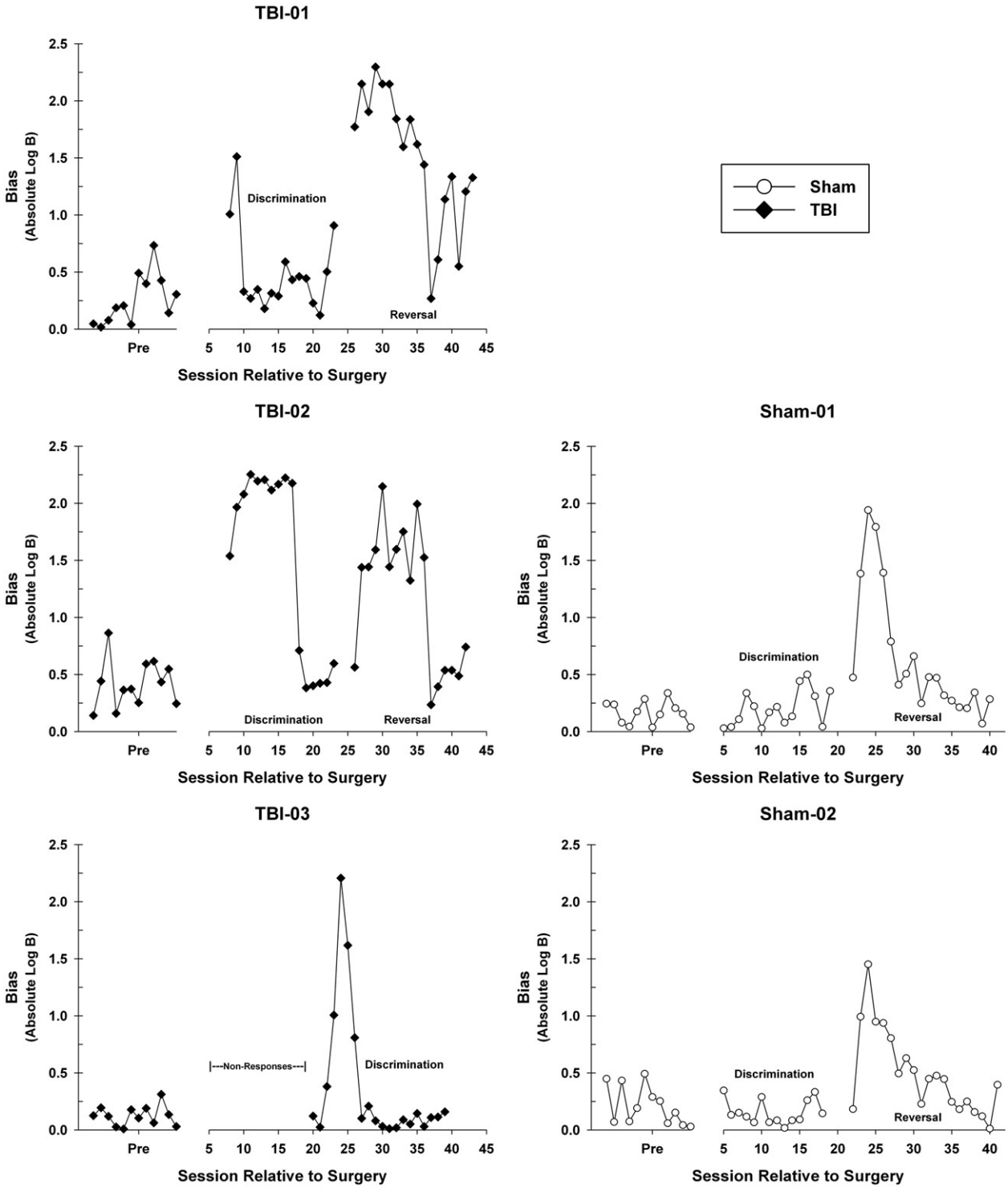

Figure 4. Bias across sessions. Injured rats develop strong biases after frontal TBI, which recover over time. A reversal causes substantial increases in bias, which remains elevated in injured rats.

this study are sensitive to analysing these deficits at a level that cannot easily be captured by basic maze learning assessments; in particular the amount of data collected and number of trials assessed lead to a more complete picture of specific deficits. In the assessment of human TBI, discrimination tests such as the Visual Form Discrimination Test and the Assessment of Basic Learning Abilities are routinely used to detect the extent of deficits [26, 27]. The use of animal outcome measures that closely replicate human dysfunction following injury can only improve the animal models and make them more sensitive to various assessments.

This study represents the fullest characterization to date of discrimination deficits following traumatic brain injury. Previous work only analysed behavioural dysfunction at the level of accuracy, not investigating the many nuances that underlie discrimination deficits [20]. The study of these deficits is enhanced by the use of a single-subject design which gives the flexibility to examine a number of very fine outcome measures at the individual level. Furthermore, this is

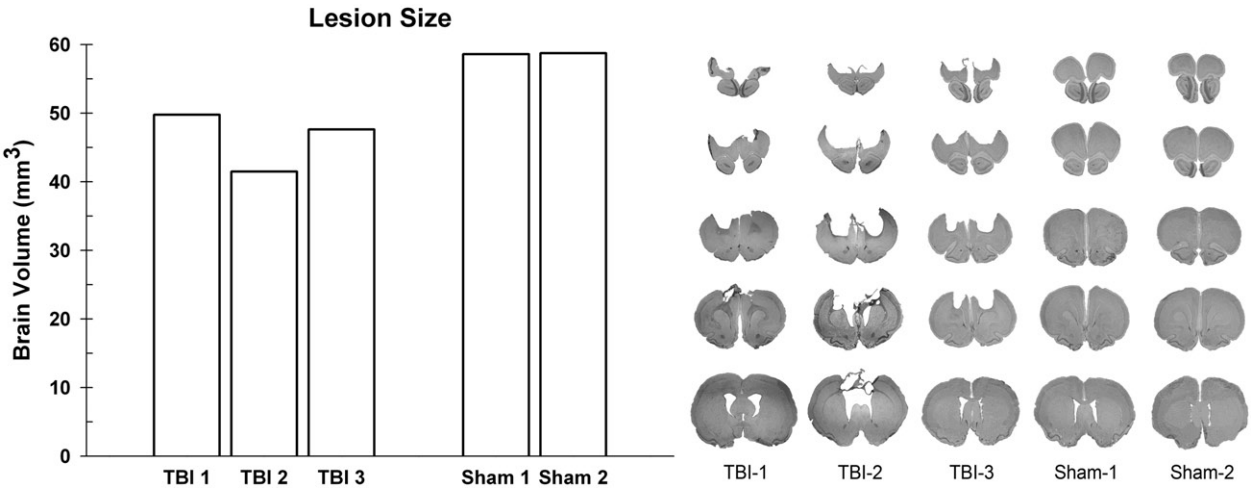

Figure 5. Brain volume. The left panel shows that injured rats had reduced brain volume following frontal TBI. The injured rats had volumes ranging from 40–50 mm^3, while sham volumes were ~60 mm^3. The right panel shows images of the brains of the five subjects.

one of very few studies to utilize non-spatial discrimination as an outcome measure after TBI, despite its social relevance [28, 29]. Based on the severe deficits seen across these studies, simple discrimination may represent an ideal method for assessing therapeutic agents. Cognitive deficits are frequently neglected in animal models of TBI, despite being some of the most enduring and difficult to deal with in humans [30]. The use of maze learning as the sole measure of cognition in animal models places researchers at a strong disadvantage when trying to evaluate the effects of a therapeutic agent on cognitive performance.

Additionally, the use of discrimination tasks in TBI highlights the potential of other operant measures for assessing dysfunction following brain injury in rats. Other forms of discrimination assessments may provide valuable information about the capabilities of animals after these types of injuries. Of specific interest would be a characterization of other stimulus modalities in rats, such as visual, as well as investigation of the degree of generalization of a stimulus after injury. Additionally, the use of compound stimuli with many relevant features could allow for the assessment of other aspects of cognition. Given the apparent anhedonia shown by rats in the current study (evidenced by lack of responses), other motivational operant measures such as progressive ratio or an assessment of the demand curve, both of which increase the response or effort requirements over time, could help evaluate whether the lack of responding is due to an inability to discriminate or due to an amotivational state. Memory tasks such as delayed match to sample could provide an estimate of the ability of injured rats to remember specific stimuli or patterns. The large downside to an operant analysis of behavioural performance after an injury is the training requirements associated with these tasks. However, based on what has been observed so far, the benefits likely largely outweigh the disadvantages, particularly if it leads to the discovery of a pharmaceutical agent or therapy that can treat the multitude of cognitive deficits associated with human TBI.

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Declaration of interest

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Appendix

Completed trials interrupted time series model parameters

Table A1. Completed trials interrupted time series model parameters.

	Model fit	Overall slope		Discrimination		Discrimination slope		Reversal		Reversal slope	
	Adj R^2	β	p	β	p	β	p	β	p	β	p
TBI-01	0.263	0.02	0.984	−0.92	0.001	1.61	0.116	−0.13	0.640	−0.86	0.006
TBI-02	0.533	0.03	0.973	−1.22	<0.001	2.24	0.007	−0.30	0.185	−1.17	<0.001
TBI-03	0.797	−0.16	0.976	−1.14	<0.001	1.08	0.022	x	x	x	x
Sham-01	−0.058	0.14	0.908	−0.39	0.264	0.47	0.702	0.01	0.975	−0.29	0.501
Sham-02	0.271	1.68	0.087	0.25	0.411	−3.90	0.001	0.74	0.016	1.65	<0.001

Log D interrupted time series model parameters

Table A2. Log D interrupted time series model parameters.

	Model fit	Overall slope		Discrimination		Discrimination slope		Reversal		Reversal slope	
	Adj R^2	β	p	β	p	β	p	β	p	β	p
TBI-01	0.929	0.31	0.306	−0.98	<0.001	1.07	0.001	−0.60	<0.001	−1.10	<0.001
TBI-02	0.826	0.59	0.206	−1.24	<0.001	1.03	0.034	−0.99	<0.001	−0.55	0.002
TBI-03	0.784	0.52	0.164	−1.44	<0.001	0.36	0.242	x	x	x	x
Sham-01	0.861	0.69	0.126	−0.09	0.515	−0.49	0.300	−1.26	<0.001	0.31	0.091
Sham-02	0.873	0.71	0.081	0.05	0.678	−0.80	0.076	−1.25	<0.001	0.52	0.006

Log B interrupted time series model parameters

Table A3. Log B interrupted time series model parameters.

	Model fit	Overall slope		Discrimination		Discrimination slope		Reversal		Reversal slope	
	Adj R^2	β	p	β	p	β	p	β	p	β	p
TBI-01	0.756	0.68	0.231	0.14	0.396	−0.93	0.110	1.36	<0.001	−0.48	0.021
TBI-02	0.586	0.12	0.867	1.28	<0.001	−2.06	0.007	0.81	0.001	0.47	0.070
TBI-03	0.147	0.03	0.969	0.70	0.041	−0.64	0.289	x	x	x	x
Sham-01	0.602	−0.11	0.880	−0.08	0.701	0.54	0.472	1.21	<0.001	−1.27	<0.001
Sham-02	0.533	−1.07	0.163	0.12	0.605	0.89	0.288	1.33	<0.001	−0.93	0.008