An Experimental Animal Model that Parallels Neurosensory Assessments of Concussion

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ABSTRACT

Introduction:
Tactile-based quantitative sensory assessments have proven successful in differentiating concussed vs. non-concussed individuals. One potential advantage of this methodology is that an experimental animal model can be used to obtain neurophysiological recordings of the neural activity in the somatosensory cortex evoked in response to the same tactile stimuli that are used in human sensory assessments and establish parallels between various metrics of stimulus-evoked cortical activity and perception of the stimulus attributes.

Materials and Methods:
Stimulus-evoked neural activity was recorded via extracellular microelectrodes in rat primary somatosensory cortex (S1) in response to vibrotactile stimuli that are used in two particular human sensory assessments (reaction time (RT) and amplitude discrimination). Experiments were conducted on healthy control and brain-injured (BI) rats.

Results:
Similar to the effects of mild traumatic brain injuries (mTBI) on human neurosensory assessments, comparable experimentally induced brain injuries in rats resulted in the following: (1) elevation of S1 responsivity to vibrotactile stimulation that depended nonlinearly on stimulus amplitude, significantly reducing its capacity to discriminate between stimuli of different amplitudes; (2) 50% reduction in S1 signal-to-noise ratios, which can be expected to contribute to elevation of RT in BI rats; and (3) 60% increase in intertrial variability of S1 responses to vibrotactile stimulation, which can be expected to contribute to elevation of RT variability in BI rats.

Conclusions:
The results demonstrate suggestive similarities between neurophysiological observations made in the experimental rat mTBI model and observations made in post-concussion individuals with regard to three sensory assessment metrics (amplitude discrimination, RT, and RT variability). This is the first successful model that demonstrates that perceptual metrics obtained from human individuals are impacted by mTBI in a manner consistent with neurophysiological observations obtained from rat S1.

INTRODUCTION

For the past decade and a half, novel tactile-based neurosensory assessment measures have been developed that have demonstrated significant utility for evaluating a wide spectrum of neurological disorders and/or neurological insults.[1–16] Because these measures were both designed on the basis of, and have proven to be sensitive to, dynamics of stimulus-evoked neural activity observed in the cerebral cortex, we have termed them "cortical dynamic metrics" or, more commonly, "cortical metrics." Most recently, a number of reports have demonstrated the impact that concussion has on cortical metrics.[1,17–22] These reports hypothesized that concussion has an impact on cortical information processing, and for that reason, we sought to investigate directly the parallels between cortical metrics measurements that were obtained from concussed individuals and the responses evoked by the same stimuli in the cortex in brain-injured (BI) rats. To pursue this line of inquiry, an experimental animal model was developed in order to assess the impact that a mild brain injury has on the specific cortical mechanisms of sensory information processing that are reflected by cortical metrics in humans. In this report, we describe the observations obtained from rat somatosensory cortex while delivering the same patterns of vibrotactile stimuli that are typically delivered during tactile-based neurosensory assessments in humans. Such observations were obtained from both healthy control (HC) and BI rats, allowing us to compare the stimulus-evoked neural responses in the rat primary somatosensory cortex (S1) to cortical metrics observations obtained from concussed and non-concussed individuals.

In our previous and ongoing cortical metrics studies of concussion, a battery of tests are administered to individuals and an overall cortical metric score is derived from a multiparametric evaluation of those values.[18,21] In the most recent report, receiver operating characteristic analysis was used to evaluate the metrics that were most sensitive to concussion, and the three most sensitive metrics evaluated were reaction time (RT), RT variability, and amplitude discrimination.[21] These three metrics are obtained with two neurosensory tasks

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(RT and amplitude discrimination), and these are the tasks that are investigated in this study. Both RT and RT variability have been demonstrated to be sensitive to concussion, and although RT variability has been demonstrated to be more sensitive than RT to concussion,[1,20–23] it is not reported as often as RT for the simple reason that most currently used methods lack the accuracy to measure it.[24,25] Examination of the neural basis of RT variability can be achieved most accurately invasively via cortical recordings and examining intertrial variability of the neuronal response. Amplitude discrimination has also been demonstrated to be impacted by concussion and it reflects the ability of the cortex to enhance the contrast between afferent inputs to neighboring cortical modules responsible for representing tactile stimuli at neighboring skin locations.[17,21] Delivering tactile stimuli to the digit tips of a rat and recording the stimulus-evoked activity in S1 allows investigation of the differential response of cortical modules representing these digit tips, which might be expected to underlie a rat's ability to differentiate the intensity of two independent stimuli.[26] These observations are compared in "Discussion" to observations made in human studies utilizing cortical metrics.

METHODS

A total of 20 Sprague-Dawley rats of either sex weighing between 190 and 400 g were used to determine the impact that a mild brain injury has on information processing in the somatosensory cerebral cortex. The experiments conformed to the Principles of Laboratory Animal Care (National Institutes of Health publication No. 86-23, revised 1985) and were approved by the Institutional Animal Care and Use Committee of the University of North Carolina at Chapel Hill.

In eight rats, brain trauma was induced using a closed-head weight-drop method.[27–29] Isoflurane anesthetized rats are placed on tin foil, with a small metal disc placed on top of the head, centered on bregma. A 175 g metal rod is dropped down a guide tube, travelling 50 cm before it hits the metal disc, which distributes the impact evenly over the skull crown. The rod's further fall is stopped by a thread attached to it. The blow to the head splits the tin foil and the animal falls down onto a soft cushion. Such a glancing impact to the unresisting head transmits acceleration, deceleration, and rotational forces upon the brain. This technique produces clinically relevant behavioral outcomes representative of post-concussion symptomatology, including minor deficits in motor coordination and balance.[28] The animals typically recover their righting reflex in 4 minutes and fully recover from anesthesia shortly after. In this study, however, the rats were not allowed to recover from anesthesia, but proceeded straight to the surgery and neurophysiological recording.

To collect neurophysiological data, each isoflurane-anesthetized rat underwent a non-survival surgical procedure involving (1) removal of a restricted section of the skull that overlies the primary somatosensory cortex of the right cerebral hemisphere and (2) attachment (using dental cement) of a hydraulically sealed recording chamber over the skull opening. Following recording chamber installation, multiple radially oriented exploratory microelectrode penetrations were performed in the S1 cortex, with the animal maintained under 0.4%-0.6% isoflurane in 50/50 nitrous oxide/oxygen anesthesia. In each such penetration, receptive fields (RFs) were mapped by lightly stroking fur, tapping the skin with von Frey filaments, palpation of the muscle bellies and tendons, as well as by passive joint rotations. The spatial location of a "minimal" cutaneous RF was determined by using the weakest still effective von Frey. The S1 cortical region devoted to processing tactile information from the digits comprises a mosaic of discrete columns. Each such column is devoted to processing tactile information from a single digit. Exploratory microelectrode penetrations were performed until finding a cortical column that had its minimal RF on the tip of the index (D2) or middle (D3) digits.

Once the D2 or D3 cortical column was found, extracellular recordings of action potentials emitted by individual cortical neurons residing in this column were obtained in response to vibrotactile stimuli such as those used in the amplitude discrimination cortical metrics task. Specifically, in-phase 25 Hz sinusoidal vertical skin displacement stimuli were applied in parallel to the tips of D2 and D3 for 500 milliseconds. One digit received 200 μm peak-to-peak amplitude vibrations, whereas the other digit received 300 μm peak-to-peak amplitude vibrations. A total of 15 such stimulus trials were performed at each recording site.

RESULTS

S1 Cortical Response to the Amplitude Discrimination Stimulation Protocol

In the amplitude discrimination task, two vibrotactile stimuli are applied simultaneously to the tips of D2 and D3. They differ in their vibration amplitude and the tested human individual is asked to judge which stimulus is stronger. To reproduce this task in rat S1, two vibrotactile stimuli of 200 μm and 300 μm amplitudes were applied simultaneously to the tips of D2 and D3. Concurrently, spike firing activity was recorded in microelectrode penetrations inserted radially into two S1 cortical columns that had minimal RFs confined to the tip of either index (D2) or middle (D3) digits. Single- and multi-unit recordings were obtained in these penetrations throughout the upper, middle, and deep cortical layers. The HC data were collected at 35 recording sites in 22 penetrations performed in 12 intact rats. The BI data were collected at 23 recording sites in 12 penetrations performed in 8 rats that were subjected to concussive head impact 6 to 12 hours prior to the neural recording.

Figure 1 shows peristimulus time histograms of the average spike firing activity of the D2 and D3 cortical columns during coincident in-phase vibrotactile stimulation of the D2 and D3 digits. The grey curve in each plot shows the activity of the cortical column whose RF was stimulated using a skin-contacting probe vibrating at 25 Hz with the peak-to-peak

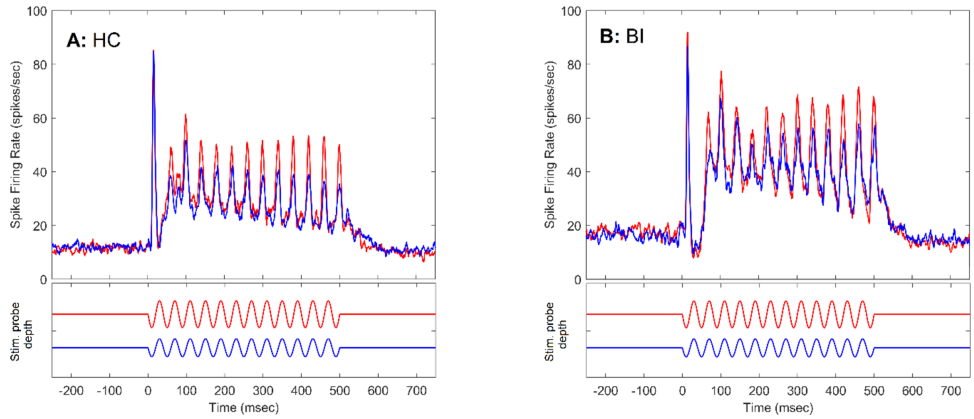

FIGURE 1. Average primary somatosensory cortex (S1) cortical response evoked by two different amplitudes of vibrotactile stimuli, 200 μm and 300 μm, delivered simultaneously to two adjacent digit tips, D2 and D3. Plotted is the spike firing rate computed for each 1 millisecond time bin (and expressed as a number of spikes per second), averaged over all the recording sites in a given cortical column. Curves plotted in gray obtained from S1 column receiving the larger of two stimuli. Black denotes response evoked by the weaker stimulus. (A) Average of the healthy control (HC) rats. (B) Average of brain-injured (BI) rats. Note that the difference between the two responses (black vs. gray) is smaller in the BI rats. Bottom: vibrotactile stimulus trace.

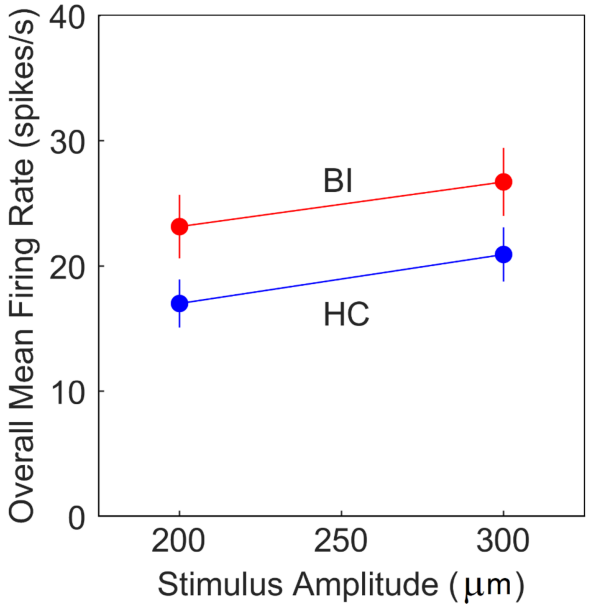

FIGURE 2. Comparison of stimulus-evoked overall mean firing rate (OMFR) vs. stimulus amplitude. Note increase in OMFR of brain-injured (BI) subjects. Error bars—SEM.

amplitude of 300 μm. The black curve in each plot shows the activity of the cortical column whose RF was stimulated with the peak-to-peak amplitude of 200 μm. As the plots show, cortical spike firing oscillated during stimulus presentation in synchrony with oscillations of the stimulating probe on the skin, exhibiting a high degree of stimulus frequency entrainment. Furthermore, 300 μm amplitude stimuli evoked noticeably greater response in the stimulated cortical column than did 200 μm amplitude stimuli.

The strength (or amplitude) of a vibrotactile stimulus is reflected in S1 cortex by the overall magnitude of spiking activity evoked in the responding cortical column, and the amplitude discrimination task can be simulated by evaluating the contrast between spiking activities evoked in the cortical columns representing the stimulated digits.[26] Thus, the relative strengths of two vibrotactile stimuli applied to D2 and D3 digits can be discriminated by comparing the magnitudes of neural responses evoked in the D2 and D3 cortical columns, as is shown in Fig. 1.

According to Tommerdahl et al. and Pearce et al., human performance on the amplitude discrimination test is negatively affected by mild traumatic brain injuries (mTBI).[18,22] Similar negative effect of head trauma can be seen in Fig. 1, which shows that in the HC rats the 300 μm and 200 μm stimuli evoked more distinct responses in the two corresponding cortical columns than in the BI rats. To make these differences more explicit, the response of a cortical column to a stimulus was computed as a difference between the mean firing rate during the stimulus presentation (averaged over all the neurons sampled in that column) and the mean firing rate in the absence of any stimulation (i.e., the spontaneous firing rate). Fig. 2 plots such stimulus-evoked overall mean firing rates in response to the 200 μm and 300 μm amplitude stimuli for the HC and BI rats. Fig. 2 shows that the main effect of the head injury was to elevate the responsivity of cortical columns, while reducing the relative difference between responses to the 200 μm and 300 μm amplitude stimuli. Similar elevations of neuronal responsivity have previously been observed in BI rats in the barrel cortex.[30] According to the paired *t*-test, the difference between neurons' responses to the 200 μm and 300 μm stimuli is statistically highly significant ($P = .0002$ for HC rats and $P = .0006$ for BI rats). And applying Welch's unequal variances *t*-test of equality of means of two independent samples, we get $P = .030$ when comparing the means of HC and BI sample responses to the 200 μm stimuli, and $P = .051$ for responses to the 300 μm stimuli.

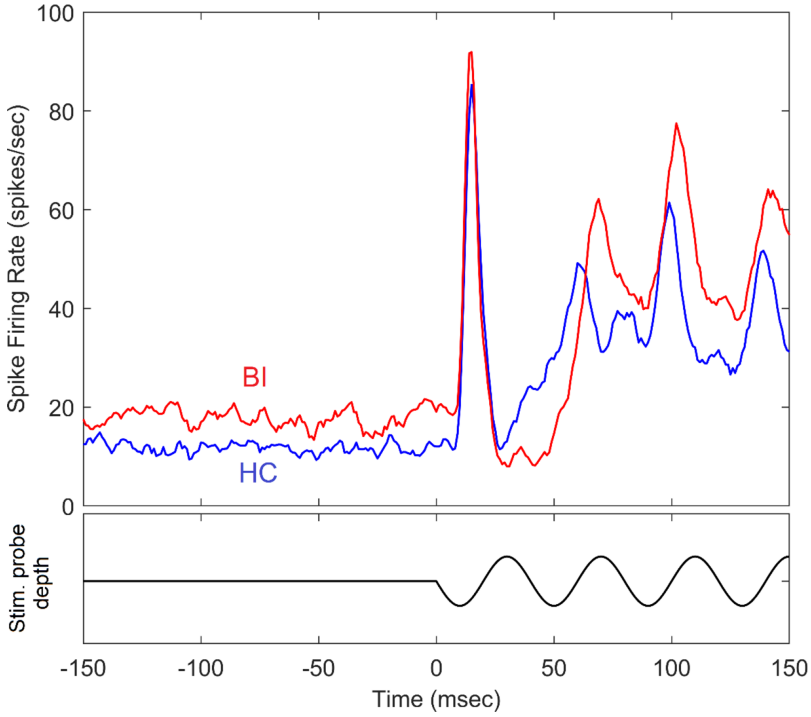

FIGURE 3. Average initial stimulus-evoked neural response in brain-injured (BI) vs. healthy control (HC) rats. Note that although the initial response is of approximately same magnitude, the pre-stimulus spontaneous baseline neural activity in BI subjects is much higher, thereby reducing the signal-to-noise ratio (SNR) of the BI response.

S1 Cortical Response to the Reaction Time Stimulation Protocol

In the RT task, a single cycle of 25 Hz, 300 μm amplitude vibrotactile stimulation is applied to the D2 fingertip and the subject is instructed to respond, by pressing a button, as quickly as possible. Human performance on the RT test is negatively affected by mTBI.[20–22] In particular, Pearce et al. reported that HC subjects had average RT = 233 milliseconds, but it was elevated to RT = 297 milliseconds in BI subjects.[22]

Average time-course of the response of a rat S1 cortical column to the first cycle of the 25 Hz 300 μm amplitude vibrotactile stimulation of its digit tip is shown in Fig. 3. Plotted superimposed are the average responses obtained in the HC (black) and BI (gray) rats. The most notable difference between HC and BI responses is a substantial elevation of the pre-stimulus spontaneous activity in BI rats, whereas the response magnitudes are very similar. This suggests that BI rats have substantially reduced signal-to-noise ratios (SNRs). To test this suggestion, SNR was computed for each recording site as:

$$SNR = P_{response}/P_{spontaneous} \quad (1)$$

where $P_{response}$ is the power of the stimulus-evoked instantaneous firing rate measured in the 10-25 milliseconds time window after the stimulus onset; $P_{spontaneous}$ is the power of the spontaneous instantaneous firing rate measured just prior to the stimulus-evoked input arriving in S1 in the −20 to +10 milliseconds time window relative to the stimulus onset. For HC rats, the average $SNR_{HC} = 20.1 \pm 3.1$ (mean ± SEM), whereas for BI rats, the average $SNR_{BI} = 9.8 \pm 2.3$. That is, the experimentally induced head trauma reduced SNR of S1 initial response to vibrotactile stimulation by 50%. This reduction is statistically significant ($P = .010$) according to Welch's *t*-test.

TBI is associated not only with a prominent increase in RT but also with a comparable increase in intertrial RT variability, RT_{var}.[20–22] For example, Pearce et al. found average $RT_{var} = 14.5$ milliseconds in HC population, but it was elevated to $RT_{var} = 19.8$ milliseconds among tested concussed subjects.[22]

An example of intertrial variability of a representative S1 neuron's spike firing, recorded in a HC rat, during a vibrotactile stimulus presentation is shown in Fig. 4A. From one stimulus trial to the next, the recorded neuron generates a fairly stereotypical pattern of intermittent spike firings, which are entrained to the stimulus cycle. For a comparison, Fig. 4B shows an example of intertrial variability of a representative S1 neuron recorded in a BI rat. This raster plot shows much greater instability in this neuron's activity, which affects spike firings both during and between stimuli.

To quantify intertrial response variability of individual recorded neurons, we used the Coefficient of Variation, CV:

$$CV = s/m \quad (2)$$

where m is the mean stimulus-evoked response of the neuron during the first cycle of the 25 Hz 300 μm amplitude vibrotactile stimulation, and s is the standard deviation of this

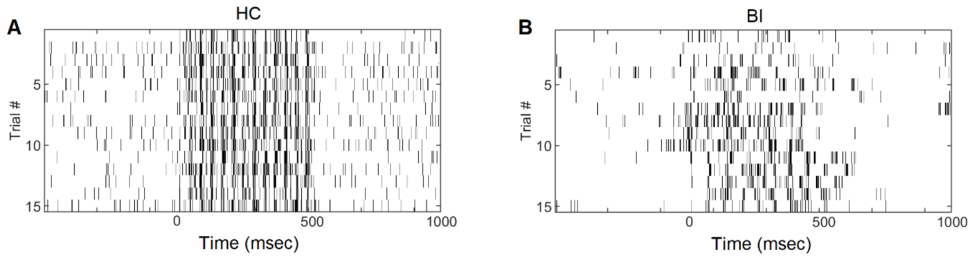

FIGURE 4. Raster plots of spike trains during 15 repeat trials of 25 Hz vibrotactile stimulation recorded in a representative healthy control (HC) neuron (A) and in a brain-injured (BI) neuron (B). Note the variability of the BI response compared to the HC response.

response across all stimulus trials. For HC rats, the average $CV_{HC} = 0.60 \pm 0.03$ (mean ± SEM), whereas for BI rats, the average $CV_{BI} = 0.97 \pm 0.13$. That is, the experimentally induced head trauma increased intertrial variability of S1 initial response to vibrotactile stimulation by 60%. This increase is statistically significant ($P = .009$) according to Welch's *t*-test.

DISCUSSION

Comparison of Rat S1 and Human Performances on the Amplitude Discrimination Task

Human performance on the amplitude discrimination task is expressed by the difference limen (DL). Therefore, to make cortical stimulus-evoked responses more directly relatable to human performance, it is desirable to express cortical responses also in terms of DLs. This can be accomplished with the help of Stevens Law and Weber Law.

According to Stevens Law, an individual's perception (P) of the strength of a vibrotactile stimulus depends on the stimulus amplitude (A):

$$P(A) = \alpha \cdot A^{\beta} \tag{3}$$

where α and β are scaling and power constants, respectively. Fitting this function to rat S1 stimulus-evoked responses plotted in Fig. 2 gives us the values of α and β constants for the HC and BI rats. We can now express the rat S1 cortical estimate of the stimulus strength as a function of the actual stimulus amplitude:

$$P_{HC}(A) = 1.13 \cdot A^{0.51} \tag{4}$$

$$P_{BI}(A) = 3.55 \cdot A^{0.35} \tag{5}$$

Thus, we find that our experimentally induced brain trauma resulted in a change of the power function relationship between the amplitude of vibrotactile stimuli and the magnitude of the spiking response it evokes in S1: i.e., the scaling constant was increased while the power constant was reduced.

In the amplitude discrimination task, we measure an individual's performance by computing the Weber Fraction, or the normalized DL:

$$DL = \frac{A_1 - A_0}{A_0} = \frac{A_1}{A_0} - 1 \tag{6}$$

where A_0 is the amplitude of the standard (200 μm) stimulus and A_1 is the amplitude of the just noticeably different stimulus. Tommerdahl et al. reported that healthy human individuals in their study had average DL = 0.15 while post-concussion individuals had average DL = 0.21.[18] Very similarly, Pearce et al. reported that healthy human individuals in their study had average DL = 0.16 while post-concussion individuals had average DL = 0.23.[22]

Making use of Stevens Law, we can convert DL to the Perceived DL:

$$P_{DL} = \frac{P(A_1) - P(A_0)}{P(A_0)} = \frac{\alpha \cdot A_1^{\beta} - \alpha \cdot A_0^{\beta}}{\alpha \cdot A_0^{\beta}} = \left(\frac{A_1}{A_0}\right)^{\beta} - 1 \tag{7}$$

If we assume that the perceived DL is the same for HC and BI subjects (i.e., if we assume that light brain traumas do not significantly alter how much perception of a stimulus has to change in order for it to be recognized by the frontal lobes and reacted to; rather, what is primarily impacted is the mechanism of converting peripheral stimulus inputs into perceptions), then the observed difference in the DLs of the two groups must be due to their β power difference. We can estimate this difference thusly:

$$P_{DL}^{HC} = P_{DL}^{BI} \tag{8}$$

$$\left(\frac{A_{1HC}}{A_0}\right)^{\beta_{HC}} - 1 = \left(\frac{A_{1BI}}{A_0}\right)^{\beta_{BI}} - 1 \tag{9}$$

$$(DL_{HC} + 1)^{\beta_{HC}} = (DL_{BI} + 1)^{\beta_{BI}} \tag{10}$$

$$DL_{BI} = (DL_{HC} + 1)^{\beta_{HC}/\beta_{BI}} - 1 \tag{11}$$

Equation 11 shows that if we know how the power constant β (governing the relationship between stimulus amplitude and the magnitude of S1 response; see eqn. 3) changes

due to brain injury, then we can estimate the corresponding change in the DL. Applying eqn. 11 to our rat neurophysiological data and published human data, we know that constant β changed from $\beta_{HC} = 0.51$ in HC rats to $\beta_{BI} = 0.35$ in BI rats (see eqns. 4 and 5). We also know that for HC humans $DL_{HC} = 0.155$ (which is the average of the values reported by Tommerdahl et al. and Pearce et al. studies).[18,22] Thus, according to eqn. 11, if HC and BI humans had the same β constants as HC and BI rats, then we can expect $DL_{BI} = 0.23$ after head trauma. This estimate is close to the published human $DL_{BI} = 0.22$ (which is the average of the values reported by Tommerdahl et al. and Pearce et al. studies).[18,22]

In our derivation of eqn. 11, we made an assumption that, while physical DL (i.e., the just noticeable difference in amplitudes of two compared stimuli) does change following head trauma, the perceived DL (i.e., the actual difference in neural representations of these amplitudes in that part of the cortex that does the comparison) remains the same. It seems a reasonable assumption when dealing with light cases of the mTBI type. However, if we want to generalize and take into consideration a possibility that brain trauma might result in a change of the perceived DL, then the relationship between amplitude-representational changes in S1 and expected changes in DL on the amplitude discrimination test is:

$$DL_{BI} = \sqrt[\beta_{BI}]{\gamma(DL_{HC}+1)^{\beta_{HC}} - \gamma + 1} - 1 \qquad (12)$$

where:

$$\beta = \frac{\log\left(OMFR(A_2) - OMFR(A_1)\right)}{\log A_2 - \log A_1} \qquad (13)$$

$$P_{DL}^{BI} = \gamma \cdot P_{DL}^{HC} \qquad (14)$$

OMFR(A) is the overall mean firing rate of S1 cortical column representing a vibrotactile test stimulus of amplitude A; γ is a scaling constant.

To conclude, by using Weber and Stevens Laws, we can go beyond qualitative comparison of the effects of brain trauma on somatosensory cortex vs. human psychophysics and develop a quantitative formalism (such as the one expressed by eqn. 11 or, more generally, by eqn. 12) linking them. Such a formalism makes it possible to express the amplitude-representational changes in S1 in term of expected changes in the DL on human amplitude discrimination test.

Comparison of Rat S1 and Human Performances on the Reaction Time Task

RT was the second human neurosensory assessment task explored in this study. Human performance on this task is quantified by two metrics—time taken to respond and its trial-by-trial variability. RT is a sensorimotor measure: It includes the time it takes for a neural signal to travel to somatosensory cortex and be processed there, then for a decision to be made in the frontal lobes to respond, and then for a signal to travel from motor cortex to the spinal cord and from there to muscles. Neurophysiological studies of S1 can only explore the first component of this process and whatever changes might be induced there by brain injury. Nevertheless, our study found that brain injury resulted in significant reduction of the SNR of the initial S1 response to the test vibrotactile stimulus. Similar SNR reductions can be expected to occur throughout the injured cortical territory, and so the status of SNR in S1 might be treated as an indicator of general cortical SNR status. Since RT task requires each of the sequence of the engaged cortical networks to detect the earliest signs of the stimulus in its input, any uncertainty in reading these signs (due to reduced SNR) can be expected to result in processing delays and RT prolongation. Thus, reduced SNR might be a significant contributor to delayed RT that has been observed in post-concussion human individuals.[20–22]

We also found in our study that our experimentally induced brain trauma resulted in significant increase of intertrial variability of the magnitude of the initial S1 response to the test stimulus. This is likely to increase trial-by-trial fluctuations in SNR and, if SNR contributes to RT, such fluctuations might contribute to increased RT variability that has been observed in post-concussion human individuals.[20–22]

Overall, in this study, we identified three cortical neurophysiological metrics that might underlie, in part, three neurosensory assessment metrics. It remains to be determined how tightly they are linked. While we derived these neurophysiological metrics from spike discharge recordings of S1 neurons, they are likely to be more readily extracted in much less laborious way from recordings of local field potentials in S1 cortex or even noninvasively from recordings of scalp EEG signals. In the latter case, EEG recordings could be obtained in human mTBI patients and directly compared with their performance on RT and amplitude discrimination tests. Another promising application of our experimental rat mTBI model is in investigating dose, time, or multi-exposure cumulative effects of blast or blunt force exposures and translating them into human metrics.

FUNDING

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