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Quantification of Mild Traumatic Brain Injury via Cortical Metrics: Analytical Methods

Oleg V. Favorov; Eric Francisco†; Jameson Holden†; Olcay Kursun‡; Laila Zai§; Mark Tommerdahl*†*

ABSTRACT Mild traumatic brain injuries are difficult to diagnose or assess with commonly used diagnostic methods. However, the functional state of cerebral cortical networks can be rapidly and effectively probed by measuring tactile-based sensory percepts (called cortical metrics), which are designed to exercise various components of cortical machinery. In this study, such cortical metrics were obtained from 52 college students before and after they experienced sports-related concussions by delivering vibrotactile stimuli to the index and middle fingertips. Performance on four of the sensory test protocols is described: reaction time, amplitude discrimination, temporal order judgment, and duration discrimination. The collected test performance data were analyzed using methods of uni- and multivariate statistics, receiver operated characteristic (ROC) curves, and discriminant analysis. While individual cortical metrics vary extensively in their ability to discriminate between control and concussed subjects, their combined discriminative performance greatly exceeds that of any individual metric, achieving cross-validated 93.0% sensitivity, 92.3% specificity, 93.0% positive predictive value, and 92.3% negative predictive value. The cortical metrics vector can be used to track an individual's recovery from concussion. The study thus establishes that cortical metrics can be used effectively as a quantitative indicator of central nervous system health status.

INTRODUCTION

Recent advances in medical science, as well as growing public awareness of the potentially disabling effects of concussions in athletes and in combat veterans, have highlighted the need for effective methods for diagnosing and quantifying the effects of acute mild traumatic brain injury (mTBI). Brain imaging techniques (see Salat et al[1] for a comprehensive literature review) can be useful in identifying large-scale changes in global functional connectivity and temporal coherence (functional magnetic resonance imaging, magnetoencephalography, electroencephalography), white matter integrity (diffuse tensor imaging), and some neurotransmitter concentration changes (magnetic resonance spectroscopy). The current standard of care for evaluating concussion using imagery is a computed tomography or magnetic resonance imaging of the brain, both of which are useful in identifying gross morphological changes but cannot rule out mTBI. Clinical neurological examinations (see Broglio et al[2] for a comprehensive literature review) are relatively insensitive to subtle changes that may be associated with mTBI. Neuropsychological testing may be effective in characterizing changes in neurocognitive functioning following mTBI, but is vulnerable to potential biases arising from individual motivations to "pass" or "fail" the test based on differences from baseline performance. Individuals often purposefully underperform on baseline testing in order to insure a more positive outcome in the event that they will be tested post-concussion. Similarly, self-reporting of symptoms is subject to potential under- or over-reporting and lacks specificity, as many symptoms of concussion overlap with other conditions, and may be prevalent in individuals with no history of TBI.

The functional status of CNS components can, in principle, be rapidly and effectively probed by making the patient perform purposefully chosen sensory tasks that would exercise these components. Such an approach targeting cerebral cortical machinery has in recent years been successfully used in evaluating individuals with neurodevelopmental disorders,[3] neurodegenerative disorders,[4] pharmacological insult,[5,6] traumatic insult,[7,8] neuropathic pain,[9] and normative aging.[10] This "cortical metrics" approach was built on cortical neurophysiological studies that revealed the existence of rich dynamics of stimulus-evoked cortical activity (for review, see Tommerdahl et al[11]). That is, the perception of the attributes of a sensory stimulus is not instantaneous, but develops in a course of several hundreds of milliseconds during exposure to the stimulus as a consequence of complex patterns of dynamical interactions among stimulus-engaged cortical functional modules (cortical columns). Such dynamics involve much of the cortical machinery, such as excitatory and inhibitory feed-forward, lateral, and feedback connectivity, neuroglia and maintenance of neurophysiological homeostasis, families of ion channels in control of the membrane potential, etc. Any interference with or malfunctioning of this machinery is likely to impact the

*Department of Biomedical Engineering, University of North Carolina at Chapel Hill, CB No. 7575, Chapel Hill, NC 27599.

†Cortical Metrics, LLC, 209 Lloyd Street Suite 360, Carrboro, NC 27510.

‡Department of Computer Science, The University of Central Arkansas, Lewis Science Center, Room 176, Conway, AR 72035.

§Applied Research Associates, Inc, 4300 San Mateo Blvd. NE, Suite A-220, Albuquerque, NM 87110.

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stimulus-evoked cortical dynamics and ultimately the acuteness of the perception of stimulus properties.

For patient evaluation, a repertoire of sensory perceptual tests have been developed incorporating vibrotactile stimulus protocols that were found in non-human primate neurophysiological studies to evoke distinct patterns of cortical dynamics. Because of the parallels observed in human sensory perceptual performance and the cortical dynamics in non-human primates in response to similar stimulus protocols, we interpret the metrics of human perceptual performance on those protocols as proxy indicators of cortical dynamics, referring to them as “cortical dynamics metrics” or just “cortical metrics.” In this paper, we explore the potential of using cortical metrics to characterize and differentiate concussed individuals from non-concussed individuals, as well as to track their post-concussion recovery.

METHODS

Subjects

Cortical metrics data were collected from 52 college students (age = 20.1 ± 1.2 years), all of whom experienced a sports-related concussion (see Table I). All concussed athletes were diagnosed with mTBI within one day of experiencing a concussion by a certified athletic trainer and the team physician with the help of the Sport Concussion Assessment Tool 2 (SCAT-2) and had no prior history of concussion or other diagnosed mental health conditions with symptoms similar to concussion. The reported cortical metrics assessments were obtained at one or more time points ranging from a few hours after concussion to 9 months after concussion (see Table 1). Baseline measures were also collected on each participant prior to beginning the sports season and were used as healthy control data. The experimental procedures were reviewed and approved in advance by an institutional review board.

Sensory Assessment

A Brain Gauge stimulator (Fig. 1) was used to deliver vibrotactile stimulation to the subjects during this study. The Brain Gauge vibrotactile stimulator was developed in our laboratories for use in experiments such as those described in this report. The design was based on the functionally equivalent CM4. The CM4 stimulator, described in detail in Holden et al[12] has been utilized to assess multiple sensory information processing characteristics in a diverse spectrum of human subject studies.[3–11] The prominent feature of these protocols, which have demonstrated significant sensitivity to alterations in CNS processing, is that they are independent of detection thresholds or skin sensitivity.[13]

During the evaluation session, subjects were seated comfortably in a chair with their hand on the Brain Gauge. Vibrotactile stimulation was conducted via 5 mm diameter probes that come in contact with subject’s digit 2 (D2; index finger) and digit 3 (D3; middle finger) of the left hand. The independent probe tips are computer-controlled and capable of delivering a wide range of sinusoidal vibrotactile stimulations of varying frequencies and amplitudes. The fingertip pads were chosen as test sites for two reasons: (1) to allow the convenience of access and comfort of the subject and (2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of the cortex in primates. The subject’s right hand was used to indicate responses on a two-button computer mouse. A computer monitor provided visual cueing during each of the experimental runs. The cues indicated when the experimental stimuli would be delivered and when subjects were to respond. Training trials conducted prior to each task familiarized subjects with the test; correct responses on three consecutive training trials were required before the start of each assessment. Stimulus parameters were specified interactively by test algorithms based on specific protocols and the responses of the subjects during those protocols.

A series of sensory perceptual measures were employed to assess tactile information processing ability. In sum, these tests lasted approximately 12–15 minutes and consisted of evaluations of reaction time, amplitude discrimination, temporal order judgment, and duration discrimination, administered in that order. Individual tests are described below.

Reaction Time

A single tap (300μm, 40 ms) was delivered to D2 and subjects were instructed to respond by clicking the response device as soon as the tap was perceived. A randomized delay ranging from 2 to 7 s separated the trials. Response times were recorded for each of the 10 trials. The two fastest and the two slowest responses were excluded, and the middle six responses were averaged. The standard deviation of the 10 reaction times (RTs) was used as a measure of reaction time variability. This method has been previously reported.[10]

Amplitude Discrimination

Amplitude discriminative capacity is defined as the minimal difference in amplitudes of two sinusoidal vibratory stimuli for which an individual can successfully identify the stimulus of larger magnitude. For the amplitude discrimination (AD) task, the device delivered simultaneous sinusoidal vibrotactile stimuli (initial stimulus parameters: 400μm peak-to-peak amplitude “test” stimulus, 200μm “standard” stimulus, 25 Hz, 500 ms, 20μm step size) to D2 and D3 over 20 trials. Discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies.[3,7,9,10] The loci of the stimuli were randomly varied on a trial-by-trial basis, and subjects were questioned as to which of the two digits received the higher magnitude stimulus. The amplitude of the test stimulus was adjusted after each trial on the basis of the response such that correct responses lowered and incorrect responses increased the test amplitude on subsequent trials.

TABLE I. Demographics of the Study's Participants and the Times (Days) After Concussion When Cortical Metrics Assessments Were Performed

Subject ID	Age	Gender	Handedness	First Test	Second Test	Third Test	Fourth Test	Fifth Test
SUBJ–5273	21	M	R	7	15	22		
SUBJ–2717	20	M	R	2	5	10		
SUBJ–9637	20	F	L	30				
SUBJ–0740	20	M	R	2	7	180		
SUBJ–2233	28	F	R	1				
SUBJ–2111	20	F	R	2	4			
SUBJ–9730	20	M	R	1				
SUBJ–9491	19	F	R	4	8			
SUBJ–1495	22	M	L	2	9	16	94	
SUBJ–0439	19	M	R	1	8	14		
SUBJ–0439*				1	8	15	30	103
SUBJ–5008	21	M	R	1				
SUBJ–8296	22	M	R	2				
SUBJ–7854	18	F	R	2	4	11	32	
SUBJ–1612	19	M	R	1	8			
SUBJ–2374	19	M	R	11				
SUBJ–1757	20	M	R	1	3			
SUBJ–1757*				4	8	14		
SUBJ–1882	22	M	R	15	22	28		
SUBJ–3070	20	F	L	4	17			
SUBJ–1019	20	F	R	2	9			
SUBJ–1019*				3				
SUBJ–1262	21	F	L	3				
SUBJ–0759	20	M	R	7				
SUBJ–9363	19	M	R	2	10	16	28	
SUBJ–2626	20	M	L	9	14	28		
SUBJ–8829	19	F	L	7				
SUBJ–2139	21	F	R	2	7	14	21	28
SUBJ–0528	20	M	R	1	8			
SUBJ–1442	21	M	R	1	8	31		
SUBJ–1406	20	M	L	1	7			
SUBJ–5914	22	M	R	1	8	27		
SUBJ–6141	24	F	R	1				
SUBJ–8339	19	M	R	1				
SUBJ–1267	22	F	R	2	16	28		
SUBJ–2577	21	F	R	8				
SUBJ–0917	20	F	L	2	7	13	20	
SUBJ–1379	21	F	R	2	3			
SUBJ–0717	20	F	R	6				
SUBJ–4431	23	M	L	2				
SUBJ–3773	21	F	R	3	15	183	270	271
SUBJ–8947	18	F	R	2	8	15		
SUBJ–3527	21	M	R	2	14	34		
SUBJ–4843	20	M	L	2				
SUBJ–2175	20	F	R	8				
SUBJ–6705	21	M	R	4				
SUBJ–1377	19	M	R	3	11	17	25	
SUBJ–6062	22	M	R	3				
SUBJ–2577	21	F	R	2				
SUBJ–9684	19	M	R	7				
SUBJ–2387	20	M	R	3	11			
SUBJ–1269	21	F	R	3				
SUBJ–2842	19	M	R	2				
SUBJ–1273	20	F	R	3				
SUBJ–6073	21	F	L	10				

Asterisks mark occasions when subjects experienced a second concussion.

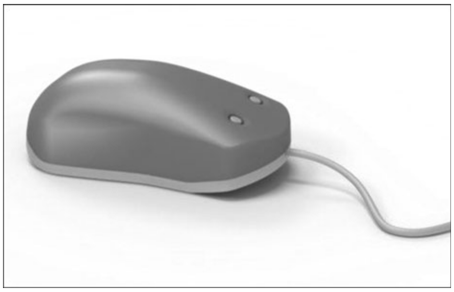

FIGURE 1. Brain Gauge 2-point vibrotactile stimulator used in cortical metrics studies. Vertical skin displacement sinusoidal stimuli are delivered to the tips of the index and middle fingers via 2 round 5 mm diameter probes.

Temporal Order Judgment

For the temporal order judgment (TOJ), two sequential taps (200μm, 40 ms) were delivered, one to each digit tip. These were initially temporally separated by an inter-stimulus interval (ISI) of 150 ms. The stimulus location that received the first of the two pulses was randomized on a trial-by-trial basis. Subjects were queried to indicate the digit that received the first stimulus. As in previously reported studies,[4,7] the temporal separation between the two pulses was adjusted on the basis of the previous response through employment of percentage tracking (15% step size) such that correct responses resulted in shorter ISIs while incorrect responses increased the ISIs. Each task consisted of 20 trials.

Duration Discrimination

The duration discrimination (DD) capacity is defined as the minimal difference in durations of two stimuli for which an individual can successfully identify the stimulus of longer duration. For the duration discrimination task, sequential stimuli were delivered to D2 and D3 in 20 trials (initial stimulus parameters: 750 ms "test" stimulus, 500 ms "standard" stimulus, 300μm, 25 Hz, 25 ms step size). Discrimination capacity was assessed using a 2 AFC tracking protocol, and the location of the stimulus of longer duration was randomly selected on a trial-by-trial basis. Subjects were asked to indicate which of the two digits received the longer stimulus duration and, as previously reported,[8] subsequent duration of the test stimulus was adjusted on the basis of subject response.

Data Analysis

Receiver Operating Characteristic Analysis

The capacity of the cortical metrics extracted from the above sensory tests to accurately predict whether a tested individual is concussed was evaluated using receiver operating characteristic (ROC) curve analysis. The classification accuracy was expressed as the area under the ROC curve (AUC). The AUC values can range between 0.5 (for classifiers whose performance is completely random) and 1 (for perfectly accurate classifiers). The AUC corresponds to the probability that the test will produce a value for a randomly chosen concussed subject that is greater than the value for a randomly chosen non-concussed subject.

Discriminative Analyses

Discriminant analysis (DA) is a classification approach that utilizes the given class-label information in finding informative projections that are used for classification of new data.[14,15] It maximizes an objective function that involves the scatter properties of classes. For DA, it is assumed that class examples are generated based on different Gaussian distributions of the predictor (input) variables. The classifier estimates the parameters of a Gaussian distribution for each class. The objective function is to maximize the between class scatter and minimize the within class scatter. Linear DA (LDA), also known as the Fisher discriminant, uses a pooled covariance matrix. Quadratic DA (QDA) takes into account that the covariance matrices can vary among classes. The LDA applied to a unidimensional input, thus, uses pooled variance for estimating class variances, which provides a better estimate of the variance than the individual sample variances. However, when using more input variables together, QDA is a more realistic choice because cortical metrics, used as the input variables, are expected to be more dependent on each other for concussed subjects, thus resulting in different covariance matrices.

Mahalanobis Distance

Mahalanobis distance[16] between two points takes into account the data distribution (correlations of the features in the dataset). Mahalanobis distance, d, between two points, x and y, reflects the amount of change in the principal components of the observed data, eliminating the excess contribution to the distance by the correlated features:

$$d(x, y) = \sqrt{(x - y)^T S^{-1} (x - y)},$$

where S is the covariance matrix of the dataset. Thus, a given Euclidean distance in a direction of high variance corresponds to a lower Mahalanobis distance than that in a low variance direction.

Partial Least-Squares Regression

The PLS is a multiple linear regression technique used with data that contain correlated predictor variables.[17] The PLS takes linear combinations of the original predictors for transforming the original predictor space into a new component space that reduces these predictor correlations while finding the best fit to the response variables.

RESULTS

Discriminative Capacities of Individual Cortical Metrics Tests

Performance of the concussed and non-concussed subjects on the four cortical metrics tests is shown in Figure 2. On both the AD test (Fig. 2A) and the DD test (Fig. 2B),

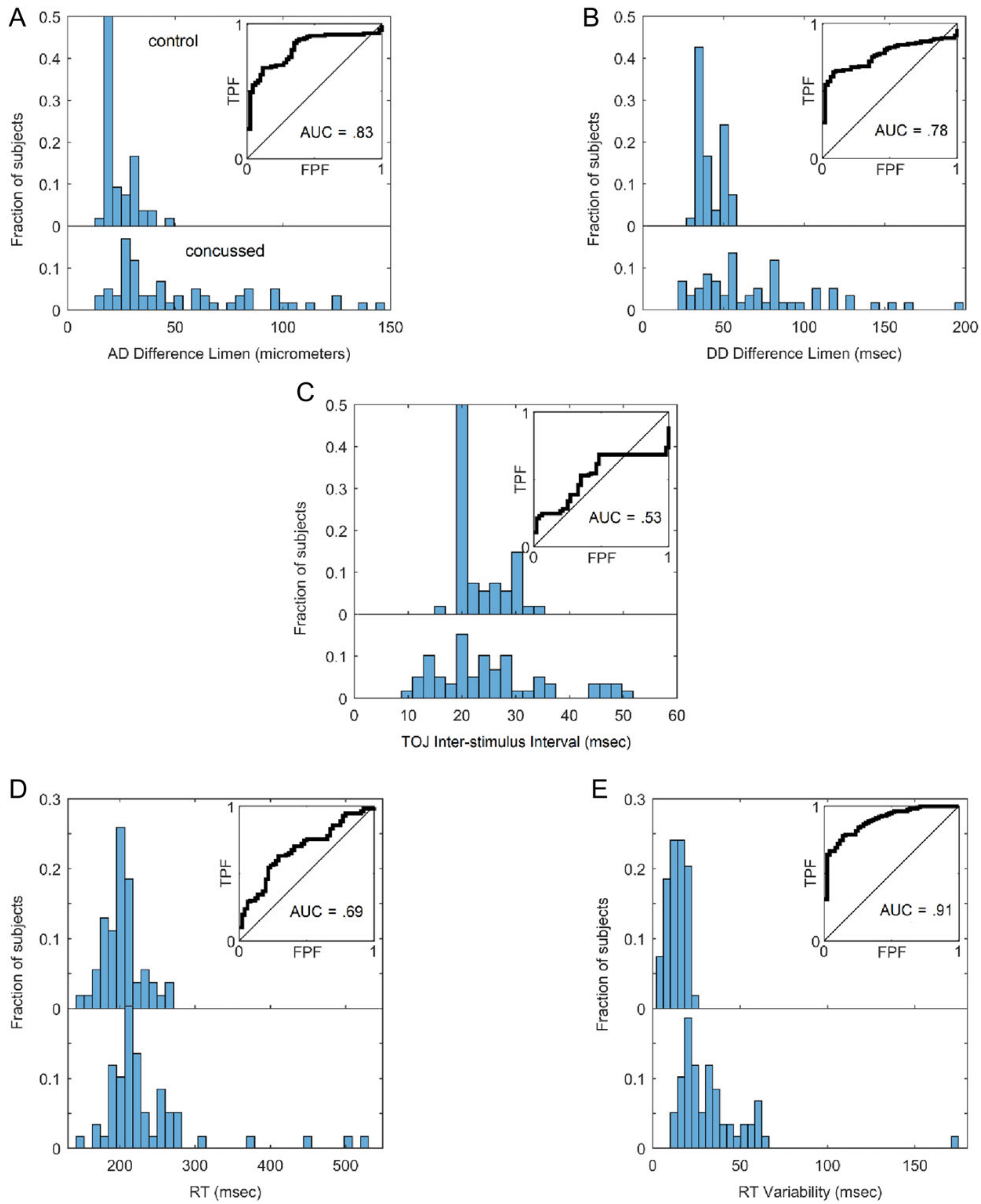

FIGURE 2. Cortical metrics of healthy control vs. concussed subjects. (A–E) Distribution histograms and ROC curves of each tested cortical metric. Post-concussion data are limited to the tests taken in the first 7 days after concussion (a total of 57 sets of tests were obtained from 45 subjects during this period; see Table I).

majorities of concussed subjects exhibited much larger discrimination limen than did the non-concussed control subjects. Correspondingly, the areas under their ROC curves were moderately elevated (AUC = 0.83 and AUC = 0.78 for AD and DD, respectively).

In contrast, AUC = 0.53 for the TOJ test. Normally, such a low value would indicate that this test is not sensitive to concussion. However, the distribution histograms in Figure 1C show that some of the concussed subjects had abnormally small inter-stimulus intervals whereas other concussed subjects

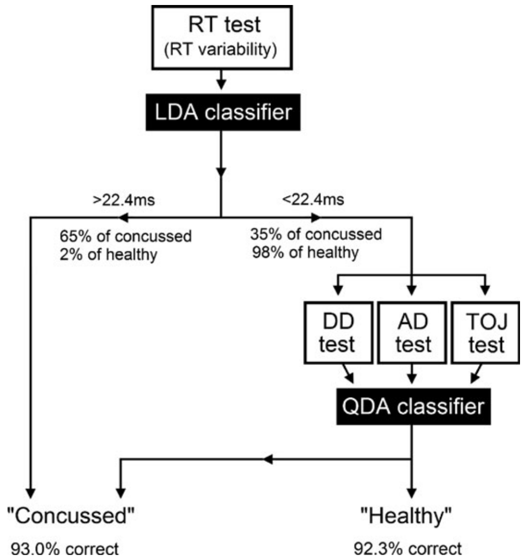

FIGURE 3. Flowchart of a healthy-vs-concussed classifier.

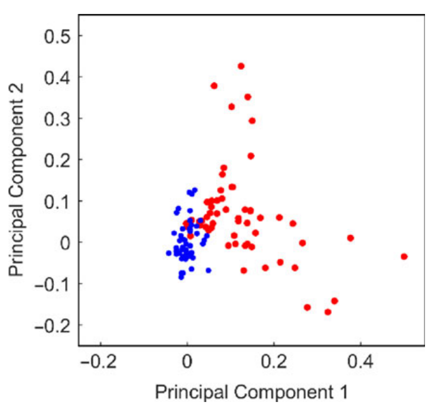

FIGURE 4. Relative distributions of the healthy control vs. concussed subjects in the cortical metrics space. For this display, the four-dimensional cortical metrics space is projected, using PLS-regress algorithm, onto a two-dimensional plane that maximizes the separation of the two distributions. Post-concussion points (red dots) are limited to the 57 tests of 45 subjects taken in the first 7 days after concussion.

had abnormally large intervals, which may reflect the heterogeneous nature of concussion.

Response times on the RT test (Fig. 1D) showed only modest sensitivity to concussion (AUC = 0.69), whereas the inter-trial variability in those responses (Fig. 1E) turned out to be highly sensitive to concussion (AUC = 0.91).

Healthy-vs-Concussed Classifier

As Figure 2 shows, the four cortical metrics tests are all sensitive to concussion and thus can be used to classify an individual as being concussed or not based on his/her performance on these tests. A highly effective such concussion classifier – i.e., the one that not only offers maximal sensitivity and specificity, but also requires the users to perform the smallest number of tests – is shown in Figure 3. According to this classifier protocol, each subject should first perform the RT test. Application of the linear discriminant analysis algorithm to our RT Variability data indicates that the optimal decision threshold is at 22.4 ms. Thus, if the individual's RT Variability is above 22.4 ms, he/she is classified as "Concussed" and no further testing is requested. Using leave-one-out cross-validation, we estimate that 65% of such individuals will indeed belong to the concussed population and only 2% will in fact be healthy.

If the individual's RT variability is below 22.4 ms, then he/she should perform the other three tests (AD, DD, TOJ). Their metrics are used as inputs to the quadratic discriminant analysis algorithm, which outputs the final classification.

The entire classifier protocol has cross-validated 93.0% sensitivity, 92.3% specificity, 93.0% positive predictive value, and 92.3% negative predictive value.

Quantifying Concussion-Induced Deviation from the Norm

Together, the metrics obtained from the four cortical metrics tests define a four-dimensional "cortical metrics" space, each orthogonal dimension of which corresponds to one of the metrics. The healthy control subjects occupy a particular region in this space, whereas concussed subjects can be expected to be displaced from it. To visualize this distribution, we project the four-dimensional space onto a two-dimensional subspace (a plane) using the PLS-regression algorithm, which finds such a projection plane that maximizes the separation of the two classes of data points (i.e., the control and concussed sets of subjects). This projection is shown in Figure 4. The blue points in the plot represent control subjects, and the red points represent post-concussion subjects.

The Figure 4 plot shows that control subjects are confined to a local region, whereas the concussed subjects are distributed much more widely and overlap only partially with the control subjects. It is noteworthy that concussed subjects are displaced in a wide range of directions away from the control cluster, probably reflecting the diversity of physical impacts and resulting brain traumas.

Figure 5 offers three examples of the paths taken in the cortical metrics space by three subjects during their recovery after concussions. In each case, when tested before a concussion, the subject's performance placed him/her within the healthy control region. In contrast, when tested shortly after the concussion, the subject was found to be placed clearly outside the healthy region. However, at each successive follow-up testing session during the recovery he/she shifted gradually back towards the healthy region. While such a gradual movement towards the control region might be indicative of the gradual recovery of CNS functionality, it is also possible that such an improved performance on the repeatedly taken tests might be due at least in part to learning.

The plots in Figures 4 and 5 suggest that we can quantify the neural impact of concussion by measuring the distance in the cortical metrics space between the location of a given

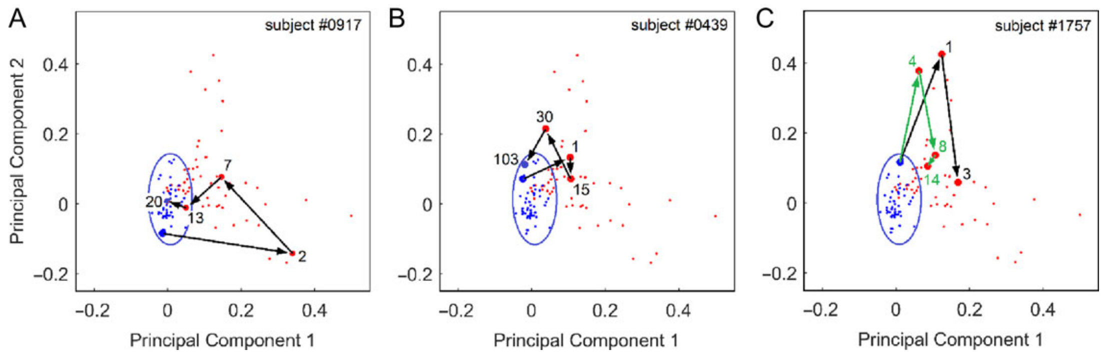

FIGURE 5. Post-concussion recovery of three exemplary subjects, tracked in the cortical metrics space. The recovery trajectories are shown by sequences of arrows, superimposed on the Figure 4 display of the cortical metrics space. The healthy control region is enclosed by a blue ellipse. Each position is marked with the number of days post-concussion when the test was taken. (A) An example of a typical recovery progress. By day 13, this subject returned to the healthy region. (B) An example of a slow recovery progress. Even at day 30 this subject was far from the healthy region, but entered it by day 103. (C) An example of repeated concussion. The second concussion (traced in green) occurred 179 days after the first concussion. Both impacts followed similar trajectories.

individual and the center of the healthy control cluster. Such a distance can be expressed in units of the standard deviation of the healthy control values in the direction of the given subject. Such a distance is called Mahalanobis Distance.

Figure 6A shows the histograms of the very different distributions of the Mahalanobis distances in our healthy control and concussed samples. The two distributions have only a small overlap and as a result their ROC curve is highly discriminatory (AUC = 0.98).

We anticipate that such Mahalanobis distance will be found useful in gauging the severity of the concussion impact on the brain, as well as tracking the progress of the brain's recovery. While the data collected in this study do not allow us to compute the average time-course of the return of Mahalanobis distance to the healthy control zone in the days and weeks after a concussion, in Figure 6B we plot average Mahalanobis distance before a concussion and at three consecutive times when the same cortical metrics battery was administered on different days to the same subject. The plot shows that there was only a small movement towards the norm between the first and second rounds of testing, but a greater and statistically significant recovery by the time of the third round ($p = 0.0039$). How much of this improvement might be due to recovery of CNS functionality and how much might be due to learning remains to be determined.

DISCUSSION

This study compared four specific cortical metrics of concussed vs. non-concussed individuals and demonstrated that with these cortical metrics used in a decision tree classifier, concussed individuals in our sample could be distinguished from non-concussed individuals at greater than 90% sensitivity and specificity. Of course, such high classification accuracy has to be confirmed on a larger new sample of concussed and healthy control individuals and the RT Variability threshold of 22.4 ms might need to be adjusted. By themselves, these cortical metrics vary extensively in their ability to discriminate between the control and concussed states, but when used together, their combined discriminative performance greatly exceeds that of any single metric. Besides using the metrics in the decision tree classifier, combining the four measures into a four-dimensional "performance" vector introduces the concept of the Mahalanobis distance between a given individual's performance vector and the center of the distribution of the healthy control vectors. Mahalanobis distance expresses the "abnormality" of a given individual's test performance in units of standard deviation (i.e., the z-score) of the healthy control population and thus it is well suited for intuitive appreciation of an mTBI patient's deviation from the norm and his/her recovery toward the norm. Thus, this study establishes that cortical metrics have an excellent promise as a possible quantitative indicator of mTBI and, in particular, for tracking recovery from concussion. The cortical metrics tests can be performed easily and rapidly (1–3 minutes per test), and the battery of four tests typically takes less than 15 minutes to complete.

The tests used in this study come from a much larger set of the available cortical metrics tests, which have been developed in recent years and used successfully in evaluating a number of neurological conditions. Future reports will describe trade-offs between longer batteries of protocols and the duration of the testing session. It is anticipated that more successful performance in recognizing mTBI and tracking its recovery will be achieved with an expanded (and/or optimized) set of cortical metrics. Different cortical metrics target different aspects of cortical function, and an increased diversity of measures will provide a better profile of CNS performance. This diversity of measures that are combined to generate a patient's CNS profile contrasts sharply with other performance task-based measures that are commonly used for concussion assessments and typically do not provide useful information toward diagnostic criteria of mTBI.

Of particular note is the significance of reaction time variability for detection of impairments introduced by mTBI. While this metric has been previously described as being

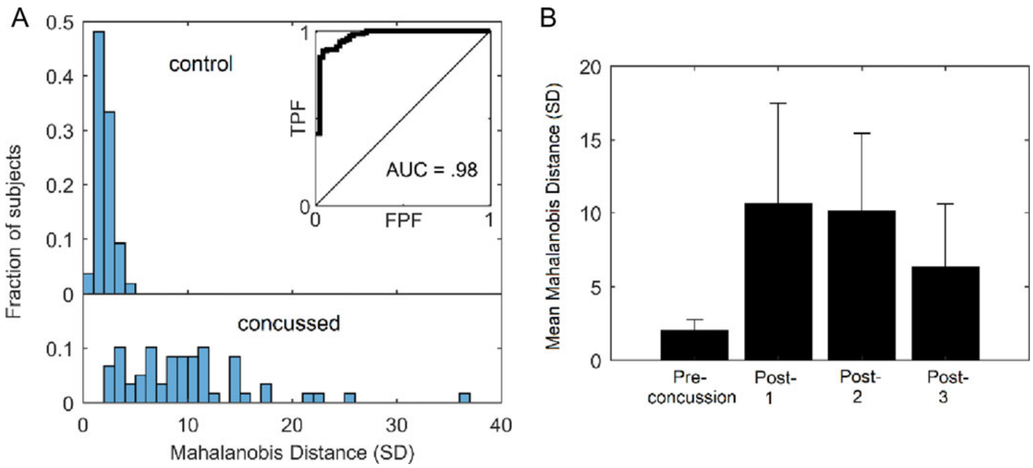

FIGURE 6. Mahalanobis distance characterization of the effects of concussion. (A) Distribution histograms and ROC curve. (B) Average Mahalanobis distance before a concussion (52 tests) and at three consecutive post-concussion testing sessions (52, 28, and 18 tests, respectively). Bars – standard deviations.

very sensitive to concussion (most recently in Cole et al[18]), the resolution provided by the method described with tactile-based testing is far superior than can be achieved with visually-based testing. In addition to the hardware resolution of the device used in this study (0.3 ms vs. the variability introduced by online cognitive tests in the range of 30–100 ms), the fidelity of the somatosensory system is much greater (i.e., more focused input–output relationship) than that of the visual system.

It is also important to note that although some tests do not independently provide accurate differentiation of concussed vs. non-concussed individuals, these tests contribute to the overall CNS profile of the individual. This speaks largely to the heterogeneity of the concussion detection problem – it would be difficult to design one task that would be very effective at detecting concussion alone. While the impact of a brain injury may lead to deficiencies in some aspects of CNS information processing in one individual, another injury may impact a completely different deficiency in another individual. Hence, it is important to test a wide spectrum of mechanistic-based CNS functions.

One of the overall objectives of our work is to develop a unifying construct that integrates multiple types of information into a CNS profile for each individual at each time point that they are tested. Individual collected measures, or cortical metrics, preferentially target different aspects of CNS functioning. The combination of all metrics allows for the generation of a performance vector, or a CNS profile, and the goal is to make the profile as comprehensive as possible. In some ways, administering multiple tasks to an individual is similar to a clinician asking a patient multiple questions – no two patients are alike, yet the questions can lead the clinician to derive a summary of the patient's health. We currently refer to this approach as the *Cortical Metrics Theory*, and this theory has been a guiding principle in the development of metrics that have proven their utility across a broad spectrum of neurological disorders. The reason that the method has proven effective is due to its multivariate approach.

In mathematical terms, each cortical metrics test in an N-test battery can be considered as one of the orthogonal coordinates of a common N-dimensional state space and an individual's performance on these tests places him/her at a particular point in that space. Thus, this is the space of all possible cortical metrics performance vectors, or the *cortical metrics state space*. A neurological disorder will alter the afflicted individual's performance on a suitably-chosen test battery, shifting him/her to a new location in the cortical metrics state space. Disorders that differentially affect patients' performance on the tests will cluster their performance vectors in different neighborhoods of the cortical metrics state space. Viewed from this perspective, therefore, the cortical metrics state space contains a latent map of neurological disorders and their underlying pathophysiological mechanisms. Aggregation of mTBI patients into one or more distinct clusters in the cortical metrics state space can then be used to define distinct mTBI syndrome(s). The significance of this is that, theoretically, the method could be used to identify mTBI even in the presence of other neurological disorders and eliminate the need for baseline measurements obtained before concussion. Future reports will characterize this type of differentiation.

PREVIOUS PRESENTATIONS

Presented as a poster at the 2017 Military Health System Research Symposium, August 2017, Kissimmee, FL; abstract # MHSRS-17–1672.

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