Relationship between DTI Brain Connectivity and Functional Performance in Individuals with Traumatic Brain Injury[*]

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***Abstract*— this study examines the relationship between brain structural connectivity, and physical and cognitive performances in individuals with Traumatic Brain Injury (TBI). Nine moderate to severe TBI participants were included in the study, and regression analysis was performed to explore if DTI connectivity of 16 regions of interest can predict individuals': 1) Maximum Voluntary Contraction (MVC), 2) time component of Wolf Motor Function Test (WMFT), 3) Reaction Time (RT) during bimanual force matching task, 4) Performance Error Measurement (PEM) during bimanual force matching task, and 5) cognitive assessment of task switching using Trail Making (TM) test. Results showed that slower WMFT, PEM, and TM can be predicted by weaker cerebrospinal tract connectivity. Higher Caudate connectivity predicted higher WMFT and slower RT, and higher right Cingulum predicted faster TM. Current results suggest that measures of cognitive-motor interference may be better indicators of functional performance than single cognitive and motor performance tests.**

I. INTRODUCTION

Traumatic brain injury (TBI) causes a wide variety of problems including motor, cognitive, emotional, and medical complications [1]. It is common for individuals with TBI to have physical disabilities, from which they don't recover [2]. Bimanual coordination deficit is common in individuals with sustained moderate to severe TBI [3]. Conventional rehabilitation approaches use massed practice and high number of repetitive task-specific activities to regain motor learning, which may lead to fatigue, short attention span, and unsuccessful physical recovery [4]. Fujiyama et al [4] hypothesize that augmented attention using action observation and motor imagery during physical training could improve the therapeutic effect of physical training, especially in subjects with short attention span. We are testing this hypothesis in an ongoing study and the main outcomes are neuropsychology assessment (NP) of task switching, physical measures of motor performance, and neuroimaging measures of brain connectivity.

Previous research studies have explored the relationship between brain structural connectivity and neuropsychology assessments of cognitive function in individuals with TBI [5]–[9]. Hanks et al. [6] studied the relationship between fractional anisotropy (FA) values and cognitive functioning such as Trail Making (TM) test, Symbol Digit Modalities Test (SDMT), Wechsler Test of Adult Reading, California Verbal Learning Test 2nd Edition, Digit Vigilance Test, and Wisconsin Card Sorting Test in TBI participants. In Hanks et al. study [6], authors found significant difference between FA values in TBI and healthy controls; however, the FA values were only associated with SDMT scores. Correlation between Diffusion Tensor Images (DTI) parameters from Corpus Callosum (CC) white matter region and a number of cognitive functioning measures was analyzed in [7], and significant correlations were observed in both TBI and healthy controls in CC regions. FA values from the TBI group were compared to several NP measures in [8] resulting in high correlations between FA values, information processing speed, and executive abilities.

Previous research studies did not explore the association between DTI connectivity and performance in dynamic tasks that include both cognitive and physical components. Hence, we analyzed the baseline data in our intervention study, and used regression models to explore if these three types of assessments can be predicted by DTI white matter integrity. We hypothesized different contributions depending on the regions of interest (predictors of cerebrospinal tract (CST) connectivity for example is different from predictor of cingulum connectivity). We also expected negative relationship between connectivity and performance i.e. lower connectivity predicts worse performance.

II. METHODOLOGY

A. *Participants*

Nine moderate to severe TBI subjects (age: 40.2 ± 12.8 years, sex: 8M/1F) with upper extremity movement deficits were enrolled in this study after signing informed consents approved by Kessler Foundation Institutional Review Board.

B. *Physical and Cognitive assessments*

Physical performance was evaluated using multiple measures. First, the Maximum Voluntary Contraction (MVC) measure of each hand was calculated based on the average of 10 MVC trials. The time component of the Wolf Motor Function test (WMFT) [10] was evaluated using the total time for all items for both limbs.

Participants performed two sets of in-phase and out-of-phase bimanual motor coordination tasks to evaluate their coherent hand movement Reaction Time (RT, see equation 1) and Performance Error Measure (PEM, see equation 2) (Fig.1c). Participants were asked to perform a force matching task by tracking a vertically sinusoidal oscillating red target line by controlling fingers' force extension or flexion

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displayed as a blue line on the screen for each hand (see Fig. 1.d). The targets were individually set to oscillate between 15 to 25% of each hand MVC. The task was performed under the following four conditions and order: finger flexion in-phase, finger flexion out-of-phase, finger extension in-phase, and finger extension out-of-phase. Each condition were 10 minutes long with 5 minutes resting time in-between. Finally, the cognitive performance was evaluated using the TM test as a measure of task switching. Higher values in all these measures, except MVC, reflect worse performance. Higher MVC values reflect stronger performance.

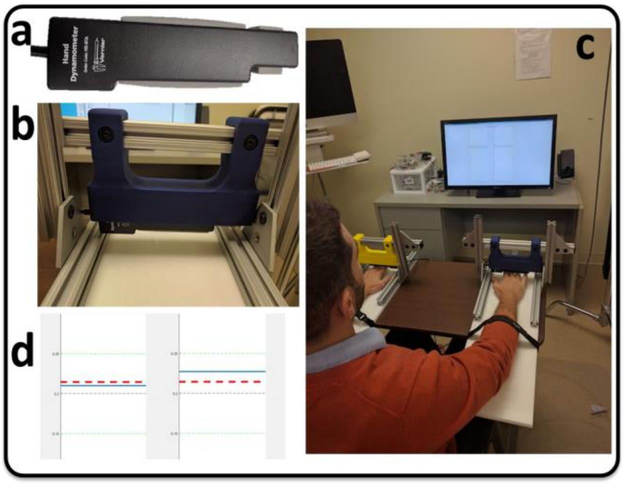

Figure 1. a) Hand grip sensor (Vernier) b) a 3D printed sensor handle, designed to hold the sensor and provide the platform for subjects to practice fingers flexion (palm up) or finger extension, c) a subject is exercising a bimanual submaximal force task (arm position is strapped), the subject applies force on both sensors to track a moving a target on the screen, d) a cropped screen shot of the visual feedback during the task, subject controls the blue horizontal line to match the red horizontal dashed target which oscillates between 15-25% MVC.

$$\boldsymbol{RT}\ in\ seconds = T_{subject\ force\ start} - T_{trial\ start} \quad (1)$$

$$\boldsymbol{PEM} = RMS\ (\frac{Force}{MVC\ per\ session} \times 100) \quad (2)$$

C. *Neuroimaging Measures:*

MRI data acquisition: All images were acquired using 3T Siemens Skyra scanner in the Rocco Ortenzio Neuroimaging Center at Kessler Foundation (KF) research campus. High-resolution structural images were acquired using a magnetization prepared rapid gradient echo (MP-RAGE) sequence with TR=2.1 sec, TE=3.43 ms, 176 slices, FOV=256mmx256mm, flip angle 9 degrees, 1 mm slice thickness. A pulsed-gradient, diffusion-weighted single-shot echo planar imaging (EPI) sequence was used to acquire DTI. Axial images were acquired with the following parameters: TE=97ms, TR=3600ms, in-plane matrix size=132x132; Flip angle=90º; FOV=132mmx132mm, b0=0, 20 diffusion directions.

MRI data analysis: The DTI volumes were processed using *diffprep* module in TORTOISE software package [11]. The processing steps are as follows: AFNI-FATCAT Axialization (fat_proc_axialize_anat) to align T2W to a reference template of same contrast, eddy motion and EPI distortion correction, and output quality check. Diffusion tensors were estimated using *diffcalc* module and robust estimation by outlier rejection tensor estimation (RESTORE [12], [13]). FA parameters were measured for the following regions of interest (ROI) for each subject: Left (L) and Right (R) Cingulum (Cing.), L and R Cerebrospinal tract (CST), L and R Superior Lateral Fasiculus (SLF), L and R anterior Corona Radiata (antCR), L and R posterior Corona Radiata (posCR), L and R Superior Corona Radiata (supCR), Body, Splenium, and genu of Corpus Callosum, Thalamus, Putamen, and Caudate.

D. *Statistical Analysis*

IBM SPSS Statistics and MATLAB R2019a were used to implement the statistical analysis. All the values were z-score normalized, i.e., converted to a common scale with an average of zero and standard deviation of one. Using multiple regression analysis, we tested which ROI structural connectivity (FA values of DTI connectivity) can best predict: 1) physical strength measured using MVC, and 2) motor function evaluated using WMFT, and 3) assessments of the ability to detect, process, and respond to a visual or cognitive stimuli; RT, PEM, and TM. Statistical significance was set at a p-value of 0.05.

III. RESULTS AND DISCUSSION

The regression analysis explored if DTI FA values in the 16 ROIs can predict TM, RT, PEM, WMFT, and MVC. Table 1 lists the correlation between these five predictors and shows a strong correlation between RT and WMFT, i.e., slower reaction time correlates with slower motor function. The regression models are tested for different ROIs and the ones with significant p-values and corresponding R-squared values are shown in Figures 2 to 6.

Fig. 2 shows significant association between RT and caudate connectivity (R^2=0.4, p=0.04). The regression fit is marginally significant and driven by one sample. Fig 3 shows that weaker left CST connectivity can predict worse (higher) PEM during bimanual task. The regression fit is not significant (R^2=0.3, p=0.06) but the regression plot shows a linear relationship between the two parameters. Prediction of TM scores by DTI connectivity is shown in Fig. 4. Lower FA values in the right Cingulum and right CST predicts worse TM (longer time to complete the TM test) with R^2=0.9 and p=0.0009. In Fig. 5, the regression model fit for WMFT shows that WMFT score can be predicted by right CST connectivity, caudate connectivity and interaction between right CST and caudate connectivity. The model fit is significant with R^2=0.8 and p=0.01.

Table 1. Relationship (correlation) between motor and cognitive

measures

	MVC	***RT***	***PEM***	***TM***	***WMFT***
MVC	1.00	R=-0.17 (p-value = 0.66)	R=-0.15 (p-value = 0.71)	R=-0.11 (p-value = 0.77)	R=-0.24 (p-value = 0.54)
RT	R=-0.17 (p-value =0.66)	1.00	R=0.16 (p-value = 0.67)	R=-0.06 (p-value = 0.87)	R=**0.88** **(p-value = 0.001)**
PEM	R=-0.15 (p-value =0.71)	R=0.16 (p-value = 0.67)	1.00	R=0.43 (p-value = 0.24)	R=0.14 (p-value = 0.72)
TM	R=-0.11 (p-value=0.77)	R=-0.06 (p-value = 0.87)	R=0.43 (p-value = 0.24)	1.00	R=0.19 (p-value = 0.62)
WMFT	R=-0.24 (p-value= 0.54)	R=**0.88** **(p-value = 0.001)**	R=0.14 (p-value = 0.72)	R=-0.03 (p-value = 0.62)	1.00

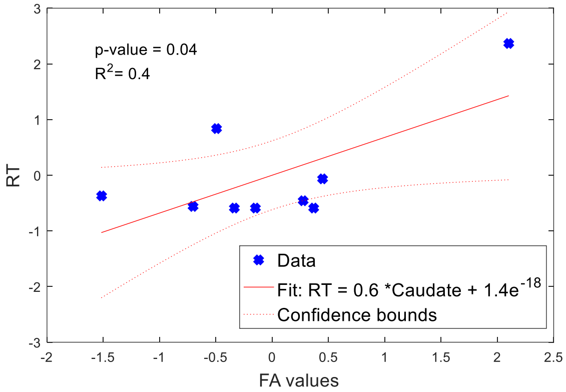

Figure 2. Regression Model for RT

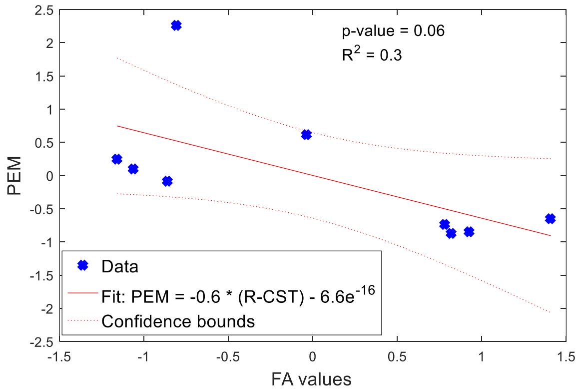

Figure 3. Regression Model for PEM

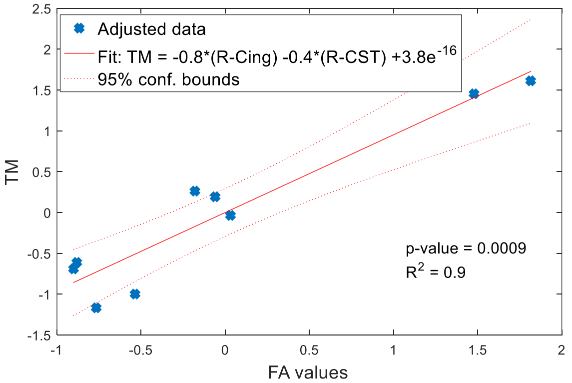

Figure 4. Regression Model for TM

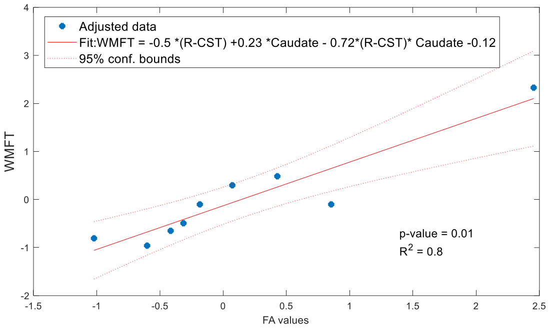

Figure5. Regression Model for WMFT

Overall results show consistent negative relationship between higher connectivity and shorter TM score, which is in line with previous research showing relationship between higher DTI connectivity and better cognitive processing [14]–[16]. The cingulum is an encircling structure along the dorsal column of the corpus callosum and interconnects frontal, parietal, and medial temporal cortices, the cingulum also receives afferent fibers from the thalamus [17]. Such anatomical connections, and the relationship between cingulum structural connections and resting state functional connectivity of the default mode network [18], explain the role of the overall integrity of executive brain networks in maintaining efficient visuospatial and task switching cognitive function. Interestingly, there is a similar negative relationship between CST and TM, suggesting that worse TM performance could also be related to weak cortical connections from the sensorimotor cortex to peripheral muscles.

The time component of WMFT showed weak negative relationship with CST integrity and positive relationship with the Caudate. The relationship between WMFT and CST suggests that weaker cerebrospinal tract contributes to slower motor function. The caudate relationship with WFMT in figure 6 should be taken with caution as it seems to be driven by a few samples. Prediction of RT by the caudate was also driven by few samples (Fig. 1). The caudate atrophy is known to be a predictor of longer action selection time [19], but the data in this sample do not provide conclusive understanding of the relationship between caudate connectivity and RT. A larger sample is required to acquire better understanding. On the other hand, absence of any relationship between MVC and connectivity of the cingulum, thalamus or other tracts that connects the subcortical nuclei and executive brain networks, suggests absence of modulatory effect of the cerebrum on muscle strength, possibly due to the low cognitive demand of the task.

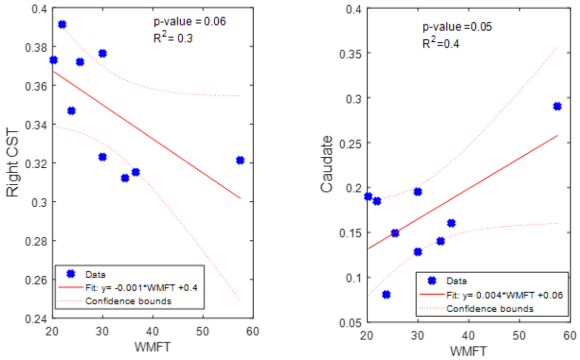

Figure 6. Relationship between WMFT and right CST (left) and caudate (right) connectivity

The RT and PEM measures are assessments of performance in a motor task but they evaluate the ability to process the information and respond efficiently. TM is a neuropsychological assessment that also tests how efficiently an individual can switch between tasks, process the information, and provide a motor response. The common features between RT, PEM, and TM suggest that poor functional performance is not solely the result of sensory or motor dysfunction but also reduced cognitive processing efficiency and cognitive-motor interference. A better understanding of this effect would necessitate more innovative and complex measures of functional performance than the simple timed tasks used in this study.

This study is innovative in using motor performance during an actual bimanual motor task (PEM and RT) to study the relation with DTI connectivity in individuals with TBI. Previous research explored the relationship between FA and TM or clinical evaluation of motor function , and between FA and motor function but did not include PEM and RT of a dynamic motor task. One of the limitations in this study is the absence of healthy controls. In future studies, we will extend this analysis to include healthy control data. We also suggest that future research on this topic should explore the relationship between DTI connectivity and measures of cognitive-motor interference; measure of dual-task cost is one example.

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