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DEPARTMENT OF PSYCHOLOGY

HETEROGENEITY IN RECOVERY: IMPACT OF GENETIC RISK FACTORS ON
WORKING MEMORY PERFORMANCE IN TRAUMATIC BRAIN INJURY

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Abstract

There is a growing body of literature using BOLD response and functional magnetic resonance imaging to examine the effect of neurological brain disorders, such as traumatic brain injury, on neurological systems including working memory. Although much work has contributed to the understanding of the injured brain, little research has been conducted on possible predictors of outcome and recovery following traumatic brain injury. In neuroscientific literature the genetic characteristics Apolipoprotein E (APOE), specifically APOE4, and the val^{66}met single neurcleotide polymorphism of brain derived neurotrophic factor (BDNF), have been shown to reduce overall brain plasticity. The present study examined if the presence either of these genetic risk factors may act as a predictor of performance or BOLD signal change in subjects with traumatic brain injury. Findings reveal important laterality effects and areas of increased BOLD signal activation that suggest genetic risk factors may play a significant role in inhibiting plasticity following neurological insult such as traumatic brain injury.

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INTRODUCTION

Each year, 1.7 million people in the United States sustain a traumatic brain injury (TBI). Over 1.6 million of those who suffer a TBI survive, but often with considerable functional impairment. Out of these 1.7 million head injuries, approximately 425,000 are considered severe (CDC). Functional neuroimaging is a noninvasive procedure that provides a novel method for examining cognitive, motor, and emotional functioning following neurological disruption. Over recent years, functional imaging literature has grown substantially, especially in respect to examining functional deficits following moderate and severe TBI. Much of this functional imaging literature has focused on the loss of basic information processing skills including working memory (Christodoulou et al., 2001; Perlstein et al., 2004; Maruishi et al., 2007; McAllister et al., 1999, 2001; Newsome et al., 2007; Sanchez-Carrion et al., 2008a, b, Hillary et al., 2011, Medaglia et al., 2011), memory encoding (Ricker et al., 2001; Levine et al., 2002; Strangman et al., 2009), executive control (Sheibel et al., 2007, 2009; Turner and Levine, 2008), and processing speed (Hillary et al., 2010).

Speeded working memory (WM) deficits have been consistently observed across forms of neurological insult including TBI (McDowell et al., 1997; Stuss et al., 1985), multiple sclerosis (Demaree et al. 1999; Mostofsky et al., 2003; Rao et al.,1989a, b), schizophrenia (Cohen et al., 1997; Saykin et al., 1991, 1994), dementia (Bradley et al., 1989; Collette et al., 1999; Morris and Baddeley 1988), and normal aging (Salthouse, 1992, 1996; Salthouse and Coon 1993). In response to the almost universal observation of WM deficit following neural trauma, functional neuroimaging literature in the clinical neurosciences focuses heavily on examining deficits in speeded WM and other basic processing deficits that result from TBI.

The growing body of functional neuroimaging literature examining WM following moderate to severe TBI yields remarkably consistent areas of increased neural activity as indicated by increased blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) signal. In almost

all cases, results indicated increased activation in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) in individuals with TBI when compared with healthy controls. In most of the literature the observed recruitment of the PFC is in the right hemisphere (Hillary et al., 2006; Hillary, 2008).

Functional Magnetic Resonance Imaging

Used in both clinical medicines, biological, and psychological research, functional magnetic resonance imaging (fMRI) has become one of the most prominent methods used for brain mapping and examining the neural basis of human cognition. The basis of fMRI lies within the interrelationship between physiological function, energy requirement, and localized blood supply. Put simply, the relationship is derived from the theory that increased neural activity requires an increase in energy. Subsequently, changes in energy requirements of the brain are proportional to changes oxygen levels within the blood (eg. glucose is aerobically metabolized within the brain). Imaging with nuclear magnetic resonance (NMR) uses magnetization differences within a strong magnetic field, varying dipole moments, and nuclear spins among atoms to measure the composition of the brain at any given moment. When these images are acquired in succession, changes in tissue and blood composition can be observed. Blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) provides a measure of neural dynamics by measuring relative contributions of oxygenated and deoxynated hemoglobin within neural blood supply. Hemoglobin in blood consists of two pairs of polypeptide chains attached to a complex if porphyrin and iron (heme). In deoxygenated hemoglobin (dHb) the iron is in a higher spin state than in oxygenated hemoglobin. Differences in spin state can be detected with NMR. These differences allow the direct observation of blood oxygenation state which subsequently reflects blood flow, metabolism, and neural activity (Logothetis, 2002). As a result of these physiological interactions, fMRI offers a secondary measure of neural firing due to oxygen metabolism that allows inferences to be made about local neural activity.

Neural Recruitment during WM

Although the role that PFC recruitment plays in WM tasks in disrupted neural networks still remains unclear, an increasing number of studies have evaluated the existence of 'latent support' as an explanation for the consistent observation that PFC is recruited during WM tasks. The latent support hypothesis asserts that recruitment is a natural mechanism operating in response to a disrupted neural network. This mechanism does not serve to enhance performance, but instead is an indication of recruitment of attentional and executive control resources in an effort to complete a task despite reduced processing efficiency. Therefore, the increased PFC involvement observed in many neuroimaging studies is a result of this latent support mechanism being brought online to withstand the high demands of novel task completion in a disrupted network (Hillary et. al, 2010). The importance of the explanation offered here is the implication of a negative performance/activation relationship when considering the role of neural recruitment in cognitive recovery (Hillary et al., 2006).

Other literature examining WM task performance and the role of PFC recruitment suggest two additional, differing explanations. The first, most easily summarized as the brain reorganization hypothesis, assumes the observed PFC recruitment reflects a permanent reorganization of the neural substrate, or changes in the physical network, required to successfully perform a WM task (Sanchez-Carrion et al., 2008a,b, see also Levin, 2003). This hypothesis also suggests that PFC recruitment functions to bolster task performance, creating a relationship in which increased PFC recruitment correlates with better task performance. The second explanation for PFC recruitment is a neural compensation hypothesis. Neural compensation is similar to reorganization in that it suggests that PFC recruitment is a mechanism that enhances task performance. However, neural compensation suggests no alterations in the underlying neural substrate (Maruishi et al., 2007; McAllister et al., 1999, 2001; Scheibel et al., 2009; Turner and Levine, 2008). The following study will examine PFC recruitment and

task performance in an effort to lend support to one of these hypotheses about the role that PFC recruitment fulfills during WM tasks in individuals with TBI.

Clinical Heterogeneity in TBI

The varied mechanisms, diffuse axonal damage, and lesioning observed following brain injury make TBI a heterogeneous population. Heterogeneity in TBI presents an ongoing problem for rehabilitation research such that and single therapy or prevention method, regardless of physical, psychiatric, or pharmacological approach, has failed to yield consistent positive result (Narayan et al., 2002). The functional and social outcome of persons suffering from TBI yield heterogenic findings as well (Dodwell, 1988; Marshall et al., 1991; Moldover et al., 2004). Significant efforts have been made towards bettering the classification of head injury in an effort to more specifically understand and treat patients with TBI. Saatman et al. (2008) suggests that a focus on the pathioanatomic features of the individual's brain injury should be the basis of a new clinical classification. Based on the current body of literature, it still remains unclear if there are reliable predictive factors for outcome in individuals with TBI.

Despite the observed heterogeneity in TBI there have been almost universal findings that show PFC recruitment during working memory tasks, but the mechanism behind this recruitment remains unclear. The heterogeneity observed in TBI (Narayan et al., 2002, Dodwell, 1988; Marshall et al., 1991; Moldover et al., 2004) combined with the consistent observation of PFC recruitment during WM tasks (Hillary et. al, 2010; Hillary et al., 2006; Sanchez-Carrion et al., 2008a,b; Levin, 2003; Maruishi et al., 2007; McAllister et al., 1999, 2001; Scheibel et al., 2009; Turner and Levine, 2008) does not provide a cohesive explanation of the functional outcomes following TBI. Specifically, a gap exists in the literature that examines how heterogeneity in outcome can be simultaneously observed with consistency in PFC recruitment. Based on cellular neuroscience literature examining the effect of genetic factors on

neuronal plasticity (Pearson-Fuhrhop et al, 2009; Barde, 1994; Lewin, 1996; Thoenen, 1991; Huang and Reichardt, 2001; Lu et al., 2005) there is reason to believe that certain genetic factors may play a role in plasticity following TBI, thus affecting outcome and task performance while maintaining the recruitment pattern that has been universally observed in TBI. This study will aim to increase that understanding by examining correlations between possible genetic predictors of WM task performance and BOLD signal activation patterns after TBI.

Genetic Influence on Neural Plasticity

The field of neuroscience has successfully liked various genetic factors to brain plasticity (Pearson-Fuhrhop et al, 2009). Brain derived neurotrophic factor (BDNF) has been shown to be directly involved in both short and long term brain plasticity. (Barde, 1994; Lewin, 1996; Thoenen, 1991). A functional single nucleotide polymorphism (snp) has been identified within the BDNF gene, in which a G to A substitution at nucleotide 196 results in an amino acid switch from valine to methionine at codon 66 (Shimizu et al., 2004). This genetic abnormality, known as the val[66]met polymorphism, has been observed as an inhibitory factor of adulthood plasticity and recovery from TBI (Huang and Reichardt, 2001; Lu et al., 2005). Apolipoprotein E (ApoE) exhibits similar common single nucleotide polymorphisms on the ApoE gene at amino acid position 112 and 158 which result in three common alleles delineated by number. (Pearson-Fuhrhop et al, 2009). The ApoE4 allele is also linked to inhibited plasticity and synaptic recovery following neurological insult (Nathan et al., 2001). One of the main aims of this study is to examine the influence of these genetic factors on plasticity and functional brain activation in TBI.

Current Study

The current study will focus on the predictive ability of the BDNF val66met polymorphism and/or the presence of the ApoE4 allele on task performance and BOLD activation following TBI using a well-established working memory task.

Hypothesis 1: Individuals sustaining TBI who are positive for val^{66}met or ApoE4 will show greater whole brain recruitment during the n-back task.

Hypothesis 2: Individuals sustaining TBI will demonstrate greater RPFC recruitment than healthy controls without a simultaneous increase in task performance.

Hypothesis 3: Individuals sustaining TBI who are positive for val^{66}met or ApoE4 will demonstrate greater recruitment of RPFC than individuals sustaining TBI without val66met or ApoE4.

METHODS

Subjects

Participants were divided into three groups; Risk TBI, Non-Risk TBI, and healthy control (HC). The Risk TBI group consisted of 8 (4 male, 4 female) right-handed individuals, ages 18-44, with moderate to severe TBI (M=30.13, SD=10.03). These individuals tested positive for the BDNF val[66]met polymorphism or ApoE4 allele genetic characteristics. The Non-Risk TBI group consisted of 8 (4 male, 4 female) right-handed individuals, ages 19-53, with moderate to severe TBI (M=34.00, SD= 10.51). These individuals tested negative for the BDNF val[66]met polymorphism or ApoE4 allele genetic characteristics. The HC group consisted of 8 (4 male, 4 female) right-handed, healthy individuals, ages 18-49, who tested negative for the BDNF val[66]met polymorphism or ApoE4 allele genetic characteristics (M=26.5. SD= 9.97).

Table #1: Subject Demographics

	Risk TBI (Mean, SD)	Non-Risk BI (Mean, SD)	HC (Mean SD)
Age (years)	30.13, 10.03	34.00, 10.51	26.5, 9.97
Education (years)	13.50, 2,78	13.38, 1.93	13.50, 2.12
Gender	4 M, 4F	4M, 4F	4M, F4
Loss of Consciousness (days)	12.29, 4.7	9.1, 10.22	n/a
Acute Stay (days)	21.14, 16.52	15.50, 9.46	n/a
Cause of Injury	8 MVC	5 MVC, 2 MVC vs. bike, 1 fall	n/a
Injury severity GCS	4.25, 1.64	3.42, 1.05	n/a

** MVC= Motor Vehicle Crash

TBI severity was defined using the Glasgow Coma Scale (GCS) in the first 24 hours after injury (Teasdale and Jennett, 1974). GCS scored from 3-8 were considered "severe" and individuals with GCS scores from 9-12, or significant neuroimaging findings, were considered "moderate". All individuals in the sample had a Glasgow Coma Score of 3-12 and/or had at least one lesion confirmed by CT scans reported in their medical records. Individuals in the study reported no history of neurological disorder such as previous TBI, stroke or seizure disorder, or significant neurodevelopmental psychiatric history (such as schizophrenia or bipolar disorder). Individuals also reported no previous inpatient treatments for substance abuse. These conditions were included in the institutional review board approved consent form and were discussed or approved with the study participant and/or family member(s) at the time of the study.

MRI Task

The n-back, a well-established sequential letter task, was used to assess working memory of each subject (Chang et al., 2001; Kirchner, 1958; Speck et al., 2000). Specifically, the 1-back version of the traditional n-back test was used. During the task, subjects were presented with strings of 10 alphabetical letters. Each letter was presented at a rate of one very two seconds (stimulus duration =1750ms, interstimulus interval = 250ms). Subjects were instructed to respond to the positive target stimuli as quickly as possible. The positive target stimuli were defined as occurring when the letter on the screen was the same as the letter immediately preceding it. Each run of the task consisted of eight 20 second blocks with 14 seconds of rest in between each block. During each 20 second block, three or four positive target stimuli were presented at pseudo-random intervals (21-24 positive targets were presented out of a total of 80 positive targets). During each 14 second rest period, subjects were instructed to fixate on a small asterisk presented at the center of the display screen. A number of the subjects were asked to complete various other, similar WM tasks in and out of the MRI scanner that were not included in this

analysis. In the case of these subjects, only the runs before the administration of out-of-scanner runs were used to eliminate any possible practice effects.

In Scanner Task Performance

In scanner task performance was assessed using a remote response system. Subjects were asked to respond by pressing a button with their thumb. A press of the right button indicated a target response and a press of the left button indicated a non-target response. All subjects were right handed to eliminate the possibility of a handed response bias. Subjects were assessed for the percent correct answers and for reaction time.

Neuropsychological Testing

Neuropsychological testing was administered to each subject on the day of scan to assess neuropsychological functioning. The battery included tests specifically targeting functional deficits commonly associated with TBI such as working memory, processing speed, and verbal comprehension. The battery included the Digit Span subtest of the WAIS-III (including digits forward and digits backward) (Wechsler, 1997), Trail Making Test A and B (Army Individual Test Battery, 1990; Reitan and Wolfson, 1985), and the information subtest of the WAIS-III (Wechsler, 1997).

MRI Acquisition

All data were acquired using a Philips 3T system and a 6-channel SENSE head coil (Phillips Medical Systems, Best). Before tasks began, 3D high-resolution T_1 – weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) images (9.9ms/4.6ms/8° repetition time/echo time/flip angle, 240 x 204 x 150mm^2 field of view, 256 x 205 x 150 acquisition matrix , two averages) were acquired to provide high level resolution underlays for functional brain activation. Echo planar imaging

was used for functional imaging. Imaging parameters consisted of: 2000ms/30ms/89°, repetition time/echo time/flip angle, 230 x 230mm^2 field of view, 80 x 80 acquisition matrix, thirty four- 4mm-thick axial slices with no gap between slices.

Data Preprocessing

Preprocessing of the functional MRI data was performed using spm8 software (http://www.fil.ion.ac.uk/spm8). The first 15 volumes were removed from analysis to control for signal instability. Preprocessing steps included realignment of functional data of each trial to the first functional image of that trial using affine transformation (Worsley and Poline, 1995; Ashburner and Friston, 1997). Functional images were then co-registered to the individual's T_1 magnetization prepared rapid gradient echo data and all were normalized using a standardized T_1 template from the Montreal Neurological Institute, using a 12 parameter affine approach and bilinear interpolation. Normalized time series data were smoothed with a Gaussain kernel of 8 x 8 x 10mm^3 in order to minimize anatomical differences and increase signal to noise ratio. In instances in which the normalization using a 12 parameter affine approach created significant distortion, the images were normalized to the individual's T_1 magnetization prepared rapid gradient echo data. Smoothing procedures remained the same in all individuals.

Functional Imaging Contrasts

First level analyses were conducted using the general linear model within SPM8 to produce intra-individual contrasts showing on-task activation relative to rest (1-back minus rest). Four separate group activation maps were computed using random affects analysis (two- sample *t*-tests) to determine group differences in on-task activation relative to rest. The first group analysis compared both TBI groups (Risk and Non-Risk) to the HC group. A within TBI contrast was created to examine the

differences between the Risk TBI and Non-Risk TBI and both Risk TBI vs. HC and Non-Risk TBI vs. HC contrasts were created in the same manner.

SPM8 software was used to isolate whole brain peak activation differences in each of the group contrasts. Peak on-task activation coordinates were reported as MNI space coordinates. MNI coordinates were converted to Talairach coordinates and the TalairachClient was used to determine the Broadmann's area in which each peak of activation difference occurred. All contrasts were analyzed at a $p < .05$ significance level.

Region of Interest Analysis

Isolation of specific regions of interest (ROI's) associated with WM deficit was conducted to allow for examination of neural networks specific to WM. Standardized ROIs from the WFU Pickatlas within the SPM software package were selected bilaterally for the dorsolateral prefrontal cortex (DLPFC) (Broadmann's areas 46), premotor and motor areas (Broadmann's areas 4 and 6), and the part of the parietal cortex defined by Broadmann's area 40. The MarsBar toolbox was used to extract individual's percent signal change within each of these regions during the n-back task. These ROIs were later combined to give "whole brain", "right hemisphere", and "left hemisphere" data that were examined for significant differences between groups.

RESULTS

In Scanner Task Performance

In scanner task performance was assessed through reaction time (RT) and percent accuracy of answers in response to the n-back task. Each group was compared using an independent two samples t-test assuming unequal variances. It was found that the reaction time of subjects only differed significantly between the Risk TBI and non-Risk TBI groups (p < .001). All other comparisons (Risk vs. HC, Non-Risk vs. HC, and combined TBI vs. HC) were insignificant as can be seen in table #2. In contrast, accuracy differed between the Risk TBI vs. HC (p< .001), the Non-Risk TBI vs. HC (p < .001), and the combined TBI vs. HC (p=2.34E-14). The Risk TBI vs. Non-Risk TBI comparison was insignificant.

Table # 2: In Scanner Task Performance Means

	Task RT		Task Accuracy	
	Mean	SD	Mean	SD
Risk TBI	671.8	100.4	0.79	0.21
Non-Risk TBI	698.2	120.8	0.89	0.14
HC	592.0	129.2	99.5	1.32

Table # 3: In Scanner Task Performance Statistical Comparisons

	Risk TBI vs Non-Risk TBI	Risk TBI vs. HC	Non-Risk vs. HC	TBI vs. HC
Task RT	p< .001	0.219	0.134	0.127
Task Accuracy	0.310	p < .001	p < .001	p < .001

All values reported are p values significance p=.05, independent samples t-test assuming unequal variances

Image Contrast Analysis

Areas that showed more BOLD signal during the WM task in the Risk TBI group when compared to the Non-Risk TBI group can be seen in Figure #1. These areas include right prefrontal cortex (RBA9, RBA10), bilateral premotor cortex (LBA6, RBA6), right primary motor cortex (RBA4), bilateral dorsal anterior cingulate cortex (LBA32, RBA32), right fusiform gyrus (RBA37), right temporopolar area (RBA38), right visual cortex (RBA19), right primary and auditory association cortex (RBA41), right pars opercularis (RBA44), and right cerebellum.

Areas that showed more BOLD signal during the WM task in the Risk TBI group vs. HC group can be seen in Figure #2. These areas include right dorsolateral prefrontal cortex (RBA46), right prefrontal cortex (RBA9), left somatosensory association cortex (LBA7, LBA5), bilateral superior temporal gyrus (LBA22, RBA22), right anterior cingulate cortex (RBA32, RBA24), right inferior prefrontal gyrus (RBA47), right retrosplenial cingulate cortex (RBA29), right temporopolar area (RBA38), left supramarginalgyrus (LBA40), left primary and auditory association cortex (LBA41, LBA42), and left cerebellum.

Areas that showed more BOLD signal during the WM task in the NonRisk TBI group vs. HC group can be seen in Figure #3. These areas include right prefrontal cortex (RBA9), left premotor cortex (LBA6), bilateral primary motor cortex (LBA4, RBA4),bilateral inferior prefrontal gyrus (LBA47, RBA47), bilateral middle temporal gyrus (LBA21, RBA21), right visual cortex (RBA19), bilateral ventral anterior cingulate cortex (LBA24, RBA24), right supramarginalgyrus (RBA40), right insular cortex (RBA13), right cerebellum, right lateral geniculum, and right caudate tail.

Areas that showed more BOLD signal during the WM task in the combined TBI group vs. HC group can be seen in Figure #4. These areas include right prefrontal cortex (RBA9), right premotor cortex (RBA6), right primary motor cortex (RBA4), right visual cortex (RBA19),bilateral inferior prefrontal gyrus (LBA47, RBA47), right superior temporal gyrus (RBA22), right dorsal posterior cingulate cortex (RBA31), right insular cortex

(RBA13), right middle temporal gyrus (RBA21), left pars triangularus (LBA45), right lentiform nucleus, and right superior temporal gyrus.

SPM8 software was used to create group image analyses that allowed the examination of the main effect of group on BOLD signal on a whole brain level. Each contrast displays the difference in BOLD signal (on-task relative to rest) between groups at a p=.05 significance level (Figures #1-4).

Figure # 1: Risk TBI >Non-Risk TBI Image Contrast
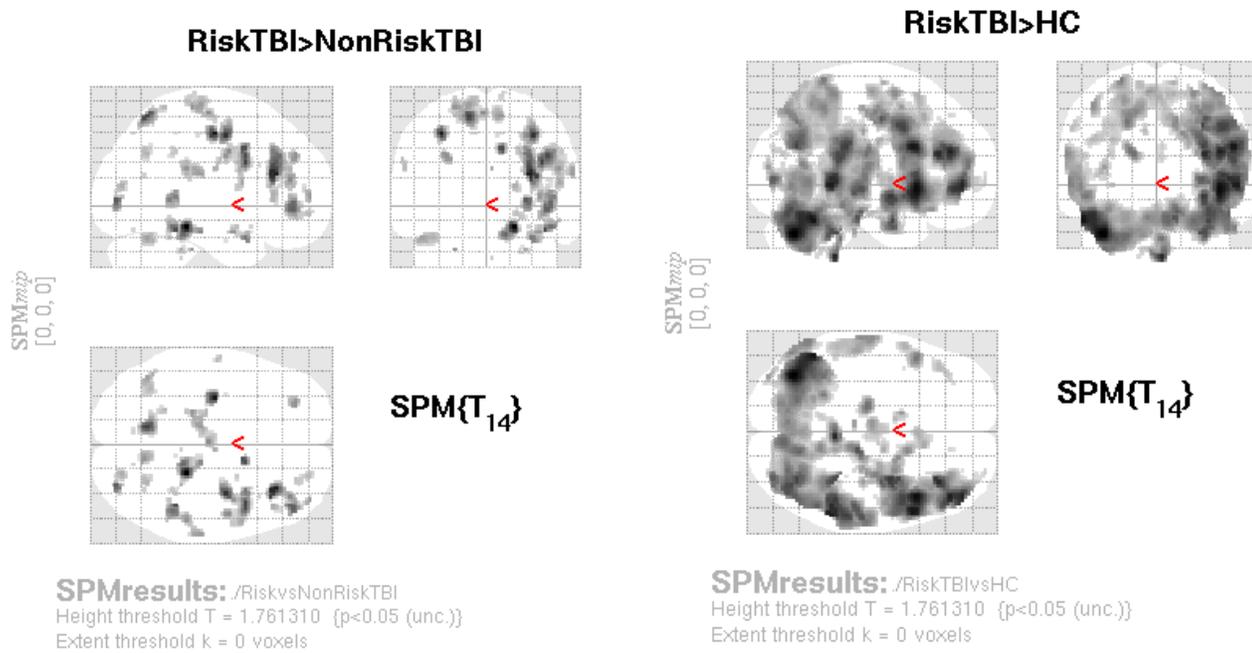
Figure # 2: Risk TBI >HC Image Analysis

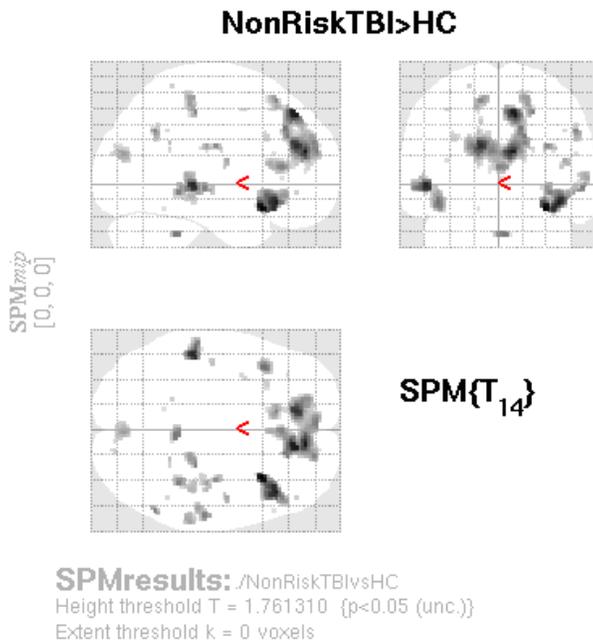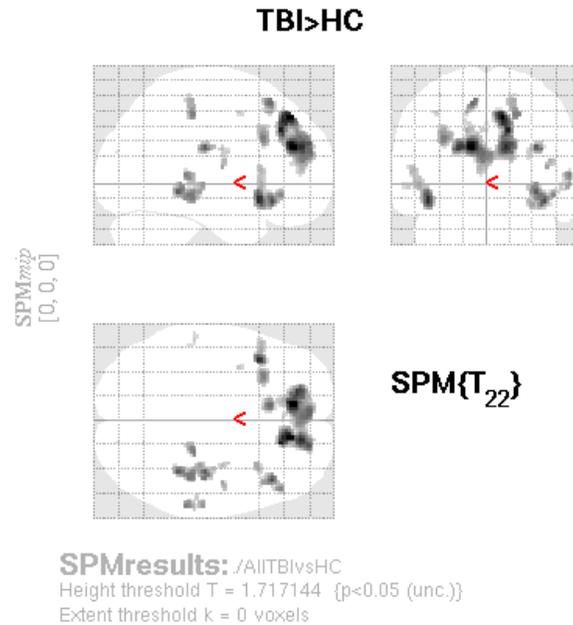Figure # 3: Non-Risk>HC TBI Image Contrast   Figure # 4: TBI>HC Image Analysis

NonRiskTBI>HC

SPM{T$_{14}$}

SPMresults: ./NonRiskTBIvsHC
Height threshold T = 1.761310 {p<0.05 (unc.)}
Extent threshold k = 0 voxels

TBI>HC

SPM{T$_{22}$}

SPMresults: ./AllTBIvsHC
Height threshold T = 1.717144 {p<0.05 (unc.)}
Extent threshold k = 0 voxels

ROI Analysis

Several independent sample t- tests assuming unequal variances were conducted on the percent signal change means of each group's ROIs compared to both of the other groups respective ROIs. Further t-tests were conducted to assess significant differences in signal change within each ROI between the combined TBI group and the HC group. Findings that approach significance may be meaningful on the basis of past literature are reported due to small sample size. Meaningful findings are reported below.
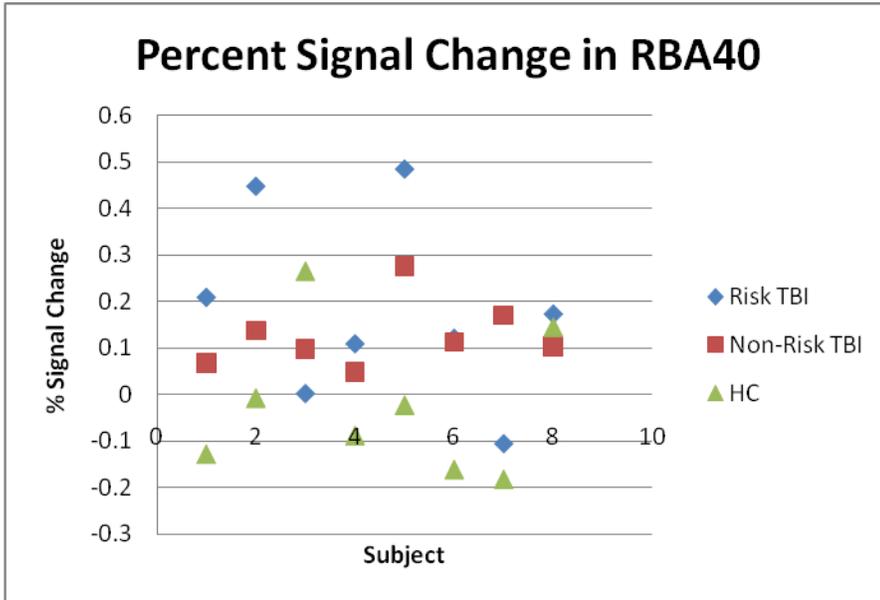
Right Broadmann's area 46 (RBA 46) showed no significant findings. However, an interpretation of a graphical representation of the data shows a distinctly lower percent signal change in the majority of the HC individuals (See figure #5). It also appears that the Risk TBI group may tend to show a higher percent signal change in the RPFC than both the Non-Risk TBI group and the HC group.

Figure # 5: Percent Signal Change in RBA46
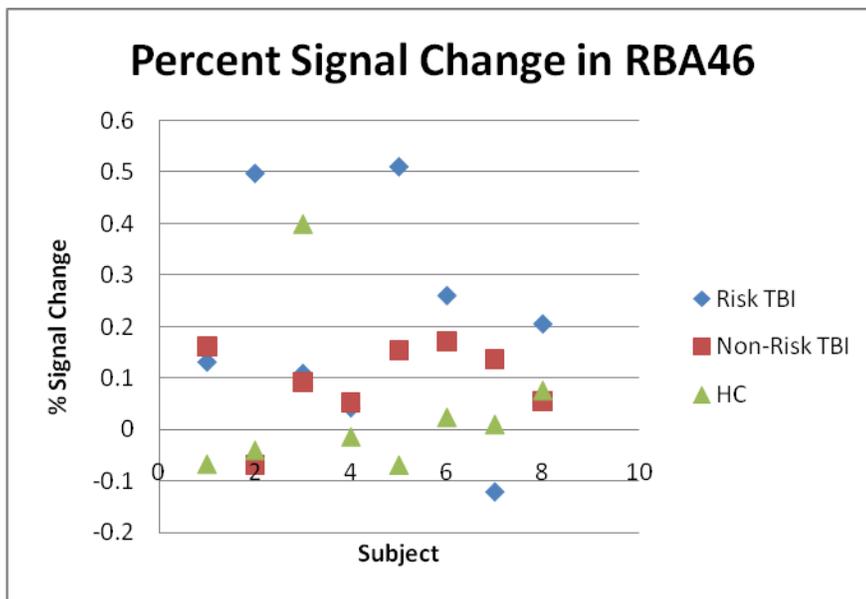
Right Broadmann's area 40 (RBA40) showed significant findings when TBI groups were compared to the HC group. Risk TBI percent signal change was significantly greater than HC percent signal change (p=0.0438) and Non-Risk TBI percent signal change was significantly greater than HC change (p=0340). A significantly greater percent signal change was observed in the combined TBI group compared to the HC group (p= .0196). No significant Risk TBI vs. Non-Risk TBI differences in percent signal changes were observed (p=.5032).

Figure # 6: Percent Signal Change in RBA40

Right Broadmann's area 6 (RBA6) percent signal change comparison between Risk TBI vs. HC groups showed a near significantly greater percent signal change in the Risk TBI ($p= .0549$). T-test analysis of the overall TBI vs. HC yielded near significant results suggesting TBI show a greater percent signal change ($p=.0537$). Similarly the graphical representation shows a trend in which the percent signal change in HC is generally lower than that of both TBI groups.

Figure # 7: Percent Signal Change in RBA6

Percent Signal Change in RBA6
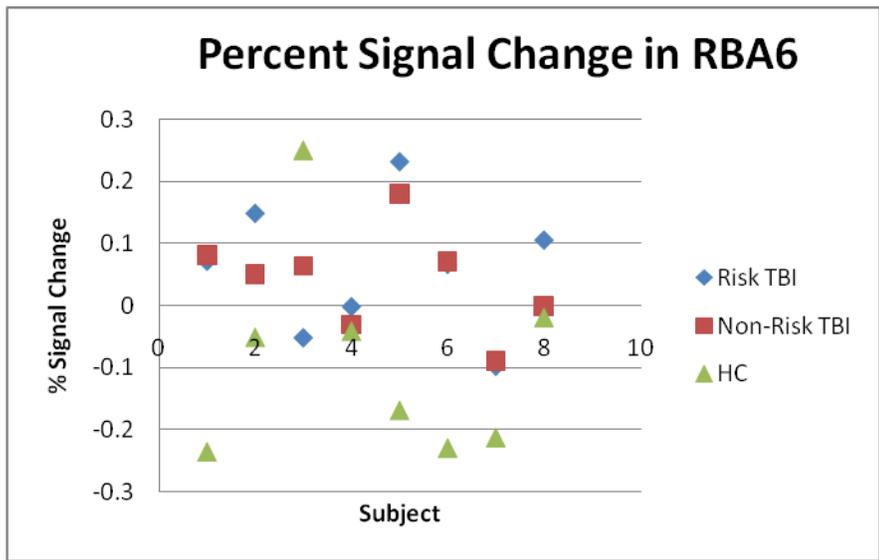
Left Broadmann's area 40 (LBA40) yielded similar findings to RBA40. The Risk TBI percent signal change was nearly significantly greater than the HC percent signal change ($p=.0796$) and the N-Risk TBI percent signal change was significantly greater than the HC percent signal change ($p=.0290$). The combined TBI group percent signal change was significantly greater than the HC percent signal change ($p=.0347$).

Figure # 8: Percent Signal Change in LBA40

Percent Signal Change in LBA40
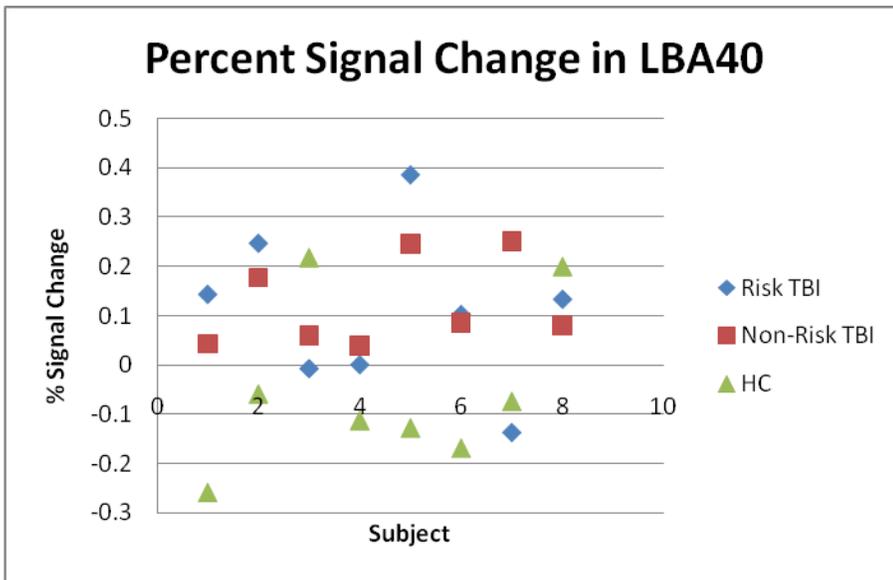
Left Broadmann'sarea 6 (LBA6) showed no significant results. However, Risk TBI percent signal change was almost significantly greater than HC percent signal change ($p=.0549$). Combined TBI percent signal change was almost significantly greater than HC percent signal change ($p=.0537$).

Figure # 9: Percent Signal Change in LBA6

Percent Signal Change in LBA6
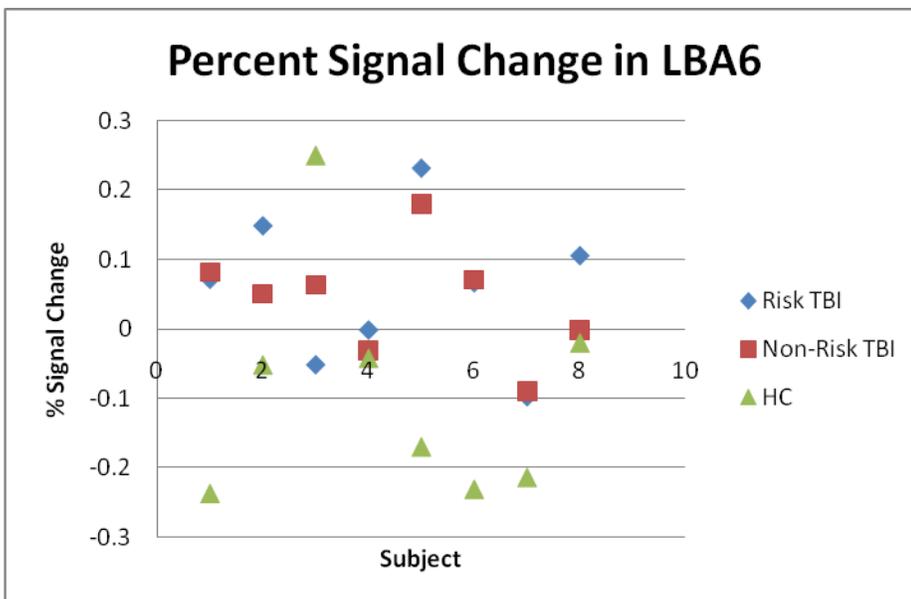
Whole brain percent signal change analysis revealed that TBI percent signal change were universally greater than HC percent signal change. Risk TBI percent signal change was significantly higher than HC percent signal change (p=6.88E-05) and Non-Risk TBI percent signal change was significantly higher than HC percent signal change (p=.000804). The combined TBI percent signal change was significantly higher than HC percent signal change (p= 1.29E-.05).Whole brain signal change was defined as the combination of the percent signal change within RBA46, RBA40, RBA4, RBA6, LBA46, LBA40, LBA6, and LBA4.

T-tests revealed that right hemisphere percent signal change in the Risk TBI group was significantly higher than the HC right hemisphere percent signal change (p=.01714). Non-Risk TBI right hemisphere percent signal change was nearly significantly higher than HC percent signal change (P=.0586). The combined TBI right hemisphere percent signal change was significantly higher than the HC right hemisphere percent signal change (P=.0131). Right hemisphere was defined as the combination of percent signal change within RBA46, RBA40, RBA4, and RBA6.

In contrast, tests of left hemisphere percent signal change revealed that only the combined TBI percent signal change was significant (p=.0232). The left hemisphere was defined as the combination of percent signal change with in LBA46, LBA40, LBA6, and LBA4.

Although there were no significant differences when right vs. left hemispheres were compared within group, a laterality effect was seen between Risk TBI and non-Risk TBI. Laterality was defined as the degree to which hemispheres differ from each other, compared between groups.

DISCUSSION

Primary Findings

The primary hypothesis in this study was that genetic risk factors (BDNF val[66]met or ApoE4) will be predictive of task performance and the BOLD signal following TBI, particularly in the right dorsolateral prefrontal cortex (McAllister et al., 1999, 2001; Christodoulou et al.,2001; Perlstein et al., 2004; Maruishi et al., 2007; Hillary et al., 2010).

Primary results indicate that successful completion of a working memory task requires differential recruitment of the right prefrontal cortex and right parietal lobe in TBI when compared to healthy controls. These findings are consistent with a larger literature (see Hillary 2008). Additionally, results in the TBI sample show that recruitment of the RPFC and right parietal lobe may be associated with genetic risk. Behavioral results indicate that, despite increased recruitment of RPFC, individuals with TBI exhibit lower task accuracy. Similarly, the same within-TBI difference is seen on task accuracy in which increased RPFC involvement corresponds with lower task accuracy.

Genetic risk (e.g., challenged neuroplasticity at the single-cell level) is a form of biological challenge that influences the brain's ability to adapt to neuropathology. The ApoE4 allele has been implicated in disrupted distribution of cholesterol in neuronal membranes that is imperative to neuritic extension growth and branching (Mauch et al., 2001; Graham et al., 2000) and the BDNF val[66]met polymorphism has been implicated in the breakdown of neurotrophins necessary for neuronal differentiation, axonal, and dendritic growth, and synapse formation (Egan et al., 2003, Kleim et al., 2006). Functional plasticity relies on a bottom-up approach in which disruptions in neuritic extension, growth, and branching, as well as synaptic formation will manifest in disruptions in functional plasticity in top level neural processing (Egan et al., 2003). Thus, it was predicted that the presence of a genetic risk factor would predict reduced behavioral task performance and greater increase in the BOLD signal during a working memory task. Specifically, it was hypothesized that the right prefrontal cortex would

be differentially recruited based on past studies of TBI during working memory tasks (Hillary et al., 2010; Hillary et al., 2011; Medaglia et al., 2011).

We interpret these findings to suggest that latent cognitive control support mechanisms are recruited in the context of cerebral challenge and brought on-line as a mechanism to combat slowed information processing. We suggest that increased cognitive control is necessary for the facilitation of a task—that is, without cognitive or attentional control, individuals cannot complete the WM task. However, slowed information processing after TBI appears to require ongoing recruitment of these resources which may be an indicator of neural inefficiency. This assertion draws from data collected in this study and past literature (Hillary et al., 2010; Hillary et al., 2011; Medaglia et al., 2011) demonstrating a negative relationship between PFC recruitment and task performance, specifically reaction time. Further, these data suggest that TBI recruit more cognitive control resources than healthy controls, yet demonstrate slower reaction time. In summary PFC recruitment in TBI may be indicative of neural inefficiency.

Past literature has interpreted the functional purpose of this recruitment in two main ways: a neural compensation or reorganization serving to facilitate performance (Maruishi et al., 2007; McAllister et al. 1999, 2001; Sanchez-Carrion' et al. 2008a, b) or an increased allocation of cognitive control resources as a latent support mechanism for a disrupted neural network (Christodoulou et al., 2001; Perlstein et al., 2004; Hillary et al., 2010; Hillary et al., 2011; Medaglia et al., 2011). The determination of the relationship between task performance and RPFC recruitment is integral to supporting either of these two conclusions within TBI literature. RPFC has been thought to play a critical role in cognitive control. Cognitive control acts to coordinate cognitive activities to establish task goals, procedures for task execution, and coordination and distribution of resources for completion of a task (Miller and Cohen, 2001). In any population, a "difficult" or resource demanding task requires increased cognitive control and often increased RPFC demand. In an inherently challenged neural

system such as TBI, completion of that same novel task likely requires more cognitive control (e.g. increased RPFC involvement) to allocate decreased resources due to disruptions within the neural network. The results of this study support that assertion by demonstrating that completion of the same cognitive task requires differing RPFC involvement. Increased RPFC involvement due to increased cognitive control demand does not correlate with increased performance. These observations are integral in discounting hypotheses that PFC recruitment constitutes a part of reorganization or "compensation". Instead, increased RPFC involvement is seen with comparable, or slightly decreased, task performance, further supporting the hypothesis that RPFC involvement and increased cognitive control are a latent support mechanism that challenged networks recruit to complete the task due to slowed processing speed.

The primary goal of this study was to examine the effect of genetic characteristics on previously observed RPFC recruitment and behavioral trends in TBI. Results show a within-TBI difference in RPFC recruitment such that the TBI with genetic risk factors demonstrate increased RPFC recruitment during the task. These findings suggest that TBI with genetic risk may represent a more challenged cerebral network than TBI without these genetic characteristics due to the increased cognitive control mechanisms required to handle similar degrees of cognitive demand. The observation that TBI with genetic risk demonstrate greater RPFC recruitment than the non-risk TBI is an indication that recovery has not been as thorough, an idea that is consistent with findings that these genetic factors reduce plasticity and therefore inhibit recovery.

Limitations

The effects seen within this study have important implications for both the understanding of RPFC recruitment and the effect of genetic characteristics on TBI recovery. However this study is not without limitations. The greatest limitation in this study is a relatively small sample size which inhibited

the statistical power and statistical significance of many of the findings. The consistency of the results with other literature (Hillary et al., 2010; Hillary et al., 2011; Medaglia et al., 2011) suggests that although the sample size is limited, the effects are present and meaningful.

Implications/Further Study

In conclusion these results are consistent with the latent support hypothesis. The findings show a marked increase in RPFC recruitment in more challenged neural networks without an increase in task completion. This lends support to the assertion that RPFC recruitment represents a latent support mechanism in which more challenged neural networks exhibit increased RPFC recruitment with the same or lesser task completion.

These results may provide a link between cellular neuroscience and functional outcome or recovery following TBI. Evidence of larger network demands in TBI with genetic risk suggest inhibited recovery, which is likely a result of reduced plasticity that has been linked to the BDNF val[66]met polymorphism and ApoE4 allele (Huang and Reichardt, 2001; Lu et al., 2005, Nathan et al., 2001).

Although causal links cannot be inferred, these findings allow for many further questions to be asked. Further study could include the effect of genetic risk factors on connectivity within networks, top level processing domains of any kind, or neuropathologies beyond TBI. These findings support the argument that it is vital to address heterogeneity in the rehabilitation of TBI.

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Alyssa L.Peechatka

ACADEMIC PREPERATION

2008-2012   Bachelor of Science Candidate-Psychology with a Neuroscience option, Minor in Biology

Pennsylvania State University, Schreyer Honors College

2009   Study abroad experience
Institute PalaisCorbelli, Vienna, Austria

RESEARCH EXPERIENCE

2010-Present   Research Assistant
Pennsylvania State University, Psychology Department

2009   Research Assistant
Boston University, Psychology Department

PEER REVIEWED MANUSCRIPTS

Peechatka, A.L.,Medaglia.J.D.,Venkatesan, U., Solocomb, J., & Hillary. F.G.
Heterogeneity in recovery: Impact of genetic risk factors on working memory performance following traumatic brain injury. In preparation.

Medaglia, J.D.,**Peechatka, A.**, Hasse, M., Ferrante, L., & Hillary, F.G.
The role of the cerebellum in a distributed cognitive system during verbal working memory.In preparation.

Medaglia, J.D.,**Peechatka, A.,**Hasse, M., Ferrante, L., & Hillary, F.G.
The Effects of Practice and Task Load on the Cerebellum During Verbal Working Memory. In preparation for resubmission to *The Cerebellum*.

Hillary, F.G., Medaglia, J.D., Gates, K., Molenaar, P., Slocomb, J., **Peechatka, A**., Good, D.(2011). Examining working memory task acquisition in a disrupted neural network.*Brain*,134(5), 1555-1570.

CONFERENCE POSTERS AND PRESENTATIONS

Peechatka, A.L., Medaglia, J.D., Chiou, K.S., Slocomb, J., Ramanathan, D. M., &Hillary, F.G.
(2012, February) A Longitudinal fMRI Study of Working Memory in TBI during Early Recovery.Poster to be presented at the International Neuropsychological Society, Quebec City.

Medaglia, J.D.,**Peechatka, A.,**Hasse, M., Ferrante, L., & Hillary, F.G.
(2012, February). Effective Connectivity Findings Suggest a Role of the Cerebellum in
Cognitive Control. Paper to be presented at the International Neuropsychological Society,
Montreal, Quebec.

Peechatka, A.,Medaglia, J.D., Chiou, K.S., Slocomb, J., Ramanathan, D. M.,& Hillary, F.G. (2011,
March) Working Memory BOLD Signal Changes in TBI during Early Recovery. Poster Presented at
Pennsylvania State University's Psi Chi Research Conference

Medaglia, J.D., Gates, K., **Peechatka, A.,** Hasse, M., & Hillary, F.G.
(2011, February).Examining Network Change with Extended Unified Structural Equation Modeling:
Implications for the Latent Support Hypothesis in Brain Trauma. Paper presented at the International
Neuropsychological Society, Boston.

TEACHING POSITIONS

2009   Native English Speaking Teaching Intern
Billroth 73 Gymnasium
Vienna, Austria
Assisted with teaching high school aged, Austrian students in the fields of English Literature and Biology.
Independently prepared and taught lesson plans and tutored students with individual academic difficulties.

EMPLOYMENT

2011   FTCAP Coordinator
Pennsylvania State University
Assisted with the coordination of incoming student schedules in the pre-biology major. Worked
individually with students and parents to create appropriate schedules and answer questions during
freshman orientation

2008-Present   Barn Manager
Windward Farm Morgans
Assist with the train and care of Morgan show horses in a professional training barn. Requires an
understanding and execution of small business management as well as clientele management and legal
obligations.

HONORS

2011   Peter T. Luckie Research Award-- Best Junior Research Poster
Outstanding poster presentation at the Pennsylvania State University Undergraduate Research Exhibit

2008-2011   Dean's List, Pennsylvania State University

AWARDS

2011   Mona Shibley Bird Memorial Academic Scholarship
Awarded by Pennsylvania State University, Department of Psychology
Value: $400

2011   Summer Research Grant
Awarded by the Schreyer Honors College, Pennsylvania State University
Value: $750

2011   Travel Award
Awarded by Pennsylvania State University, Department of Psychology
Value: $300

2010   Summer Research Grant
Awarded by the Schreyer Honors College, Pennsylvania State University
Value: $750

2009   Summer Research Grant
Awarded by the Schreyer Honors College, Pennsylvania State University
Value: $1,000

2009   Schreyer Ambassador Travel Grant
Awarded by the Schreyer Honors College, Pennsylvania State University
Value: $700

2008-2011   Schreyer Honors College Academic Excellence Scholarship
Awarded by the Schreyer Honors College, Pennsylvania State University
Value: $3,000

OTHER ACTIVITIES

2009-2010   Member
             Penn State Intercollegiate Equestrian Team
             Pennsylvania State University

2009   Rules and Regulations Committee Member
             Penn State IFC/Panhellenic Dance Marathon
             Pennsylvania State University

2010   Morale Committee Member
             Penn State IFC/Panhellenic Dance Marathon
             Pennsylvania State University

2011   Entertainment Captain
             Penn State IFC/Panhellenic Dance Marathon
             Pennsylvania State University

The Penn State IFC/Panhellenic Dance Marathon is a year round fundraising effort that culminates in a 26 hour no-sitting, no-sleeping Dance Marathon. THON is the largest student-run philanthropy in the world and is held by the Penn State student body as an effort to provide emotional and financial support to the children, families, researchers, and staff of the Four Diamonds Fund, a fund dedicated to finding a cure

for pediatric cancer. I am part of a 25 person captain committee that plans and executes all of the entertainment events throughout THON weekend.

AFILIATIONS

2010-Present   Psi Chi
         Member

2011-Present   International Neuropsychological Association
         Student Member

2011-Present   National Academy of Neuropsychology
         Student Member