Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814 935 1081

5. **Grant SAP Number:** 4100050904

6. **Project Number and Title of Research Project:** 31. MRI Marker(s) for Neuropsychological Outcomes in Adolescents with Mild Concussion

7. **Start and End Date of Research Project:** 9/1/2010 - 6/30/2013

8. **Name of Principal Investigator for the Research Project:** Mechelle Lewis, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 34,107

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Burson, K.	Neuropsych tech	24%	$9,496.43
Jones, B.	Study coordinator	0.25% Yr 1, 0.35% Year 3	$197.25

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Lewis, M.M.	Principle Investigator	5%
Silvis, M.	Co-Investigator	5%
Bramley, H.	Co-Investigator	5%
Eslinger, P.	Co-Investigator	5%
Yang, Q.	Co-Investigator	5%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____ No___X

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

Subjects for the study have been recruited, the data outlined collected, and analyses performed. Although the initial analyses at this time did not reveal significant imaging results when comparing concussed to non-concussed subjects, the data will be stored for potential future analyses (as new techniques become available) by our group or others who may have an interest in this area.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male			2	2
Female			3	1
Unknown				
Total			**5**	**3**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic			5	3
Unknown				
Total			**5**	**3**

	Undergraduate	Masters	Pre-doc	Post-doc
White			5	1
Black				
Asian				
Other				
Unknown				2
Total			**5**	**3**

14. **Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

    Yes_____ No____X_____

    If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. **Impact on Research Capacity and Quality**. Did the health research project enhance the quality and/or capacity of research at your institution?

    Yes___X_____ No_____

    If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

    As a result of this project, Drs. Silvis, Bramley, and I spawned two other research projects that were retrospective chart reviews of pediatric patients admitted to the trauma service with a concussion (project 1) or those seen by the Hershey Medical Pediatric Concussion Clinic service since its inception (project 2). The trauma project involved one medical student and one resident, and we currently have a manuscript under development that is close to being ready for submission. The pediatric concussion clinic review involved several medical students and two residents. We have presented some of this work (e.g., risk factors for post-

concussive headache in adolescents and potential treatment with amitriptyline) at the 2013 Resident Research Day. In addition, we have three manuscripts under development that we hope to publish in the near future.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No___X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No___X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes____X_____ No___ _____

If yes, please describe involvement with community groups that resulted from the research project:

As part of this research project, I met several times with the local trainers from the Central PA Rehabilitation Services (CPRS). These trainers work in the surrounding middle and high schools in the area and often are the first to encounter adolescents once they have sustained a concussion. I reached out to them not only to enlist their assistance in identifying and recruiting subjects for the study, but also to learn about what they do on a daily basis. In addition, I mailed recruitment materials to many/most of the pediatric and family medicine practices in the area in an effort to recruit additional subjects and also inform physicians of our research endeavors and clinical expertise.

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims <u>for the period that the project was funded (i.e., from project start date through end date).</u> Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research

goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Mild traumatic brain injury (concussion) affects >1 million adolescents annually and is a leading cause of disability in this population. As recent news reports have highlighted, there is a dearth of data to guide the response to concussion, particularly in adolescents. Whereas most mild concussion symptoms resolve in adolescents, patients can develop neurocognitive impairments that affect memory, attention, and executive function that interfere with their ability to participate in school and other activities. Outcomes often are variable, and presently difficult to predict. The diverse neuropsychological outcomes in concussed adolescents may relate to specific disruptions of brain function in susceptible regions related to axonal integrity, microbleeding, and functional interruption that can be measured using MR imaging [diffusion tensor (DTI), susceptibility weighted (SWI), and functional (fMRI) imaging, respectively]. Indeed, recent imaging studies in adults with concussion have demonstrated not only alterations in these imaging parameters but also correlations with outcome measures. The current project will extend these results to adolescents with mild concussion to test the central hypothesis that axonal injuries, microbleeding, and/or functional interruption occurring during concussion may be responsible for the observed neuropsychological dysfunction and predictive of recovery patterns in adolescents. We propose to study 20 mildly concussed and 15 non-concussed adolescents (age 13-18 y) using DTI, SWI, fMRI, and neuropsychological evaluations, with follow-up neuropsychological evaluation of concussed adolescents two months after injury in an

effort to determine the predictive value of MRI markers in mild concussion. Our aims are: 1) Demonstrate the axonal disruption, increased microbleeding, and functional interruption in susceptible regions of brain (i.e., deep white matter regions of the corpus callosum, internal capsule, and frontal lobe) in adolescents with mild concussion; 2) Delineate the functional correlation of brain changes in adolescents with mild concussion; and 3) Explore the predictive value of brain MRI changes in the specified regions of interest to neuropsychological outcomes in adolescents with mild concussion.

The overall goal of the current research project is to better understand mild concussion in the adolescent population and attempt to use MRI to predict outcome, as with current clinical methods it is impossible to determine which patients will recover fully and those that may continue to have long-term difficulties. Although capturing behavioral, functional, and imaging data soon after a concussion occurs may be ideal from a research perspective, practically this is difficult, particularly in the pediatric or adolescent population.

Demographic data

A total of 20 subjects were enrolled in the study, eight concussed and 12 non-concussed. Demographic information for study participants is listed in Table 1. The control and concussed subjects are matched well in terms of gender and handedness (compared using Fisher's exact test). Although the concussed subjects are slightly older, the comparison of age between the two groups is not significant (compared using Student's t-test).

Although we had outlined in the grant that we would recruit 20 concussed and 15 non-concussed subjects, this proved more difficult than we anticipated. Dr. Lewis made several trips to Dillsburg, PA (3-4) to present the study to the CPRS training group in an effort to recruit subjects. The CPRS trainers were receptive but the feedback I received from several of them was that it was difficult to present the study to parents and children who were dealing with an acute injury. Dr. Lewis also was in regular contact by email with the athletic trainers at the local middle and high schools (e.g., Hershey, Lower Dauphin, Cedar Crest), along with dropping off recruitment flyers and other materials. In addition, our goal of recruiting subjects within the first week of their concussion might have been overly optimistic, as we had several people express interest (~5-6) but eventually they chose not to participate due to worsening symptoms, not wanting to create any stress for an injured child, etc. Drs. Silvis and Bramley, who run the Pediatric Concussion Clinic here at HMC, also saw a shift in their practice such that they were not seeing adolescents with acute concussions – many of their patients were those that had a concussion several weeks prior and were continuing to experience symptoms. As a result, they were not able to recruit and refer eligible patients to study, thus limiting our ability to meet our projected subject numbers.

In an effort to increase recruitment, Dr. Lewis identified many/most pediatric and family medicine practices within ~2 hrs of the Hershey Medical Center. She then drafted a letter to these physicians and their offices, obtained approval from the IRB on the wording, and mailed the letter and recruitment materials to each of these offices – totaling ~100 packages sent. Despite these efforts, only one subject was referred to the study and this person opted not to participate.

Neuropsychological test results

Each of the 20 subjects completed a neuropsychological battery that assessed working memory, executive function, and attention (for a complete list of neuropsychological tests used, please see original grant application). Comparison of control and mildly concussed subjects on these different neuropsychological measures did not yield overall significant differences between the two groups, although there was a trend toward significance in several tests. For example, mildly concussed subjects were slower on tasks related to attention (the Trailmaking test, p=0.07; color word naming test, p=0.17; and the backward digit span, p=0.09), processing speed (the color word naming test), executive function (the color naming test and the Tower test, p=0.18), and working memory (the color naming test and the backward digit span test). Although mildly concussed subjects also appeared to have slower reaction times on some measures (the hit rate block change, p=0.06 and the hit rate SE block change, p=0.19), they improved their reaction times across trials compared to controls (the hit SE ISI change t-score, p=0.07, percentile, p=0.08). Interestingly, mildly concussed subjects also appeared to show decreased thrill seeking tendencies compared to control subjects (p=0.16). A list of these tests with the average and standard deviation for each group is detailed in Table 2 (a complete listing of neuropsychological results are available upon request).

The eight mildly concussed subjects returned for their follow up neuropsychological testing. The average length of time between initial and follow visits was 83 days (SD=33 days). Comparison of neuropsychological test scores between the two visits indicated that mildly concussed subjects showed significant improvement on measures related to attention (the Trailmaking test, raw score p=0.04; color word naming, both raw score and percentile, p=0.04) and task switching (the Trailmaking task). Although previous analyses indicated concussed subjects demonstrated faster reaction times compared to control subjects (*vide infra*), comparison within concussed subjects over time indicated reduced reaction time at the follow up visit (hit SE ISI change raw score p=0.0001, t-score p=0.002, and percentile p=0.003). There also were some trends towards improvement in several measures including verbal fluency [letter test (p=0.10) and switching accuracy (p=0.07) raw scores], attention (color word reading and inhibition raw scores and percentiles, the Tower test, digit span forward; please see Table 3), processing speed (symbol search, p=0.18; color word tests), working memory (color word tests, digit span forward), and executive function (color word tests, Continuous Performance Test omissions t-score and percentile p=0.17 and 0.13, respectively). There also was a trend for slight decrease in reaction time as measured by the hit SE block change (p=0.11).

Imaging behavioral results

For the imaging functional tasks, subjects completed both the N-back (0, 1, and 2 back) and the face-name recognition tests. Control and mildly concussed subjects had similar accuracies (control subjects: 95.3±0.8%, 95.4±0.7%, and 88.5±0.6% correct for 0, 1, and 2 back tasks, respectively; concussed subjects: 99.2±0.01%, 97.0±0.03, and 92.1±0.05% correct for 0, 1, and 2 back tasks, respectively) and response times (0 back, control=631±351 sec vs. concussed=570±42 sec; 1 back, control=716±171 sec vs. concussed=727±132 sec; 2 back, control=867±201 sec vs. concussed=837±161 sec), although concussed subjects were slightly better on both measurements. For the face-name task, concussed subjects correctly matched the face and names more accurately (74.2% correct for concussed vs. 53.0% correct for control

subjects) but the two groups had similar response times (2101±330 sec for controls vs. 2077±128 sec for concussed subjects).

Functional imaging data analysis

Functional data were preprocessed using Statistical Paramagnetic Mapping version 8 (SPM8, Wellcome Trust Center for Neuroimaging, London, UK) software. For each subject, the imaging data first were smoothed, then slice timed to align all of the images to the first image, and then normalized into the standard Montreal Neurological Institute (MNI) space. First level analyses were conducted to generate a t-map for each subject for the comparison of each task to the rest condition. The t-maps for control and concussed subjects first were entered into a one sample t-test looking at effects within each group. The t-maps then were entered in to a second level analysis to compare control and concussed subjects during each of the tasks (0, 1, and 2 back for the N-back task and the face-name recognition task).

Within subject comparisons of fMRI data

N-back task

Control subjects demonstrated increased activity in frontal and parietal regions for all three N-back contrasts (1>0, 2>0, and 2>1). For the 1>0 contrast, concussed subjects had more diffuse activity in midbrain, cerebellum, temporal, and frontal areas, whereas increased activity was confined to frontal areas for the 2>0 contrast. For the 2>1 contrast, concussed subjects demonstrated increased activation primarily in frontal regions, but also showed more activity in occipital, temporal, parietal, and limbic areas.

Face-name recognition task

Within control subjects, increased activity was observed primarily in the parietal lobe but also in frontal and occipital regions during the face-name recognition task. Concussed subjects, however, demonstrated increased activation primarily in the frontal lobe, with additional activity seen in parietal and occipital regions.

Comparison of fMRI data between control and concussed subjects

N-back task

Comparing the 1>0 back tasks, control subjects had increased activity in frontal and parietal regions compared to concussed subjects (Fig. 1A). The reverse comparison (concussed>control) yielded slightly increased activation in frontal regions that appeared to be more ventral to that for the control>concussed comparison (Fig. 1A). For the 2>0 contrast, control subjects had increased activity only in frontal areas (Fig. 1B) and minimally increased activation in sub-lobar areas for the 2>1 contrast (Fig. 1C). Concussed subjects, however, had significantly increased activity compared to control subjects in frontal and parietal regions for the 2>0 contrast (Fig. 1B), and even greater activity in frontal and limbic areas for the 2>1 contrast (Fig. 1C).

Face-name recognition task

Control subjects demonstrated significantly increased activity in sub-lobar, parietal, frontal, and temporal regions during the face-name recognition task (Fig. 2). In contrast, concussed subjects showed increased activation only in frontal regions compared to control subjects during this task (Fig. 2). The frontal regions demonstrating increased activity in control and concussed subjects, however, were different, with concussed subjects showing a more superior and lateral distribution and the control subjects a more inferior-medial activation pattern (Fig. 2).

Summary of control and concussed neuropsychological and fMRI data

Although there were no significant differences between control and concussed subjects on any of the neuropsychological tests conducted, there were trends for concussed subjects to demonstrate decreased attention, processing speed, concentration, and working memory and executive function compared to controls. These data suggest that even a mild concussion may have cognitive effects that could impair a subject's ability to engage actively in school or other activities. Mildly concussed subjects, however, do show improvement over time, indicating that these effects may be transient and resolve.

Within group comparisons indicated that both control and concussed subjects demonstrated increased activity in a variety of areas during the N-back and face-name recognition tasks. The pattern of activation, however, was different for the two groups across the tasks. These results may indicate that mildly concussed subjects need to recruit different brain regions to accomplish the same task. This is consistent with the results when control and concussed subjects are compared directly, as even though control and concussed subjects demonstrated increased activation in frontal regions the exact areas are different. Additional analyses are on-going to determine more accurately the brain location of activation, as well as conduction of additional contrasts and comparisons to determine subtle differences that may prove to be important.

On-going studies also include analyses of the other imaging data collected (SWI, DTI), as well as recruitment of additional subjects to the study population.

DTI and SWI Imaging data

We continued to develop methods for the analysis of susceptibility weighted (SWI) and diffusion tensor (DTI) imaging datasets from the current study. In collaboration with our renowned colleague, Dr. Martin Styner of the University of North Carolina at Chapel Hill, we have utilized the most up to date and cutting edge tools for the analysis of DTI data, including DTIPrep (http://www.nitrc.org/projects/dtiprep/), the DTI Process Toolkit (http://www.nitrc.org/projects/dtiprocess/), the DTI Fiber Tract Statistics tool (http://www.nitrc.org/projects/dti_tract_stat/), the Tractography with Unscented Kalman Filter (http://www.nitrc.org/projects/ukftractography/), and the FiberViewerLight tool (http://www.nitrc.org/projects/fvlight/), all of which can be accessed and downloaded from the Neuro Image Research and Analysis website (http://www.med.unc.edu/psych/research/niral/download-software). The DTIPrep performs a 'study-specific protocol' that is based on an automatic pipeline to ensure quality control and preparation of DTI data. The DTI Process toolkit provides tools for DTI estimation, average, and

fiber processing. The fiber tract statistics tool applies an atlas fiber to all individual subjects from a study, extracts profiles, and generates fractional anisotropy (FA) maps. The tractography and FiberViewLight tools allow for the tracing of fibers within the brain and 3D visualization. The development of the pipelines for these analyses is on-going. The most efficient and accepted approach for this type of analysis is to 'run' all subjects through the pipeline at the same time. Preliminary analysis of the DTI data indicated no difference in any of the areas sampled (deep white matter regions of the corpus callosum, internal capsule, and frontal lobe). The imaging data will be stored, however, in the event new analysis techniques are developed or others in the research community wish to analyze the data.

We also gathered multi-echo SWI data on each subject. We used the phase information collected as part of each scan to assess iron in the brain using both a region of interest and voxel-wise analysis approach. We developed pipelines for similar analyses as part of other projects on-going in the lab and revised them to fit the needs of the current study. Similar to the DTI analyses, the analysis of the SWI data were held in abeyance until the entire cohort was established. Preliminary analysis of these data also indicated no difference between concussed and non-concussed subjects. Similar to the DTI data, this imaging data will be stored for future analysis by our group or others in the research community.

Table 1: Demographic information for control and concussed subjects included in the study.

	Controls	Concussed	P value
N (M/F)	12 (7/5)	8 (7/1)	1.00
Age (yrs, mean±SD)	16.1±2.3	16.8±1.3	0.45
Handedness (R/L/A*)	11/0/1	7/1	0.47

*Ambidextrous

Table 2: Mean and standard deviation of neuropsychological tests with trends toward significance when comparing control and concussed subjects.

	Controls	Concussed	P value
Trailmaking test (raw score)	72.3±14.8	95.1±29.3	0.07
Color word naming (%ile)	24.4±18.8	40.9±26.2	0.17
Backward digit span test (%ile)	15.5±8.2	41.4±25.3	0.09
Tower test (raw score)	17.4±3.5	15.4±2.0	0.18
Hit rate block change measure	0.014±0.005	0.030±0.014	0.06
Hit rate SE block change (t-score)	46.2±4.7	51.9±10.6	0.19
Hit SE ISI change measure (t-score)	51.1±10.4	41.7±7.6	0.07
Hit SE ISI change measure (%ile)	53.7±32.1	26.8±20.7	0.08
Sensation seeking (%ile)	44.3±23.3	61.5±23.0	0.16

Table 3: Mean and standard deviation of neuropsychological tests in concussed subjects at initial and follow up visits.

	Concussed initial visit	Concussed follow up visit	P value
Trailmaking Test (raw score)	25.3±7.3	19.8±5.3	0.04
Trailmaking Test (%ile)	33.2±29.4	56.3±25.3	0.06
Verbal Fluency Letter (raw score)	36.8±9.7	44.2±7.7	0.10
Verbal Fluency Acc Switch (raw score)	2.3±3.8	8.7±4.8	0.07
Color Word Naming (raw score)	33.0±5.2	27.8±2.6	0.04
Color Word Naming (%ile)	28.3±20.3	52.0±17.0	0.04
Color Word Reading (raw score)	26.0±7.1	22.5±3.8	0.11
Color Word Reading (%ile)	34.8±35.6	48.8±29.7	0.10
Color Word Inhibition (raw score)	53.7±3.1	50.8±5.0	0.09
Color Word Inhibition (%ile)	45.8±13.1	54.3±17.2	0.10
Tower Test (%ile)	41.0±23.3	59.0±22.9	0.14
Symbol Search (raw score)	37.3±5.9	40.5±4.6	0.18
Digit Span Forward (%ile)	53.7±5.0	55.5±55.9	0.08
Omissions (T score)	44.4±1.2	47.1±3.2	0.17
Commissions (%ile)	30.1±5.0	41.8±12.5	0.13
Hit RT Block Change (%ile)	31.3±27.3	52.7±30.2	0.17
Hit SE Block Change (T score)	46.2±5.3	56.0±9.6	0.11
Hit SE Block Change (%ile)	38.9±18.9	67.0±23.0	0.10
Hit SE ISI Change (raw score)	0.030±0.009	0.062±0.012	0.0001
Hit SE ISI Change (T score)	42.0±2.3	49.8±4.2	0.002
Hit SE ISI Change (%ile)	23.8±8.0	52.6±15.6	0.003
Sensation Seeking (raw score)	9.5±1.9	10.8±.8	0.08
Sensation Seeking (%ile)	33.7±12.5	43.7±6.5	0.06

Figure 1: N-back contrasts between control and concussed subjects.

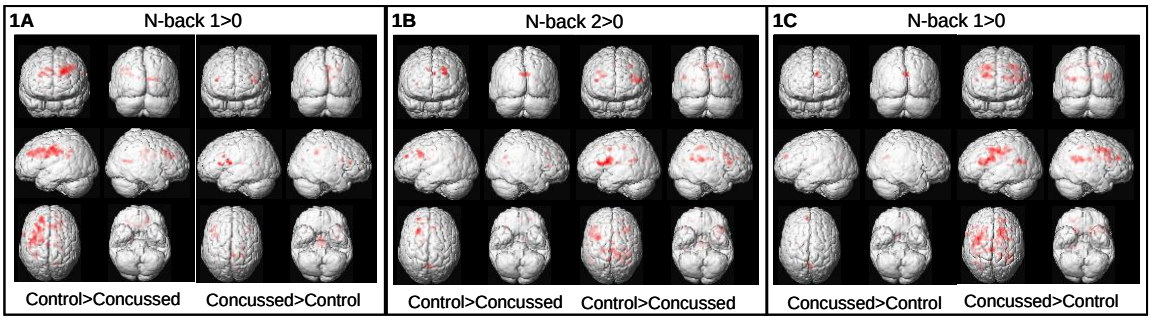
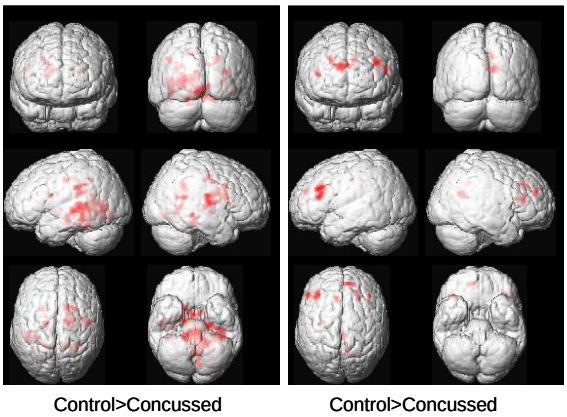


Figure 2: Face-name comparisons in control and concussed subjects.



18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

__X__Yes

_____No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

__X__Yes

_____No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

__10___Number of hospital and health care professionals involved in the research project (not including students or postdocs)

18(D) How many subjects were included in the study compared to targeted goals?

__35__Number of subjects originally targeted to be included in the study
__20__Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
__15__Males
___5__Females
___0__Unknown

Ethnicity:
__0__Latinos or Hispanics
__20__Not Latinos or Hispanics
___0__Unknown

Race:
___0__American Indian or Alaska Native
___0__Asian
___1__Blacks or African American
___0__Native Hawaiian or Other Pacific Islander
__19__White
___0__Other, specify:_____
___0__Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

Dauphin County at the Hershey Medical Center

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes___X _____ No_____

If yes, please describe your plans:

We have plans to submit a manuscript based on the imaging and neuropsychological data collected.

As a result of this project, Drs. Silvis, Bramley, and I spawned two other research projects that were retrospective chart reviews of pediatric patients admitted to the trauma service with a concussion (project 1) or those seen by the Hershey Medical Pediatric Concussion Clinic service since its inception (project 2). The trauma project involved one medical student and one resident, and we currently have a manuscript under development that is close to being ready for submission. The pediatric concussion clinic review involved several medical students and two residents. We have presented some of this work (e.g., risk factors for post-concussive headache in adolescents and potential treatment with amitriptyline) at the 2013 Resident Research Day. In addition, we have three manuscripts under development that we hope to publish in the near future.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None at this time.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable."

Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None at this time.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes__ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No___X _____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

Dr. Mechelle Lewis has a broad background in neurobiology, with specific training in key research areas (MRI imaging techniques) for this application. After earning a PhD in neuropharmacology, she obtained extensive postdoctoral training including a fellowship in structural and functional MRI. Dr. Lewis has worked on all aspects of several imaging-related clinical projects (design; subject recruitment; imaging data collection, data management, and analysis; and interpretation). She has a successful history of working with clinicians and is a co-investigator on a current two NIH-funded R01 projects to define MRI markers of Parkinson's disease and those exposed to neurotoxicants, respectively, along with a U10 project focused on biomarkers in Parkinson's disease. Holding a primary appointment in a clinical department (neurology), she not only is committed but also qualified to lead this multi-faceted, collaborative, translational project with a significant public health impact. Most importantly, she has been assisted by strong administrative and departmental support, as well as support from collaborators who are experts in the fields of concussion (Drs. Silvis and Bramley), imaging (Dr. Qing Yang), neuropsychology (Dr. Paul Eslinger), and statistics (Drs. Michele Shaffer and Lan Kong).

Dr. Harry Bramley has extensive training and experience in pediatrics and a long-standing interest in the area of concussion in this population. He is the founder and current director of the Penn State Milton S. Hershey Concussion Program and particularly adept in assessing, treating, and managing adolescent patients with concussions. In addition to Dr. Silvis, he assisted in identifying and recruiting concussed subjects for inclusion in the proposed study, as well as providing best medical care for those enrolled. Dr. Bramley also lent my expert insight into the neuropsychological and imaging data and these data translate to medical and neuropsychological outcomes. His extensive clinical expertise in both concussion and the adolescent population made him particularly well suited to participate in the proposed study.

Dr. Paul Eslinger's participation in the project was to provide expertise with regard to administering, scoring, and interpreting standardized neuropsychological measures of cognition, executive function, and behavior in adolescents who sustain concussion. In addition, he collaborated in analysis of neuropsychological results in relationship to quantitative MRI measures of concussion effects. Dr. Eslinger also lent his expertise for the

fMRI studies of working memory and other neurocognitive processing based on the extensive studies of adolescent functional brain imaging of cognition in his lab.

Dr. Lan Kong is the key biostatistician of the Biostatistics /Epidemiology Research Design (BERD) core of the Penn State Clinical and Translational Science Institute. Prior to joining the Penn State University, she had a long-time collaboration with the clinical investigators at the University of Pittsburgh and served as a primary statistician on several NIH-funded grants. Her solid track record of publications in both biostatistics methodology research and collaborative research were an asset to the current project.
Dr. Michele Shaffer has served as a biostatistician for more than 15 projects funded by the NIH, CDC, HRSA, and FDA including two ongoing neuroimaging studies. This work includes study design, sample size and power calculations, data summarization, model building, and interpretation. She has contributed to statistical research in areas related to missing or unobserved data, modeling clinical studies in heterogeneous populations, and clustered data analysis. Her methodological work complemented her extensive experience as a project biostatistician and made her particularly suited to participate in the study.

Dr. Matthew Silvis has broad experience in disciplines that were directly relevant to the current study. After earning an MD, he completed further training in both family medicine and sports medicine. Dr. Silvis has worked on all aspects of projects related to injury risk in adolescents and have demonstrated success in working with clinicians and researchers alike. In addition to his clinical expertise, he also is the co-director of the PSU-HMC adolescent concussion clinic. As such, he not only was deeply committed to this project but also qualified to lend expertise. Moreover, Dr. Silvis saw a lack of specific and predictive guidelines for the response to adolescents with mild concussion. He worked and continues to work closely with local school districts and athletic departments, and routinely treat and manage adolescent athletes that suffer concussions. Dr. Silvis had strong administrative and departmental support, along with support from our expert collaborators Drs. Qing Yang, Paul Eslinger, Michele Shaffer.

Dr. Qing Yang's research in the last ten years has been focused on the developments of quantitative MRI and fMRI data acquisition methodologies and image analysis tools for the study of neurodegenerative diseases such as Alzheimer's disease. His experiences and normative human brain image data set (T1-weighted, T2*/T2-mapping, and SWI) provided a solid foundation for the success of the project. He has broad experiences and developed tools for quantitative image analysis. Dr. Yang provided expertise in image data acquisition and analysis to the proposed research. In addition, he is in charge of our institutional MRI Core Facility that is well-equipped with state-of-the-art MRI and computer systems for both human and animal research. The MRI system is well-maintained with a full-time MRI technologist responsible for image data acquisition and quality assurance. Within the Core facility the image data are archived and distributed with our research PACS system. Thus, as our collaborator, he provided all the necessary imaging expertise for the research. As the

Director for the MRI Core facility, he also provided all the administrative support to guarantee the image data quality and reliability for the proposed research.