British Journal of Sports Medicine

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Journal:	*British Journal of Sports Medicine*
Manuscript ID:	bjsports-2014-093877
Article Type:	Original Article
Date Submitted by the Author:	19-May-2014
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Keywords:	Neurology, Epidemiology, Concussion, Contact sports, Boxing/Kick Boxing

The effect of repeated head trauma on brain structure and cognition: The Professional Fighters Brain Health Study

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Key Words: Traumatic Brain Injury, Chronic traumatic encephalopathy, MRI volumetrics, boxing, mixed martial arts

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Word count: 4935

Abstract

Objectives: Cumulative head trauma is thought to result in changes in brain structure and function, though the nuances of this association have not been described. This study explores the relationship between exposure variables, cognition, and MRI brain structural measures in a cohort of professional combatants

Methods: 224 fighters participating in the Professional Fighters Brain Health Study, a longitudinal cohort study of licensed professional combatants, were included for analysis. Each subject underwent computerized cognitive testing and volumetric brain MRI. Fighting history, including years of fighting and fights per year were obtained from self report and published records. Statistical analyses of the baseline evaluations were applied cross sectionally to determine the relationship between fight exposure variables and volumes of the hippocampus, amygdala, thalamus, caudate, putamen. Moreover, the relationship between exposure and brain volumes with cognitive function was assessed.

Results: Increasing exposure to repetitive head trauma measured by number of professional fights, years of fighting, or a composite index of exposure was associated with lower brain volumes, particularly the thalamus and caudate. In addition, speed of processing decreased with decreasing caudate, thalamic, amygdala, and hippocampal volumes and with increasing fight exposure. Higher scores on a composite index used to reflect exposure to repetitive head trauma was associated with greater likelihood of having measurable cognitive impairment.

Conclusion: Greater exposure to repetitive head trauma is associated with lower brain volumes and speed of processing in active professional fighters.

What are the new findings?

- Caudate and thalamus volumes were associated with more extensive fight history
- Volumes of these structures were related to processing speed
- We introduce a new exposure measure, a Composite Index combining duration of fight career and intensity of fight career, which is predictive of the above relationships

How might it impact on clinical practice in the near future?

- Identification of an imaging biomarker that can detect injury from repetitive head trauma and potentially predict change over time
- Work building on the present study may identify parameters by which to advise on Utilization of specific cognitive measures as part of regulatory requirements for professional fighting
- The Composite Index may provide an important tool in establishing when in a career decisions regarding neurological checks or retirement from the sport are advisable

Introduction:

Repetitive head trauma is a reported risk factor for Alzheimer's disease and considered the primary cause of chronic traumatic encephalopathy (CTE) [1-3]. These long term effects on the brain of cumulative head trauma have come to public view with the recognition that many athletes in contact sports have been found to have pathologicalfindings associated with CTE; a few of these reported cases harboring very focal lesions have occurred in individuals under 20 years of age [4].. Yet, despite the attention that this issue has engendered, little is known about how the brain responds to recurrent head trauma.

One of the fundamental questions that need more exploration is the relationship between the amount, or dose, of head trauma and change in brain structure and function. Previous studies in boxers have reported frequency and duration of fighting to be associated with CTE [5 6]. However, the nuances of this potential relationship have not been described.

The Professional Fighters Brain Health Study (PFBHS) is a longitudinal cohort study of boxers and mixed martial art fighters designed to better understand the effects of repeated blows to the head on brain structure and function over time. The PFBHS began enrolling subjects in 2011. This cross sectional analysis of participants' baseline evaluation explores the relationship between exposure to repeated blows to the head and MRI measures of brain structure and function, along with cognitive performance.

Methods:

Participants in the PFBHS are athletes, age 18 and older, who have at least a 4th grade reading level and are licensed in Nevada to fight professionally in one of the combat sports, boxing or mixed martial arts. In addition, we recruited a control group who were matched on age and education to the fighter group. The control subjects had no reported history of head trauma in civilian or military life, nor could they have played a sport associated with head injuries(e.g. football, rugby, hockey, boxing, MMA, wrestling, soccer, rodeo) at a high school level or beyond. Participants are seen for baseline evaluation and on an annual basis thereafter over the next 4 years. Methods of recruitment and study procedures have been described previously [7]. Data for this study comes from the baseline evaluations.

At the baseline visit, participants answer questionnaires with the assistance of the study coordinator that collect information on demographics; educational attainment; family and medical history; previous head trauma, both related and unrelated to athletic activities, prior involvement in other contacts sports, as well as their amateur fighting history . Before the study visit, the fighters' professional record is obtained from commonly cited websites (boxrec.com for boxers and mixed martial arts.com and sherdog.com for MMA fighters) to determine number of years of professional fighting, number and outcome of professional fights, number of rounds fought, weight class of each fight, frequency of professional fighting, and number of times knocked out (which includes both knock outs and technical knockouts).

Cognitive function was assessed by a computer based battery that consists of 4 subtests of the CNS Vital Signs (CNS Vital Signs, No. Carolina) including verbal memory, symbol digit coding, Stroop and finger tapping test. Raw summary scores were used for all analyses. Results from these tests are used to make up scores in various clinical domains: verbal memory, processing speed, psychomotor speed and reaction time. The test battery was performed in the subject's native language (English or Spanish). These forms have established equivalency [8].

A high resolution T1-weighted anatomical MRI scan was obtained on all fighters. Scans were performed using the same Siemens 3T Verio scanner with a 32 channel head coil (Siemens Medical Systems, Erlangen, Germany). Acquisition protocol details are TR/TE/TI=2300/2.98/900, flip angle=9, BW=240 H z/Px, 240x256 matrix, 160 slices, voxel size =1 x 1 x 1.2mm , scan time: 9 :14. Volumes of the hippocampus and amgydala and subcortical gray matter including, thalamus, caudate, and putamen were calculated using the automated full brain segmentation process in Freesurfer software [9]. The volumes of each structure were measured in both hemispheres separately.

To assure that the participants in the PFBHS did not differ significantly from all those who fight professionally, results from every sanctioned professional fight in Nevada from January 1, 2011 to December 31, 2011 were reviewed from the Nevada Athletic Commission website (boxing.nv.gov). Age, professional record, years of professional fighting, and KOs /TKOs were recorded for each fighter. Participants in the PFBHS were slightly younger and had a shorter duration of professional fighting than all fighters who fought in Nevada. However, there were no significant differences in fighting success (winning percentage) or number of knockouts.

Statistical Analysis:

The primary goal of the study is to test for an association between fight exposure and brain volumes. Repeated measures ANOVA was performed to test the association between the outcome variables and fight exposure variables. Five pairs of dependent variables, left and right thalamus, left and right hippocampus, left and right caudate, left and right putamen, and left and right amygdala were evaluated in separate models. Fight exposure was characterized by the total number of professional fights and the number of years of professional fighting. In univariate analyses the associations of these two continuous variables with brain volume were assessed using linear and quadratic effects, as well as cubic splines. An exposure composite score (ECS) as a function of cumulative and intensity of exposure (i.e. total number of professional fights and number of professional fights per year) (see Table 1) was also evaluated. Scores on the ECS ranged from 0-4 with 4 representing the greatest exposure. Though there was only 1 subject with a score of 3, this category was maintained to ensure symmetry with scores of 1 and 2.In each model we included the type of fighter (boxer or MMA); we tested the significance of the interaction term for the type of fighter with the other exposure variable. All analyses were adjusted for intracranial volume (ICV; treated as a continuous variable), age (treated as a continuous variable), education (defined as no college-level vs. some college-level), and race (defined as: (i) Caucasian, (ii) African American, and (iii) other (Asian, Pacific Islander, American Indian, and Alaskan Native)). A significance level of 0.05 was used to test the effect of the exposure variables on brain volumes.

Table 1: Exposure Composite Score

Composite Score	# pro fights	# pro fights/year	Boxer Age mean [min, max, n]	MMA Age mean [min, max, n]
0	0	0	24.8 [19, 35, 28]	26.6 [19, 40, 21]
1	1-15	≤1	28.2 [19, 39, 12]	28.8 [21, 40, 18]
2	1-15	>1	26.5 [18, 40, 29]	27.6 [19, 39, 55]
3	>15	≤1	44 [44, 44, 1]	-
4	>15	>1	31.8 [24, 43, 23]	30.1 [22 38, 36]

Models were also constructed to assess differences between the fighter groups and controls in brain volume. A comparison of estimated reduction in brain volume between boxers, MMA, and control while controlling for age, years of education, race, and number of professional fights was completed to assess the specificity of our findings to fighters Dunnett's test was used for contrasting mean responses against control and making adjustments for multiple comparisons within a particular measure.

Brain volume data were collected on 12 female fighters. Since many of the findings on brain volume and cognitive test scores differed by gender, in order to include female fighters in the analysis we would need to adjust for gender and many two-way interactions with gender. We felt that our sample size was too small to include the additional covariates for appropriate gender adjustment in our analysis. Thus, we decided to omit the female fighters from the main analysis.

Secondary goals of the study were to test for associations between brain volume and cognitive test scores and between fight exposure and cognitive test scores. Generalized linear models were constructed with cognitive scores as the dependent variables and brain volume or fight exposure variables as the independent variables of interest; analyses were adjusted for ICV, age, race, and education. Cognitive scores were compared against age- and education level-matched normative values (based on cutpoints at 1.5 × SD below the mean) provided to our group by CNS Vital Signs to define presence/absence of impairment. Associations between types of impairment and the composite index were evaluated using chi square tests. All analyses were performed in SAS 9.2.

Results:

Complete data were collected on 224 fighters: 93 boxers and 131 MMAs, and 22 controls. The fighters' age ranged from 18 to 44 with median of 27 years. There were 89 (39.7%) Caucasians, 59 (26.3%) African Americans, and 76 (33.9%) others. 54% of the subjects had less than or equal to a high school education; 46% had at least some college-level education.

The total number of years of professional fighting ranged from 0 to 24, with a mean of 4 years. The total number of professional fights ranged from 0 to 101, with a mean of 10 fights. Table 2 summarizes the amateur and professional years of fighting, number of fights, and knock-outs by the type of fighting.

Table 2: Fight Exposure by Type of Fighting*

	Boxers (n=93)	MMA (n=131)
Years of Fighting:		
Amateur	3.8 [0-23]	1.8 [0-22]
Professional	4.0 [0-25]	4.3 [0-16]
# of Fights:		
Amateur	38.1 [0-242]	14.6 [0-397]
Professional	10.5 [0-101]	11.8 [0-81]
Knock-Outs:		
Amateur	0.05 [0-2]	0.06 [0-2]
Professional	0.9 [0-13]	0.6 [0-6]
Age (Years)	27.7 [18-44]	28.2 [19-40]

*mean [low value-high value]

A summary table of the results of various measures of exposure and brain volumes is given in Table 3. Type of fighting was correlated with thalamic and hippocampal volumes with boxers having lower volumes than MMA fighters. In general, increasing exposure, either as measured by the number of professional fights or years of professional fighting is associated with lower brain structure volumes, particularly with subcortical structures. The most consistent relationship between exposure variables and brain volume was seen in the thalamus and caudate. Utilizing the Composite Index, each increase in the score was associated with reductions of 0.8%, 0.9%, and 0.8% in volumes of the caudate, amygdala, and thalamus (see Figure 1) respectively. There was no specific threshold of number of professional fights or Composite Index score where the relationship between number of professional fights or composite index and brain volumes was seen.

When comparing brain volumes by type of fighter and controls, significant differences were seen between boxer and MMA fighters for all right and left brain measures and for several right and left brain measures for boxers and controls (Table 4). There are no significant differences between MMA fighters and controls (P < .05) for any of the measures.

Table 3: summary of correlations between exposure measures and brain volumes. Analysis adjusted for ICV, age, race and education NS= Not statistically significant at the 0.05 level. *=Statistically significant brain side effect.

	Thalamus	Hippocampus	Caudate	Putamen	Amygdala
Estimated Reduction in volume for boxers relative to MMA fighters	3.3% p=0.006	2.0% (L) and 4.2% (R)* p=0.007	p=0.349 (NS)	2.3% p=0.089 (NS)	2.9% p=0.051 (NS)
Estimated Reduction in volume per Professional fight	0.3% (L) and 0.4% (R) for boxers*; 0.2% (L) and 0.3% (R) for MMAs* p=0.001**	0.1% (L) and 0.2% (R) for boxers*; 0.1% for MMAs p=0.080** (NS)	0.3% p=0.008	p=0.516 (NS)	0.2% p=0.076 (NS)
Estimated Reduction in volume per year of Professional fighting	0.5% for boxers only P=0.050** (NS)	P=0.828 (NS)	0.4% P=0.023	P=0.750 (NS)	P=0.259 (NS)
Estimated Reduction in volume for each unit increase in Composite score	0.8% P=0.042	P=0.415 (NS)	0.8% p=0.075 (NS)	p=0.665 (NS)	0.9% p=0.052 (NS)

Table 4. Summary of difference in volume between fighter groups and controls on the various brain measures. NS indicates no significant difference.

Hemisphere	Thalamus	Caudate	Putamen	Hippocampus	Amygdala
	%(p-value)	%(p-value)	%(p-value)	%(p-value)	%(p-value)
Left Side					
Boxer vs. MMA	7%(<.0001)	5.1%(.01)	4.5%(.009)	4.1%(.007)	5.7%(.006)
Boxer vs. Control	6.8%(.045)	NS	7.2%(.02)	NS	8.6%(.02)
MMA vs. Control	NS	NS	NS	NS	NS
Right Side					
Boxer vs. MMA	7.0%(<.0001)	6.3%(.001)	4.8%(.003)	4.7%(<.0001)	6.4%(.0007)
Boxer vs. Control	6.6%(.02)	NS	8.0%(.007)	6.1%(.03)	NS
MMA vs. Control	NS	NS	NS	NS	NS

Among the various cognitive domains, only speed of processing was significantly related to both volume and exposure. Smaller volumes of the thalamus, amygdala, and left hippocampus were associated with lower scores on speed of processing measures (Figure 2). Boxers had significantly lower scores than MMA fighters ($p<0.001$). Moreover, there was a significant relationship between the number of professional fights and speed of processing ($p=0.041$), with an estimated 0.19% reduction in processing speed per fight. Similarly, there was a significant relationship between the composite score and speed of processing ($p=0.023$), with an estimated 2.1% reduction in processing speed scores for each decrease in composite score. The effect was most evident at the extremes of the composite index, where fighters with a score of 4 have an 8.8% age-, race-, and education-adjusted reduction in scores relative to fighters with a composite score of zero. In models constructed to compare the three participant groups on the four cognitive measures, (and including age, education and race), no differences were seen for verbal memory. On the other hand, processing speed showed a significant relationship with fighter type and years of education, with both fighter groups scoring worse than controls,

Figure 3 illustrates the proportion of subjects impaired, defined as 1.5 SD below age- and education level-matched normative values, for the various cognitive domains as a function of the subjects' composite exposure index. The proportions of subjects with verbal memory impairment and with psychomotor speed impairment increased significantly with the magnitude of the composite index (p=0.036 and p=0.046, respectively). Note that although we saw a significant association between the composite score and speed of processing scores, this correlation was not seen when the analysis was limited to the proportion of those who were in an impaired range (p=0.244).

Discussion:

From a cross sectional analysis of professional fighters participating in the PFBHS, increasing exposure to recurrent head trauma measured in several different ways was associated with lower MRI based volumes of various cortical and subcortical brain structures, particularly the thalamus and caudate. In addition, lower scores on tests of processing speed were correlated with both lower brain volumes and increasing levels of exposure. Brain structure volumes were generally less for boxers than mixed martial arts fighters or controls, and there were differences incognitive measures between both fighter types and controls which were independent of any relationship with age. Finally, higher scores on a composite index used to reflect exposure to repetitive head trauma was associated with a greater likelihood of having measurable cognitive impairment.

This is, to our knowledge, the first report linking fight exposure to regional volumes using MRI measures. There are several potential implications of these findings. Not only does it appear that differences in MRI volumetric associated with fight exposure can be detected in relatively young individuals using readily available technology, but these differences occur in particular subcortical structures. Moreover, the volumetric findings are correlated with at least some clinical measures.

The fact that the thalamus and caudate showed the strongest correlation with fight exposure is not too surprising given their extensive connections with other cortical and subcortical structures [10 11]. The thalamus acts as a “gateway” to the cortex, and when affected can influence many neurological functions. There may be several mechanisms by which the thalamus and caudate are vulnerable to volumetric loss. Rotational movement of the head as induced by punches in boxing or MMA can result in diffuse axonal injury in white matter tracts [12]; it is possible that

Wallerian degeneration can follow this white matter injury resulting in neuronal loss in subcortical gray matter structures [13]. In addition, torsional forces could produce fluid waves in the lateral ventricles that conceivably may directly injure adjacent structures [i.e. thalamus, caudate] [14]. Pathological series of retired boxers have also reported gross atrophy and neuronal loss in thalamus and basal ganglia structures, among others [4 15]. Our results point to subtle differences even in young, active boxers compared with controls.

Though the relationship between greater fight exposure and lower subcortical volumes was seen in both boxers and mixed martial arts fighters, the finding that boxers had lower brain volumes than the mixed martial arts fighters could also be due to several factors. Perhaps the most obvious explanation is that boxers get hit in the head more. Unlike professional boxing where the intent is to inflict a concussion (i.e. knock out) on their opponent , mixed martial art fighters can utilize other combat skills such as wrestling and jiu jitsu to win their match by submission, forcing their opponents to "tap out" without causing a concussion [16]. In a review of 60 consecutive fights within the 125 – 145 pound weight class utilizing reports from professional services that count number of punches in professional fights (compuboxonline.com, fightmetric.com), boxers received, on average, 175 total punches per fight versus 58 for MMA fighters . However, other differences between the two combat disciplines that could influence the volumetric findings include premorbid brain volume due to socioeconomic and nutrition factors, age at which the individual began fighting, and differences in glove size.

Among the cognitive measures obtained in this study, only processing speed was correlated with reduced volume in several cortical and subcortical structures. Processing speed is very non-specific; its reduction is consistent with repeated concussion and is considered a component of the clinical manifestation of CTE [17 18]. Interestingly, processing speed was lower with higher values of the composite index but, unlike brain volumes, only when comparing the extremes of the exposure composite index scale. Perhaps consistent with what is seen in other neurodegenerative diseases, the clinical expression of underlying pathology may not appear in a measurable way until a substantial amount of structural damage has occurred [19].

There is a recognized need for instruments or tools that can be used by regulatory agencies, or even the fighters themselves, to identify individuals who may be at higher risk of having brain injury from cumulative head trauma and require closer safety surveillance. Though exposure to head trauma is likely the primary predictor of injury, one of the challenges in understanding the effects of repetitive head trauma on brain structure and function is measuring the "dose" (amount and severity) of exposure. Fighters are on the receiving end of blows to the head not only in competition, but also during training (sparring) and potentially in activities outside the ring as well. Short of having a direct monitoring system that could record forces on the head, several surrogate measures of head trauma that are verifiable include total number of professional fights and years of professional fights. Number of fights may be an indicator of *amount of training*. Some have postulated that the effects of repeated blows to the head, even at a sub concussive level, that occur during sparring may play as important a role in causing cumulative brain injury as the match itself [20 21]. Frequency of fighting (factoring in years of fighting) may be a complementary variable that requires consideration; fighting more frequently may reduce the time the brain has to fully recover from prior trauma and be a risk factor that interacts with number of fights [22 23].

As a multidimensional measure of exposure, we utilized a composite index (CI) based on number of professional fights and average fights per year, with scores ranging from 0-4, higher scores representing greater exposure. Approximately one in four fighters with a CI of 3 or 4 scored in an impaired range on tests of verbal memory compared to only about 1 in 10 of those who had a CI of 0. A similar effect was seen in tests of psychomotor speed, with participants in the CI 3/4 group being three times more likely to be in an impaired range on psychomotor speed compared with a CI score of 0. Pending review of its performance longitudinally and replication of our findings in a larger cohort of fighters, the CI (or some modification of it) may be an easy to use, practical tool that can select out fighters that may be more likely to have cognitive impairment or be going down that road.

While the Professional Fighters Brain Health Study is one of the largest reported cohorts of well characterized active professional combatants, several limitations need to be acknowledged. The study group included in this report was not a random sample of fighters; participants were self selected and may be less skilled or more susceptible to be knocked out. However, when we compared our subjects with all those who fought in Nevada over the same year, subjects in the PFBHS only differed by being younger and having slightly less professional fights, without difference in winning percentage or times knocked out. As mentioned above, all of our measures of exposure to head trauma are indirect and may not truly reflect the actual degree of head trauma each subject experienced. The cognitive testing was limited to a computerized battery that admittedly is not comprehensive, though it particularly has advantages over manual recording in assessing timed tasks. Furthermore, while the study coordinator would encourage the subject to exert their best effort during the testing period, the effort exerted by the subject may have been influenced by a variety of extraneous factors such as fatigue and dehydration. Because the participants may be sparring in close temporal relationship to the study visit, it is difficult to tease out acute from chronic effects of head trauma on cognitive performance. Finally, the relationship between exposure and brain volumes and cognition may have been due to some other factor related to exposure and not the exposure itself. While this large cross-sectional study cannot speak to causality, it provides extensive baseline data which will be used in future longitudinal studies of cognitive and neuroanatomical changes in this population to further understand the nature and of the correlational findings.

Many investigators speculate that CTE is a neurodegenerative disease instigated by repeated head trauma that then continues to evolve even in the absence of further exposure [2]. While this study is not specifically focused on CTE, the findings suggest that greater exposure to head trauma is related to detectable brain structural and performance deficits in active fighters. The answer to whether brain volumes and performance change over time with, and in the absence, of further exposure will hopefully emerge as this cohort is followed longitudinally.

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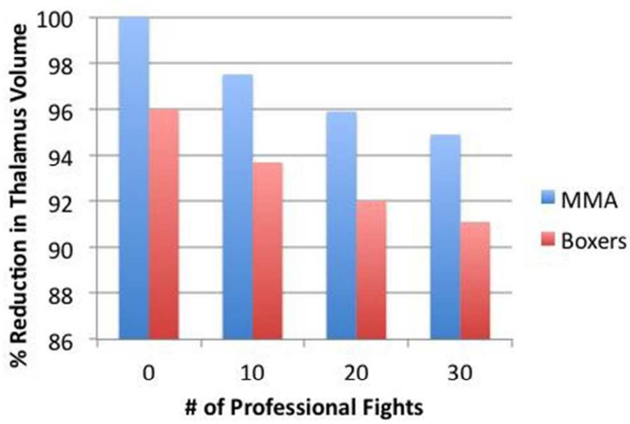
Figure legends:

Figure 1: Illustration of association between thalamus volume and the number of professional fights for boxers and MMA fighters. The estimated mean volumes are standardized relative to a MMA fighter with zero professional fights.

Figure 2: Association between Brain Volume (in one-unit SD increments below and above the mean) and Processing Speed Scores. Scores decrease 2-3% per one SD decrease in brain volume.

Figure 3: Illustration of the proportion of impaired fighters for the four cognitive domains as a function of the composite score. Values above bars indicate the number of impaired subjects with the given composite score. There were 49 subjects with a composite score of 0, 114 subjects with scores of 1 or 2, and 11 subjects with scores of 3 or 4.



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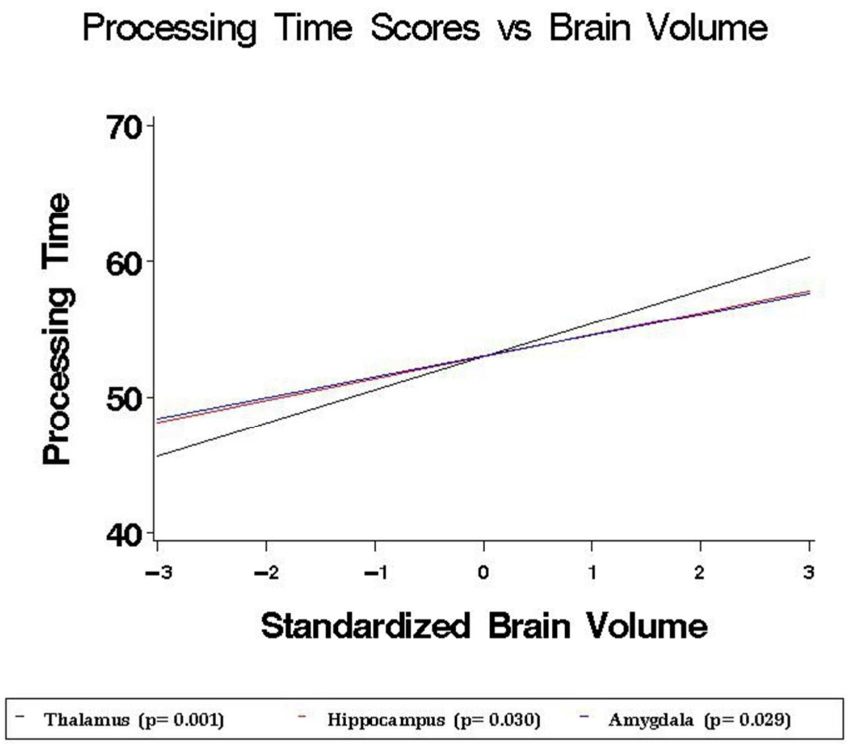

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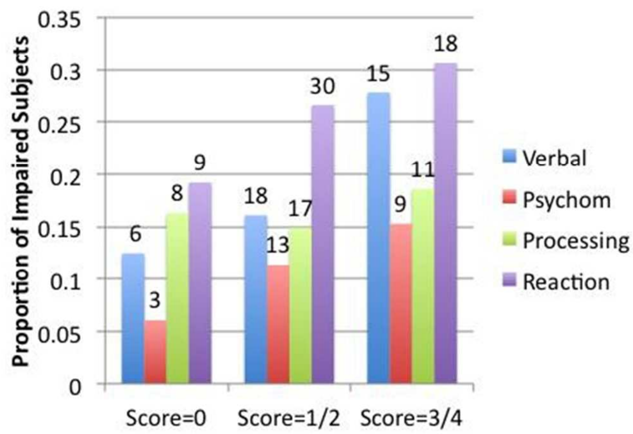

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