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The Relations Among Depression, Cognition, and Brain Volume in Professional Boxers: A Preliminary Examination Using Brief Clinical Measures

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Objective: Depression, neuropathology, and cognitive decline are commonly observed with repetitive head injuries (RHIs). We examined whether in boxers (*a*) clinically significant depression is associated with structural brain changes and cognition; (*b*) minimal symptoms of depression moderate the relations among RHI and brain volumes and cognition; and (*c*) baseline depression is associated with longitudinal cognitive changes. **Setting:** Clinical Research Center. **Participants:** A total of 205 male professional boxers. **Design:** Cross-sectional and longitudinal (subsample: $n = 45$; first visit to follow-up range = 1-6 years; mean = 2.61 years). **Main Measures:** Patient Health Questionnaire-9 depression; CNS Vital Signs cognitive battery; brain imaging. **Results:** Clinically significant depression was associated with smaller regional volumes in insula, cingulate, orbitofrontal cortex, thalami, and middle corpus-callosum subregions; and with poorer verbal memory and psychomotor speed performance. Depression symptoms moderated the relations between RHI and bilateral thalami, left hippocampus, left medial orbitofrontal cortex, and bilateral insula volumes; but not cognition. Baseline depression was associated with poorer psychomotor speed and reaction time longitudinally and improved verbal memory performance longitudinally. **Conclusion:** Clinical depression is associated with volumetric and cognitive changes occasioning RHI exposure, and even minimal depressive symptoms may moderate the relations between exposure and brain volumes in key regions. Longitudinally, there is preliminary evidence that depression precedes cognitive changes. **Key words:** *boxing*, *head injuries/concussion*, *imaging*, *magnetic resonance*

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RECENT RESEARCH suggests that repetitive concussive and subconcussive head impacts (RHIs) are potentially associated with a significant permanent decrease in cognitive functioning and an increase in the occurrence of movement disorders and mood symptoms; however, the extant literature is inconsistent.[1] Nonetheless, depression is the most frequently cited psychological consequence of traumatic brain injury.[2] Moreover, depression positively correlates with concussion history; retired professional athletes reporting a history of 3 or more concussions are 3 times more likely to be diagnosed with depression (while controlling for age, years since retirement, years of competition, self-reported physical ailments, and diagnosed medical comorbidities).[2,3] Research on former National

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Football League players further shows that, compared with matched controls, those with a concussion history perform more poorly on tests of word-finding, naming, visual and verbal/episodic memory; and white matter abnormalities in frontal and parietal regions bilaterally, the left temporal lobe, and the corpus callosum in those with cognitive and/or mood impairments.[4,5] Volumetric imaging has demonstrated that older subsets of a cohort of former National Football League players with a history of a grade 3 concussion had smaller bilateral hippocampal volumes compared with controls and smaller right hippocampal volumes compared with athletes without concussion.

Although depression has been proposed as one of 3 core clinical features associated with chronic traumatic encephalopathy (CTE), a degenerative condition thought to be caused by RHIs, no studies have specifically assessed depression in active professional fighters.[6] As boxers are subjected to a particularly high number of RHIs, they provide a unique opportunity for assessing the relation between RHI and depressive symptoms. Even in the absence of trauma, depression has been shown to negatively affect cognitive performance,[7] and volumetric or functional differences have been observed in cortical and subcortical brain structures such as the frontal cortices, insula, anterior cingulate cortex, thalamus, hippocampus, and amygdala of depressed individuals.[8–10] Boxers with more RHI exposure demonstrate brain volume reductions in the thalamus, hippocampi, and caudate, as well as structural alterations in the corpus callosum[11–14] consistent with global atrophy observed in confirmed cases of CTE.[12] It may also be of particular importance to examine whether such changes are borne out in readily available clinical measures of depression and available measures of cognition in neurology practice.

As the literature stands, it is known that contact sports athletes are at risk for neurologic damage as a function of repeated concussive and subconcussive head impacts. Although structural and functional differences, increased prevalence of depression, and poorer cognition have been seen in contact sports athletes, the relations between depression and various brain volumes and the role of depression in cognitive functioning have yet to be investigated in this population. Clinically, further information that characterizes cognitive and neurologic changes that accompany depression in those with repetitive head trauma may help guide decision-making regarding referrals and identifying those who may warrant follow-up.

To explore the relations between RHI, regional brain volumes, depression, and cognitive functioning, 4 hypotheses were tested: (1) fighters with clinically significant depression (CSD) would have smaller volumes in brain regions associated with depression in nonathletes (ie, hippocampi, amygdalae, caudate, insula, medial orbitofrontal cortex, rostral anterior cingulate cortex, and thalami); (2) fighters with CSD would demonstrate poorer cognitive performance than fighters without CSD; (3) depression would moderate the relations between number of fights and certain brain regions, as well as the relations between number of fights and aspects of cognition; and (4) baseline depression symptoms would be associated with cognitive decline longitudinally.

METHODS

Study design

Study participants were recruited as part of an ongoing, institutional review board-approved, longitudinal study of professional combatants: the Professional Fighters Brain Health Study (PFBHS).[15] For a thorough review of study methods, readers are directed to this publication; however, pertinent details are included below. Participants were drawn from those seeking initial or renewing licensure to fight professionally in the state of Nevada who have at least a fourth-grade reading level. Participants were assessed at baseline (ie, upon enrollment in the PFBHS) and 1-year intervals throughout the study, and all participants were assessed at least 45 days after their most recent professional or amateur bout. Baseline data included imaging, depression, and cognitive screening data. Longitudinal cognitive data were used to assess for cognitive change.

Participants

A total of 205 retired and active professional male boxers participated. Longitudinal data were available for 45 individuals. Numbers of self-reported amateur fights and concussions were excluded from analyses, as these data are highly variable and uncorroborated. Longitudinal comparisons were made between baseline assessment and most recent follow-up visit for each participant, with a minimum interassessment interval of 1 year, a maximum of 6 years, and an average of 2.61 (standard deviation = 1.09) years. This interval was chosen to increase sensitivity to detecting cognitive changes, which in theory may be subject to subtle declines over a 1-year interval in those with cognitive decline, especially as professional fights per year for boxers may be few. Mann-Whitney *U* tests were run to examine group differences between fighters who returned for follow-up and those who did not, where appropriate.

Cognitive and psychological variables

Participants completed a battery of computerized tests via the CNS Vital Signs program[16]: symbol digit coding, finger-tapping, word memory, and Stroop-like tests. Estimates of processing speed (number correct on symbol

digit coding minus incorrect responses), psychomotor speed (right- and left-hand finger-tapping and number correct on symbol digit coding), verbal memory (word list recognition), and reaction time/inhibition (Stroop-like task) were gathered. The Patient Health Questionnaire Depression (PHQ-9), an empirically validated brief measure of symptoms and severity of depression in medical settings,[17] was used to assess depression.

Imaging

Brain MRI was performed with a MAGNETOM Verio 3-T scanner (Siemens Medical Systems, AG, Erlangen, Germany) with volumetric values derived from T_1-weighted images via FreeSurfer version 6.[18]

Analyses

Certain brain regions (hippocampi, amygdalae, caudate, insula, medial orbitofrontal cortex, rostral anterior cingulate cortex, thalamus, and corpus callosum subregions) were chosen a priori for analysis based on research suggesting structural or metabolic changes in individuals with RHI.[14,19–22] At baseline, cognitive, imaging, and mood data were collected. Longitudinal data focused on the correlation between baseline depression and cognitive change. Analyses were conducted in SPSS version 22 (IBM Corp, Armonk, New York).[23] Moderation analyses were computed via the PROCESS v3.0 macros.[24]

Clinical depression analyses

To examine hypothesis 1, the relations between regional brain volumes and CSD in fighters who scored at or above 10 on the PHQ-9 (as suggested by the validation study[17]) were compared with those of nondepressed fighters (nCSD) via a 2 (group) by 19 (region) analysis of covariance (ANCOVA), accounting for total brain volume. To test hypothesis 2, similar ANCOVAs were computed for the depressed groups and the 4 cognitive variables, accounting for education.

Hypothesis 3: Depression moderation analyses

To assess the moderating role of depression in the relations between fight exposure and brain volumes, a series of regression models were computed using median-split-dichotomized PHQ-9 depression scores as a moderator (minimal depressive symptom, MDS: PHQ-9 score of 0-1; and depressive symptom, DS: PHQ-9 >1). Number of professional fights served as a predictor, and the target brain region served as the criterion variable. Median split was used in favor of a higher cutoff to retain an adequate number of individuals in each group. Notably, the DS group was not conceptualized as being depressed; rather, the presence of any DSs was examined as a moderator. Seventeen models were computed, one for each brain region identified a priori (excluding posterior and anterior corpus callosum subregions due to lack of meaningful findings as a function of CSD). To account for multiple comparisons, α was set to .003 for each overall moderated regression model per the Bonferroni method. Depression as a moderator within models was considered at $P < .05$. Probing analyses to characterize models were considered at $P < .05$. In addition, 4 models were computed to assess whether depression moderated the relations between fight exposure and cognition for each CNS Vital Signs domain using the same parameters.

To test hypothesis 4, Pearson product moment correlations were computed between baseline PHQ-9 scores and cognitive change (ie, the difference score between first visit and last visit for each fighter in each cognitive domain).

RESULTS

Demographic and depression data

Demographic data and statistical analyses are presented in Table 1 for the CSD and nCSD groups used in the ANCOVA and for the DS and MDS groups used in moderation analyses. The proportion of fighters reporting CSD in our sample was low (8.2%). Fighters in the CSD group ($n = 17$) had more professional fights and were older than nCSD ($n = 188$) fighters. χ^2 analyses suggested differences in the distribution of depression status by race; Caucasian participants were represented disproportionately in the CSD group relative to African American participants, consistent with research in nonathlete populations with CSD[25] There were no significant differences in age ($U = 3530$, $z = -0.66$, $P > .05$), years of education ($U = 3486$, $z = -0.14$, $P > .05$), or number of professional fights ($U = 3111$, $z = -1.55$, $P > .05$) between fighters who returned for a follow-up visit and those who did not. Fighters who returned for a follow-up visit reported a significantly higher average rank frequency of baseline DSs ($U = 2886$, $z = -2.27$, $P = .023$). Fighters who returned for a follow-up visit had a significantly higher average rank frequency of reaction time performance ($U = 2871$, $z = -2.02$, $P = .043$). Regional brain volumes did not significantly differ between the fighters who returned for follow-up and those who did not (all Ps $< .05$).

For median-split depression groups used in moderation analyses, fighters with DS ($n = 97$) had more professional fights and were older than MDS fighters ($n = 108$). χ^2 analyses suggested no significant differences across race by median-split depression. As expected, PHQ-9 depression scores were significantly correlated with the number of professional fights ($r = 0.28$; $P < .001$) and age ($r = 0.49$; $P < .001$).

TABLE 1 *Demographic information*[a]

	Total sample ($n = 205$)	CSD fighters ($n = 17$)	nCSD fighters ($n = 188$)	Significance	DS fighters ($n = 97$)	MDS fighters ($n = 108$)	Significance
Age	31.3 (9.5) [18-72]	42.7 (11.0) [20-72]	30.2 (8.6) [18-62]	**$F = 31.36$; $P < .001$**	33.93 (10.58) [19-72]	28.89 (7.63) [18-57]	**$F = 15.51$; $P < .001$**
Years of education	13.0 (2.3) [3-19]	12.2 (3.2) [3-18]	13.0 (2.3) [6-19]	$F = 1.74$; $P = .19$	13.27 (2.54) [3-19]	12.70 (2.15) [6-19]	$F = 3.02$; $P = .08$
Number of professional fights	16.2 (19.0) [0-101]	32.5 (22.0) [0-98]	14.8 (18.0) [0-101]	**$F = 14.52$; $P < .001$**	19.25 (18.78) [0-98]	13.52 (18.90) [0-101]	**$F = 4.72$; $P = .03$**
African American/black	78	2	76	**$\chi^2 = 22.24$; $P < .001$**	29	49	$\chi^2 = 7.52$; $P = .11$
American Indian/AK Native	5	2	3	...	3	2	...
Asian/pacific islander	7	3	4	...	5	2	...
White	73	10	63	...	41	32	...
Other/not provided	44	2	42	...	20	24	...

Abbreviations: AK, Alaska; CSD, clinically significant depression; DS, depressive symptoms; MDS, minimal depressive symptoms; nCSD, nonclinically significant depression.
[a]Some participants indicated more than one race. Brackets indicate sample ranges.

First-visit clinical depression and regional brain volumes

As seen in Figure 1A, CSD fighters (PHQ-9 > 9; $n = 17$) differed significantly from nCSD fighters ($n = 188$) in left ($F(1, 202) = 5.25$; $P = .02$) and right ($F(1, 202) = 8.50$; $P < .01$) insula thickness, left medial orbitofrontal thickness ($F(1, 202) = 7.06$; $P = .01$), and left rostral anterior cingulate thickness ($F(1, 202) = 6.80$; $P = .01$), accounting for total brain volume. Right-sided medial orbitofrontal and rostral anterior cingulate cortex volumes were not significantly different as a function of depression status ($P = .091$ and .051, respectively; Figure 1). Mid-posterior ($F(1, 202) = 6.77$; $P = .01$), central ($F(1, 202) = 5.51$; $P = .02$), and mid-anterior ($F(1, 202) = 8.04$; $P < .01$) corpus callosum volumes; and left ($F(1, 202) = 8.94$; $P < .01$), and right ($F(1, 202) = 9.74$; $P < .01$) thalamic volumes also differed significantly, accounting for total brain volume (see Figure 1B). There were no significant differences between CSD and nCSD fighters in volumes of bilateral hippocampi, amygdalae, caudate, anterior corpus callosum, or posterior corpus callosum (all Ps > .05). This suggests that CSD fighters have thinner cortices and smaller subcortical volumes across multiple brain regions that have been associated with depression in healthy controls (ie, insula, cingulate, orbitofrontal cortex, and thalami), and show unique volumetric differences not seen in nonathlete populations (ie, mid-corpus callosum subregions).

First visit clinical depression and cognition

CSD fighters had poorer performance on tests of verbal memory ($F(1, 198) = 7.10$; $P = .008$) and psychomotor speed ($F(1, 200) = 19.28$; $P = .01$) than nCSD fighters. There was no significant difference in processing speed ($F(1, 201) = 2.84$; $P = .09$) or reaction time ($F(1, 200) = 2.03$; $P = .16$) as a function of depression. All analyses accounted for education.

Depression as a moderator of brain volume

To test whether depression moderates the relations between fight exposure and brain volumes, a series of moderated regression analyses (see Figure 2A) on median-split depression levels (ie, DS and MDS group membership) were computed according to the above-stated parameters. Results of statistical tests are presented in Table 2. Due to the strong correlation between age and number of fights, age was not accounted for in these analyses. Regression models including number of professional fights, depression group, and depression by fight interaction significantly predicted volumes of the right and left thalami, mid-anterior, central, and mid-posterior corpus callosum, right and left amygdalae, right and left hippocampi, and the thickness of the left

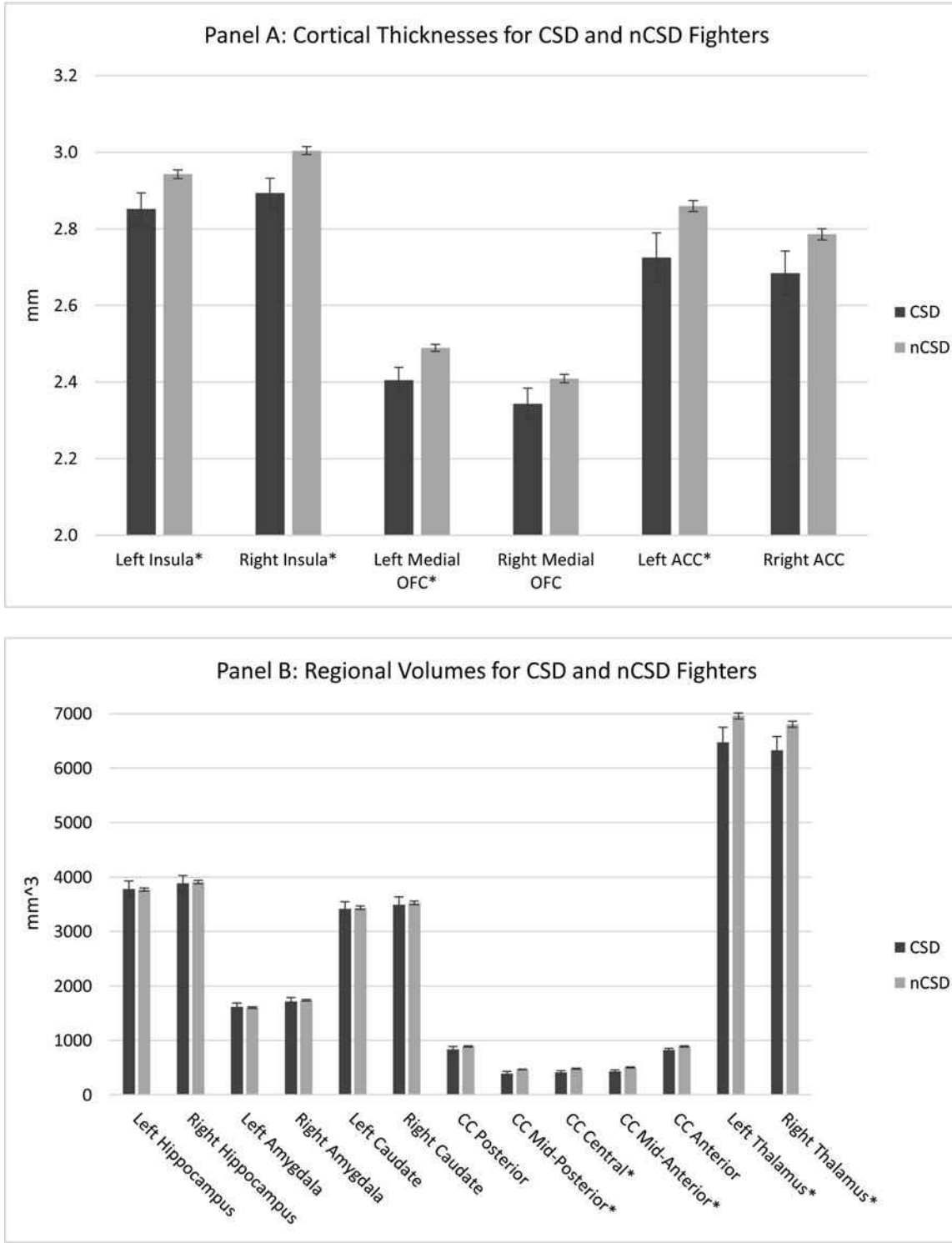

Figure 1. Brain volumes and cortical thicknesses as a function of depression status. Bars represent standard error and asterisks (*) show significance at the .05 level. CC indicates corpus callosum; CSD, clinically significant depression; nCSD, nonclinically significant depression.

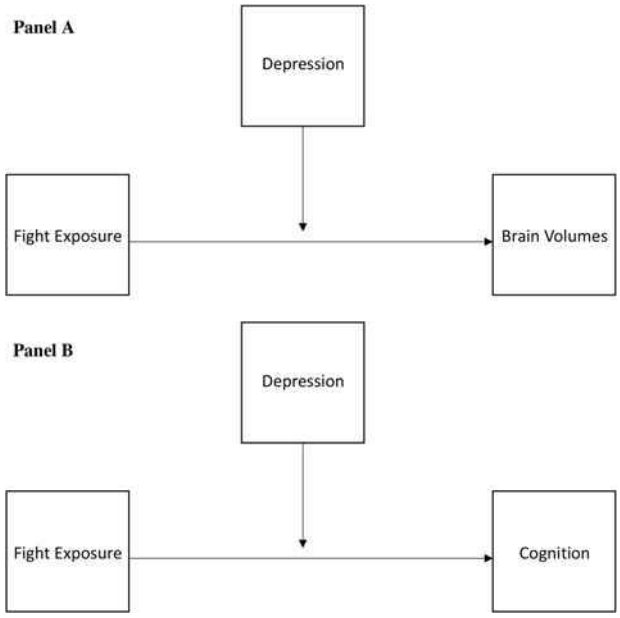

Figure 2. Conceptual diagrams of moderated regression models.

medial orbitofrontal cortices, left anterior cingulate cortex, and right and left insula. Bilateral caudate, right medial orbitofrontal cortex, and right anterior cingulate cortex regions were not volumetrically predicted by regression modeling. Depression significantly moderated the relations between number of fights and right and left thalamic volumes, left hippocampal volume, left medial orbitofrontal cortex thickness, and left and right insula thickness.

To characterize the moderating effect of depression on the relations between fight exposure and certain brain volumes, "probing" analyses were used. These analyses examined differences between the influence of the 2 levels of our moderating variable (MDS and DS) on predictions of brain volumes at 0, 10, and 32 fights (the 16th, 50th, and 84th-percentile ranks of fight exposure; labeled as few, moderate, and many fights, respectively, in Figure 3). It should be noted that these models test the theoretical impact of our moderator on the relations between fight exposure and brain volumes by plotting points on the regression line and use whole-sample variances to accomplish significance testing. In essence, these analyses model what may be expected of brain volumes in those with DS and MDS as a function of exposure to RHI. As seen in Figure 3A, the model predicted that, for the DS group only, right thalamic volume significantly decreases by number of fights ($P < .001$). The model also predicted that, for fighters in both the DS ($P < .001$) and MDS ($P = .02$) groups, left thalamic volume significantly decreases by number of fights (see Figure 3B). Increased fight exposure predicted lower left hippocampal volume for the DS group ($P < .001$; Figure 3C) while not for the MDS group. Only among the DS group, increased fight exposure was related to thinner left medial orbitofrontal thickness ($P < .001$). Similarly, there were significant relations between fight exposure and left and right (both

TABLE 2 *Regression and moderation model statistics*

	Overall regression model				Moderation		
Brain region	***r***	***R*²**	***F* (3, 201)**	***P*[a]**	***R*² change**	***F* (1, 201)**	***P***
R thalamus	*0.41*[b]	*0.17*	*13.680*	*<.001*	*0.04*	*9.33*	*.003*
L thalamus	*0.41*	*0.16*	*13.130*	*<.001*	*0.03*	*5.92*	*.016*
Mid-anterior CC	*0.33*	*0.11*	*8.210*	*<.001*	0.01	3.52	.062
Central CC	*0.42*	*0.17*	*14.000*	*<.001*	0.02	3.55	.061
Mid-posterior CC	*0.34*	*0.11*	*8.480*	*<.001*	0.00	0.50	.482
R amygdala	*0.26*	*0.07*	*4.940*	*.003*	0.01	2.30	.131
L amygdala	*0.29*	*0.09*	*6.310*	*<.001*	0.01	1.25	.265
R hippocampus	*0.27*	*0.07*	*5.180*	*.002*	0.02	3.57	.060
L hippocampus	*0.27*	*0.07*	*5.040*	*.002*	*0.02*	*4.97*	*.027*
R mOFC	0.22	*0.05*	3.514	.016	...	...	...
L mOFC	*0.29*	*0.08*	*6.100*	*.001*	*0.02*	*4.69*	*.035*
R ACC	0.25	*0.06*	4.362	.005	...	...	...
L ACC	*0.28*	*0.08*	*5.500*	*.001*	0.01	1.82	.179
R insula	*0.33*	*0.11*	*7.920*	*<.001*	*0.03*	*6.42*	*.012*
L insula	*0.30*	*0.09*	*6.840*	*<.001*	*0.02*	*4.78*	*.030*
R caudate	0.23	*0.05*	3.843	.011	...	...	...
L caudate	0.24	*0.06*	4.171	.007	...	...	...

Abbreviations: ACC, anterior cingulate cortex; CC, corpus callosum; L, left; mOFC, medial orbitofrontal cortex; R, right.
[a]Alpha set to .003.
[b]Italicized figures are significant.

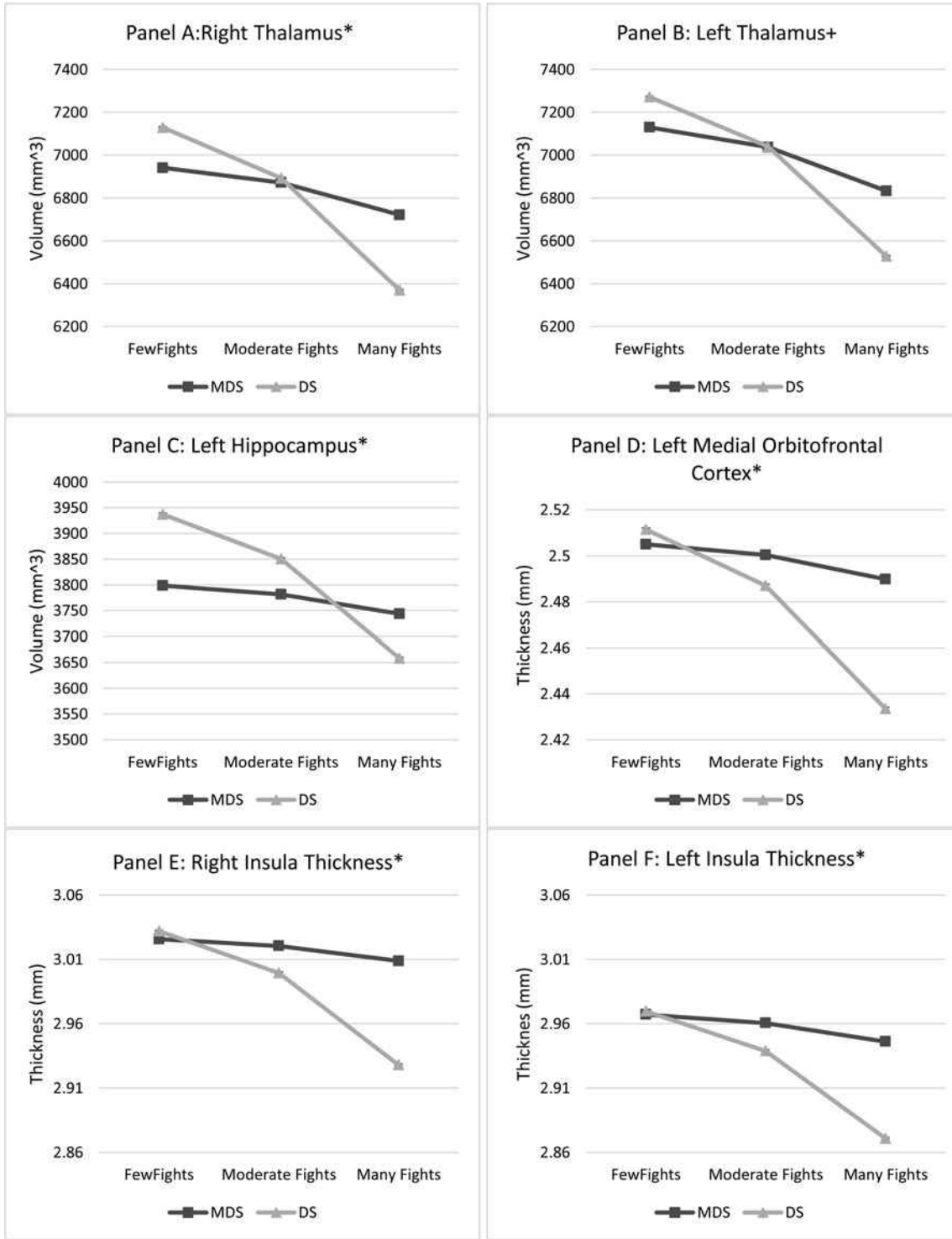

Figure 3. Interactive effects of number of fights and depressive symptoms on brain volumes. Few fights = 0 fight; moderate fights = 10 fights; many fights = 32 fights. In panel titles, * indicates that the relationship was significant for DS group only, while + indicates that the relationship was significant for DS and MDS groups. DS indicates depressive symptoms; MDS, minimal depressive symptoms.

*P*s < .001) insula thickness only for the DS group, such that increased exposure predicted lower volume (see Figure 3E/F). Subsequently, for the right thalamus, left hippocampus, left medial orbitofrontal cortex, and bilateral insula, moderation models predict a significant decline in brain volumes as fight exposure increased *only* in the DS condition. There are similar relations between number of fights and brain volume in both the DS and MDS groups in the left thalamus.

Depression as a moderator of cognitive performance

Regression models including number of professional fights, depression group, and depression by fight interaction (see Figure 2B) significantly predicted psychomotor speed ($r = 0.393$; $F(3, 201) = 12.20$; $P < .001$), reaction time ($r = 0.327$; $F(3, 201) = 7.98$; $P < .001$), and verbal memory ($r = 0.263$; $F(3, 201) = 4.90$; $P = .0026$). This regression model did not predict processing speed ($r = 0.071$; $P = .80$). Depression was not found to be a significant moderator in the relations between number of fights and any domain of cognition ($P > .05$) in any model.

First-visit depression and longitudinal cognitive change

Longitudinally, depression at baseline was significantly correlated with declines over time in psychomotor speed ($r = -0.38$; $P = .01$) and reaction time performance ($r = 0.65$; $P < .001$). Depression at baseline was significantly correlated with improvements in verbal memory ($r = 0.45$ $P < .01$) performance over time. Depression at baseline was not significantly correlated with processing speed changes ($P > .05$).

Age-matched analyses

Given significant differences between depressed and nondepressed fighters as a function of age, follow-up analyses were completed on the 17 depressed fighters and an age-matched group of nondepressed fighters drawn from the initial sample of participants. Partial correlations exploring the relations between depression and volumes of the chosen brain regions, while accounting for total brain volume, were nonsignificant (all *P*s > .07), although matching the overall pattern of findings outlined in our prior analyses. Similarly, depression and cognition were not significantly related in our age-matched sample, but observed relations were in the expected direction.

DISCUSSION

These data represent novel findings about the role of depression in the relations between exposure to RHIs and both cognitive and volumetric changes and provide insight into the moderating role of depression in these relations. These data provide new information about the potential role of depression in cognitive change over time in professional boxers. The present study found significant volumetric and cognitive differences at baseline between fighters with and without CSD. Clinically, this may point to an important hallmark and reinforce the importance of screening for both depression and cognitive declines in athletes with potential exposure to RHI. Athletes with RHI exposure who demonstrate significant depression may benefit from referral for brain imaging and/or neuropsychological assessment, as this may indicate the presence of pathological and/or cognitive change. Even minimal symptoms of depression were found to moderate the relations between fight exposure and brain volumes, but not cognition. Clinicians may consider this in advising patients about future involvement in contact sports, as this observation may suggest an increased risk of brain volume reduction in critical areas among those with even minimal symptoms of depression as a function of RHI exposure. Longitudinally, relations between baseline depression and cognitive changes over time were observed. Age is important when characterizing this association, and its relation to fight exposure may be an important focus of future study.

Prevalence of depressive symptoms

Research suggests that the prevalence of CSD in athletes with histories of concussion may be higher (10.4% by self-report; PHQ-9 > 9 by concussion history suggests 5.6% with 1 concussion, 10.4% with 2 concussions, 8.9% with 3+ concussion)[26] than in 2016 National Institutes of Mental Health data that found the annual prevalence of major depressive episodes in the general population to be 4.8% among men.[27] Our sample's 8.2% who scored above a PHQ of 9 fell between population estimates and those of athletes with concussion histories. Differences in the racial distribution of CSD symptoms were consistent with previous research indicating higher reporting of DSs among white males relative to men of other demographics.[25] Overall, these data suggest that rates of significant depression symptoms in our sample may be somewhat lower than other samples of athletes with concussion, although our demographic distribution of reported symptoms parallels that of the general population.

First-visit depression and cognition

It is well-established that depression can impair cognitive functioning. While prior research highlights a negative impact of depression on processing speed, this was not demonstrated in the current study. It may be that participation in a sport so reliant upon quick interpretation of and reaction to the environment is a protective

factor, as is seen in elite football players.[28] It is also possible that, in order to rise to the professional level in boxing, one must have faster-than-average baseline processing speed. Notably, prior studies assessing processing speed in athlete populations have used different cognitive measures. As such, the present study's use of a briefer measure in lieu of more robust neuropsychological testing may have reduced sensitivity and prevented the replication of this finding.

Brain volumes and clinical depression at first visit

Depressive symptoms were associated with regional brain changes that largely mirror those documented in prior research with nonathlete populations. However, we also found a relation between mid-corpus callosum volumes and depression status. The corpus callosum was chosen as it is a major white matter tract that may be susceptible to damage in boxing and has previously shown to be associated with CTE.[12,13] In nonathlete populations, the thalamus has been implicated in depression due to its functional connectivity with diverse neural networks,[29] and reduced thalamic activity is related to depression in those with neurodegenerative conditions such as Parkinson disease.[30] A similar explanation for the role of the corpus callosum in the present sample may apply (ie, disruption of this important interhemispheric white matter tract disrupts circuitry important for the regulation of mood). Interestingly, only the middle regions of the corpus callosum were significant, sparing anterior and posterior subdivisions. It is conjectured that these subregions may be more vulnerable to the types of inertial factors encountered in boxing; hence, alterations in the genu and body of the corpus callosum seen via diffusion tensor imaging methodologies[31] in nonathletes with depression may be restricted to central regions due to mechanism of injury. As severe white matter damage is rare in those without exposure to head trauma or neurodegenerative processes, it is unsurprising that such volumetric findings have not emerged from the depression literature. Replication of this finding in future research via longitudinal investigations of imaging and mood may help clarify this relation.

Depression as a moderator of brain volumes and cognition

Our data suggest DSs moderate the relations between fight exposure and brain volumes in regions previously shown to be related to depression. Specifically, decline in volume of the right thalamus, left hippocampus, left medial orbitofrontal cortex, and bilateral insulae as a function of number of fights was only predicted from those endorsing symptoms of depression. In the left thalamus, this relation was found for both those with and without DSs. This suggests that even mild symptoms of depression may identify those at risk of volumetric decline with exposure to repetitive head trauma. It is possible either that depression interacts with fight exposure to exacerbate volumetric changes or that depression occasions more severe volumetric declines in professional boxers. Future research may benefit from longitudinally examining brain volumes and mood in this population.

Interestingly, depression did not significantly moderate the relations between exposure and any of the outlined cognitive variables. These findings are notable when contrasted with John et al's[32] recent meta-analysis demonstrating depression's association with cognitive decline. This may be due to the lack of sensitivity and specificity of the computerized cognitive tasks used in the current study, the relative youth of our population, the mildness of DSs in this cohort, or other factors yet to be considered.

Cognitive changes over time and first-visit depression

Our longitudinal data demonstrate that first-visit depression positively correlated with declines over time in reaction time/inhibition (Stroop-like task) and psychomotor speed. These findings are important because they support depression as a potential clinical phenotype of those at risk for a degenerative process in those with exposure to RHI. Cognitive performance may, however, vary as a function of depression at both intervals, and this relation will be examined as more data become available from our cohort. Interestingly, depression at baseline was related to improvements in verbal memory across time. This may be attributable to regression to the mean or tied to reliance on recognition memory, as it may be particularly sensitive to practice effects. Future studies would benefit from using more robust, multicomponent memory assessments including learning, recall, and recognition trials and alternate forms to determine whether these results reflect practice effects or if there is a protective relation of depression on memory performance over time, contrary to the extant literature.

The role of age and exposure

Age is important but difficult to parse with analyses that are statistically viable in the current study sample. Specifically, there is a strong collinearity between age and number of fights, as aging necessarily occurs as experience in the ring accrues. It is interesting that when age-matched comparisons are made, there are (nonsignificant) correlations between depression as a continuous variable and brain volumes and between depression and cognitive variables that demonstrate a pattern consistent with non-age-corrected analyses. Given the small size of the age-matched groups of depressed and nondepressed fighters, further investigation of these relations is necessary as the PFBHS accrues more longitudinal data.

Limitations

The present study represents a preliminary examination of the role of depression in cognition and brain volumes of professional fighters and is not a control-matched study. The manner in which depression was assessed was via a self-report measure, not corroborated by a formal evaluation. Further, because the PHQ-9 contains items that are not specific to depression (eg, poor appetite), respondents could report no depression-specific symptoms and be in the MDS group; hence, although some common depression symptoms were assessed, these symptoms may derive from other conditions. Depressive symptoms may also vary transiently during training as athletes are exposed to concussive and subconcussive blows. This exposure was not controlled in our analyses. Cognitive performance was assessed via CNS Vital Signs, which has the benefit of common accessibility in neurology settings; however, cognitive screening measures are limited. In particular, as the assessment of verbal memory relies on a single repetition of a word list and on recognition memory, performance may be particularly subject to attentional difficulties. Follow-up assessments may also be subject to practice effects. A thorough cognitive assessment (ie, a more comprehensive neuropsychological test battery) would improve predictive utility and validity. Finally, as substance use was not considered, the possible impact of substance use on depression and cognitive performance cannot be ruled out.

Future directions

The present study employed cognitive and depression screening tools, as they provide clinically generalizable results. Future studies may benefit from using neuropsychological measures and more in-depth measures of depression that may have greater sensitivity and specificity than those used in the present study and may shed light on our surprising finding that baseline depression was related to improvements in memory performance over time. Given the novel finding that major white matter tracts are disrupted in depressed boxers, it may be beneficial to further explore this relation using other imaging techniques such as diffusion tensor imaging. In addition, qualitative research focusing on cognitive change and fight exposure may be useful in better characterizing their experiences beyond what quantitative data can provide. Qualitative interviews may also address concerns regarding concussions and injury during training, as well as elucidating other potentially important targets for future research. Finally, although some longitudinal analyses were presented in this article, as data collection continues in the PFBHS, more robust analyses may be conducted longitudinally to quantify changes over time in this population.

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