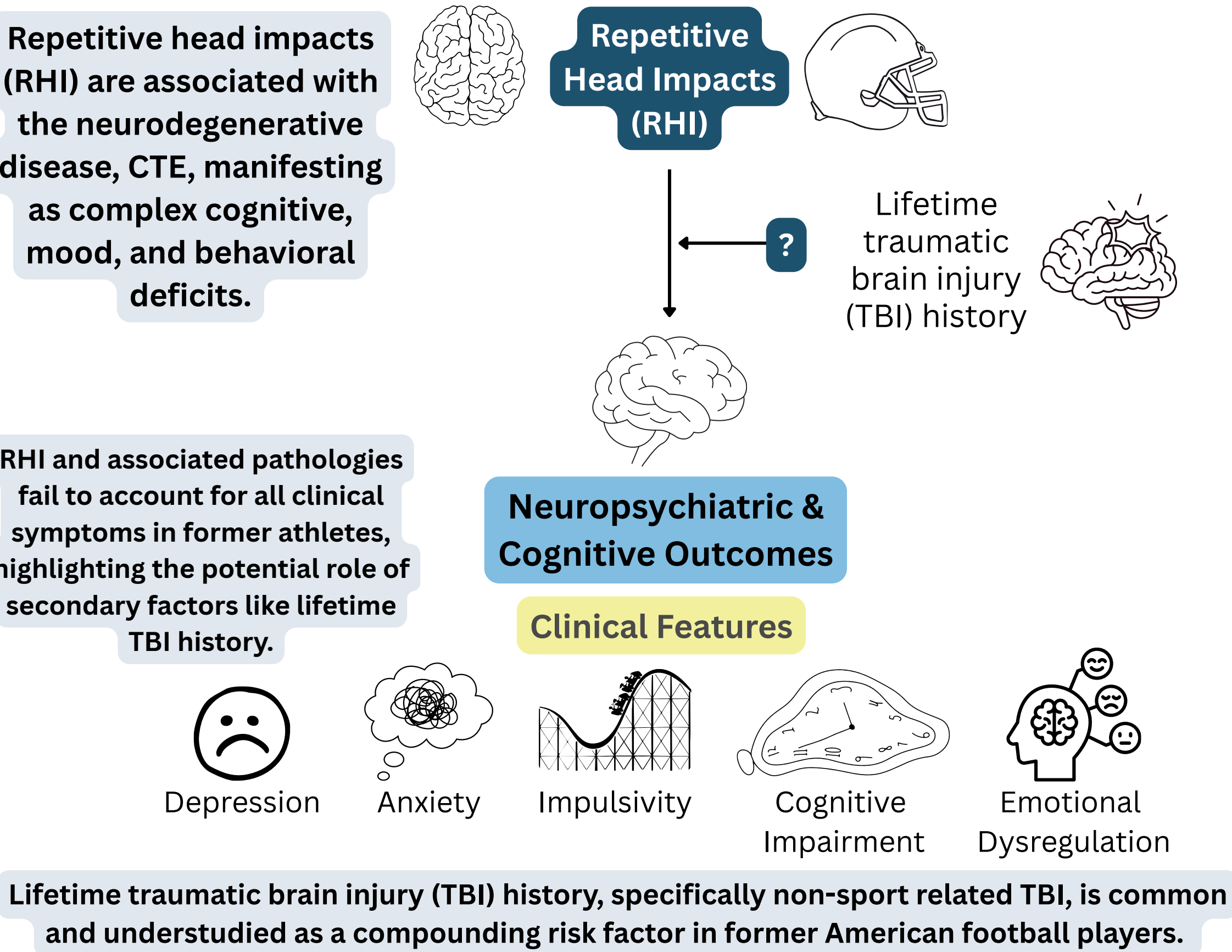


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Introduction

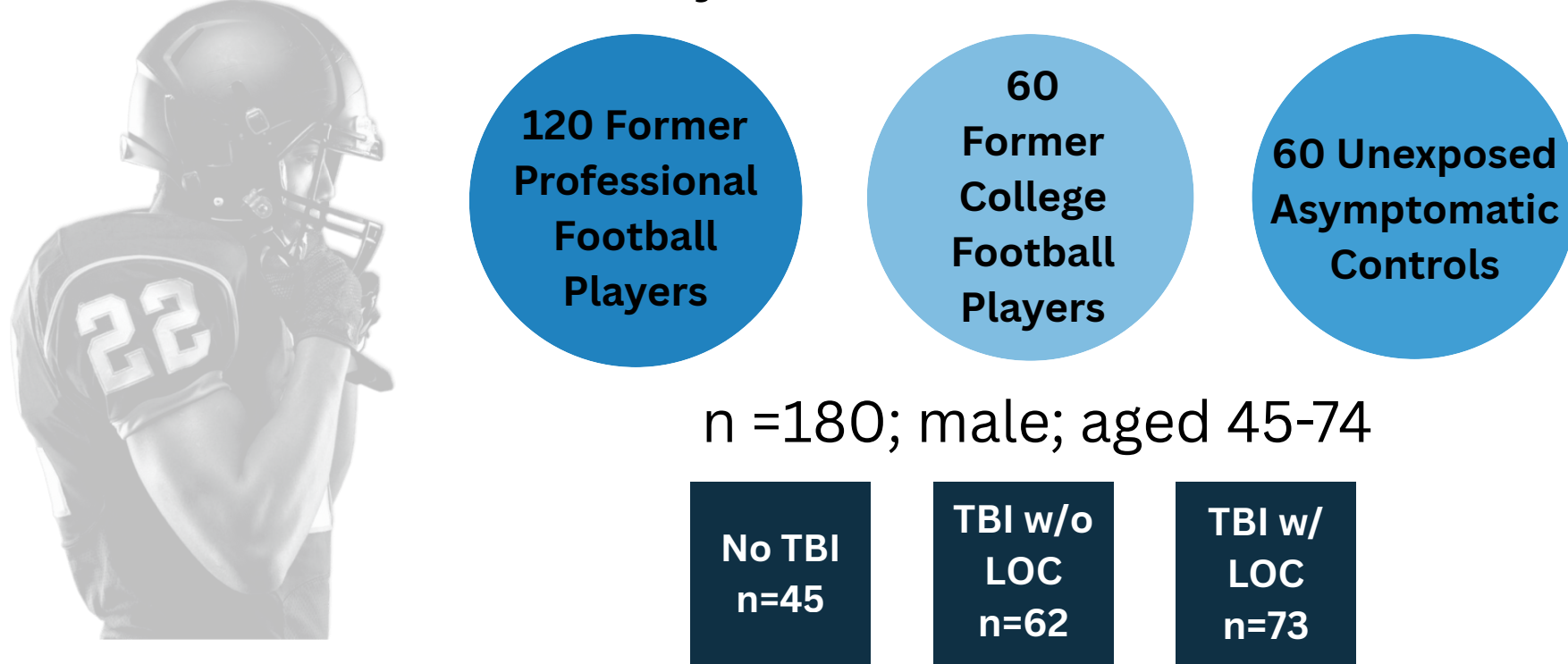


Objective

To investigate how a lifetime history of TBI contributes to and modifies cognitive, mood, and behavioral symptoms in former American football players at risk for CTE.

Participants and Methods

DIAGNOSE CTE: Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy Research Project; 8 year, multi-center study aimed to identify in vivo biomarkers for CTE (2016-2023)



Ohio State University TBI Identification Method (OSU-TBI-ID):

- Participants were classified by lifetime TBI history: No TBI, TBI without loss of consciousness (LOC), and TBI with LOC.
- Focuses on lifetime TBI sources (e.g., vehicular accidents) rather than sports-related concussions per se.

Concussion History Questionnaire:

- Assessed symptomatic impacts often missed by standard instruments like the OSU-TBI-ID which heavily rely on LOC.
- Probes with a comprehensive, symptom-driven concussion definition.

OUTCOME MEASURES

- COGNITIVE**
- MoCA:** Global Cognitive Function
 - Trail Making Test A & B:** Processing Speed and Cognitive Flexibility
 - NAB List Learning Long Delay:** Verbal Memory
 - COWAT:** Verbal Fluency and Executive Functioning
- MOOD**
- Beck Depression Inventory-II (BDI-II):** Depression
 - Beck Anxiety Inventory (BAI):** Anxiety
- BEHAVIORAL**
- Barratt Impulsiveness Scale (BIS-11):** Attentional, Motor, and Non-planning Impulsiveness
 - Neurobehavioral Dysregulation (NBD):** Impulsivity, Explosiveness, Disinhibition
 - Behavioral Regulation Index (BRI) Participant and Informant:** Poor Impulse Control, Emotional Lability, and Difficulty Shifting Behavior

STATISTICAL ANALYSES

- Linear regressions compared groups, adjusting for age, education, BMI, *APOE4*, and vascular risk.
- Pairwise comparisons of TBI groups were performed using Tukey-adjusted estimated marginal means.
- Sensitivity analyses adjusted for total years of football and total concussions.

Results

Table 1: Participant Characteristics

		TBI Status (based on OSU-TBI-ID)				
	<i>n</i>	Overall <i>n</i> = 180 ¹	No TBI <i>n</i> = 45 ¹	TBI without LOC <i>n</i> = 62 ¹	TBI with LOC <i>n</i> = 73 ¹	<i>p</i> value ²
Participant Characteristics						
Age Group	180					0.36
	45-54	86 (48%)	24 (53%)	28 (45%)	34 (47%)	
	55-64	55 (31%)	16 (36%)	17 (27%)	22 (30%)	
	65-74	39 (22%)	5 (11%)	17 (27%)	17 (23%)	
Years of Education	180	16.74 (1.45)	16.51 (1.10)	16.77 (1.78)	16.84 (1.32)	0.26
Total Years of Football Play	180	15.85 (4.36)	16.47 (3.69)	16.23 (4.49)	15.15 (4.95)	0.19
BMI	180	32.59 (4.65)	32.17 (4.87)	33.16 (4.77)	32.38 (4.42)	0.38
APOE4 Carrier	174	53 (30%)	13 (29%)	20 (33%)	20 (29%)	0.84
Revised Framingham Stroke Risk Profile	171	0.03 (0.03)	0.03 (0.03)	0.04 (0.04)	0.03 (0.03)	0.22
Total Concussions						
Total Concussions ³	179	30 (12, 100)	68 (10, 150)	21 (10, 100)	30 (15, 120)	0.21
TBI Source						
Vehicular	180	37 (21%)	0 (0%)	13 (21%)	24 (33%)	<0.001
Falls	180	111 (62%)	0 (0%)	48 (77%)	63 (86%)	<0.001
Violence	179	27 (15%)	0 (0%)	9 (15%)	18 (25%)	0.001
Blasts	180	11 (6.1%)	0 (0%)	3 (4.8%)	8 (11%)	0.035
Other	180	68 (38%)	0 (0%)	25 (40%)	43 (59%)	<0.001

¹ Mean (SD); Median (IQR); n (%); ² Kruskal-Wallis rank sum test; Pearson's Chi-squared test; ³ Total number of concussions after being provided with a formal definition and targets sports-related concussion.

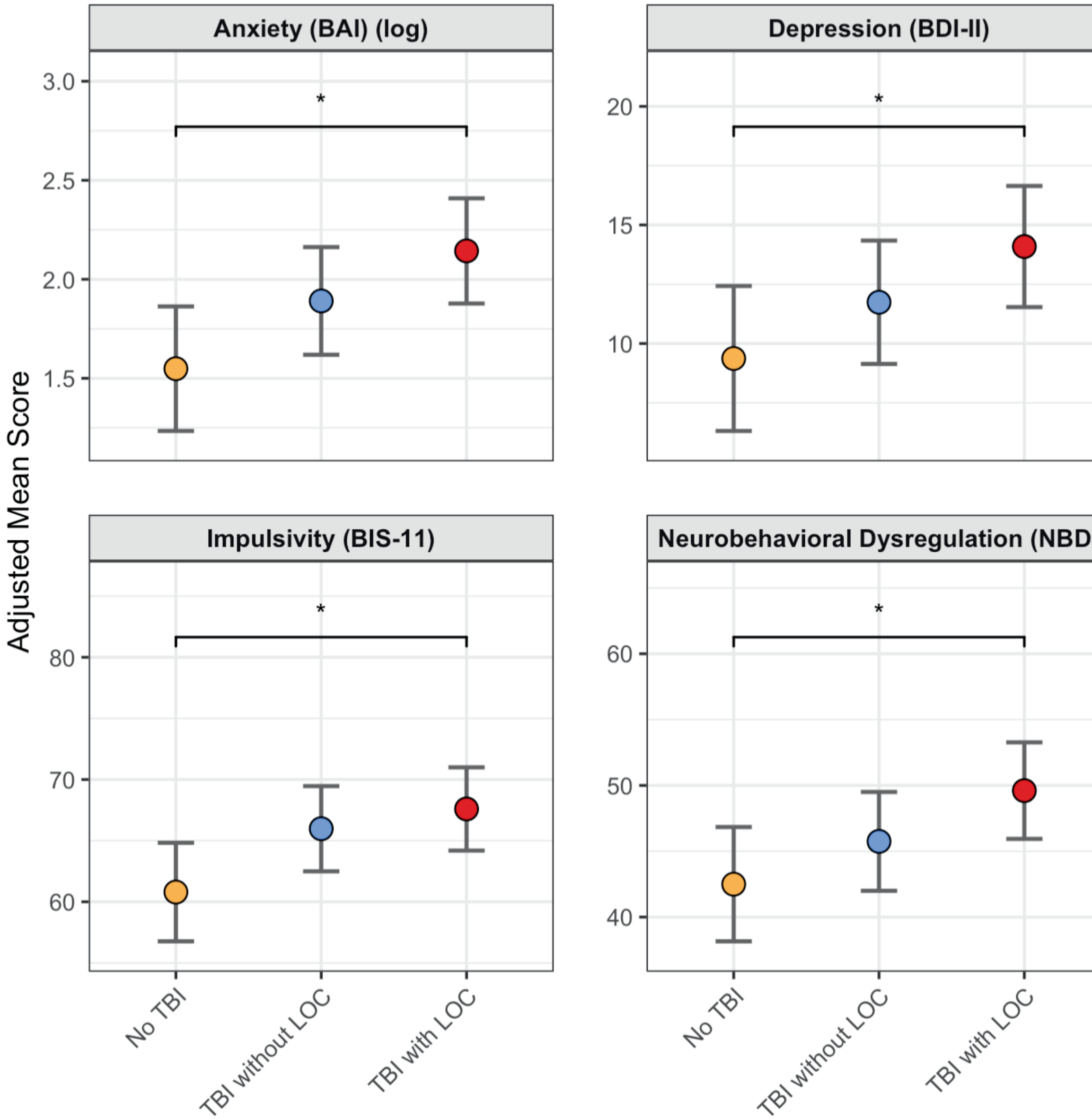
TBI with LOC is associated with mood and behavioral, but not cognitive symptoms, in former football players independent of exposure to RHIs and concussions.

Table 2: Associations Between Cognitive, Mood, and Behavioral Outcomes and TBI Status

Domain	Outcomes	Factors	B (95% Confidence Interval)	Adjusted p Value
Cognitive	MoCA (<i>square root</i>)	TBI without LOC	-0.06 (-0.32, 0.21)	0.821
		TBI with LOC	0.01 (-0.25, 0.26)	0.926
	NAB List Learning Long Delay	TBI without LOC	2.45 (-2.75, 7.64)	0.643
		TBI with LOC	0.36 (-4.73, 5.45)	0.821
	Trail Making Test A	TBI without LOC	1.91 (-2.17, 5.99)	0.643
		TBI with LOC	1.85 (-2.15, 5.84)	0.643
	Trail Making Test B	TBI without LOC	2.97 (-1.34, 7.27)	0.614
		TBI with LOC	4.5 (0.27, 8.72)	0.272
	COWAT	TBI without LOC	1.21 (-2.73, 5.15)	0.812
		TBI with LOC	3 (-0.87, 6.86)	0.467
Mood	Depression (BDI-II)	TBI without LOC	2.33 (-1.46, 6.12)	0.218
		TBI with LOC	4.88 (1.18, 8.57)	0.0245
	Anxiety (BAI) (<i>log</i>)	TBI without LOC	0.337 (-0.0536, 0.728)	0.114
		TBI with LOC	0.612 (0.231, 0.993)	0.0093
Behavioral	Impulsivity (BIS-11)	TBI without LOC	5.09 (0.100, 10.1)	0.0853
		TBI with LOC	7.10 (2.23, 12.0)	0.0328
	Behavioral Regulation (BRI)	TBI without LOC	2.48 (-3.15, 8.12)	0.502
		TBI with LOC	6.45 (0.958, 11.9)	0.0645
	Behavioral Regulation (BRI Informant)	TBI without LOC	-1.71 (-8.25, 4.83)	0.652
		TBI with LOC	1.62 (-4.65, 7.89)	0.652
	Neurobehavioral Dysregulation (NBD)	TBI without LOC	3.18 (-2.21, 8.58)	0.377
		TBI with LOC	7.34 (2.08, 12.6)	0.0328

¹ Reference Group = No TBI; ² False discovery rate correction based on Benjamini Hochberg Method

Mood and Behavioral Outcomes by TBI Status



Conclusions and Future Directions

TBI represents a significant comorbid injury alongside RHI in former American football players. Our findings demonstrate a key clinical distinction: TBI with LOC, even when accounting for RHI, appears to be associated with mood and behavioral symptoms in RHI-exposed individuals.

Investigating TBI as a secondary risk factor is essential in understanding heterogenous clinical presentations in former RHI-exposed athletes due to the high rate of concurrent neuropathologies (AD, LBD, LATE) and psychiatric conditions in this population.

Future work will aim to incorporate more granular details of lifetime TBI history, including age at injury, cumulative injury count, and acute symptom severity beyond LOC, as well as integration of clinical histories with objective biomarkers (e.g., p-tau, NfL) and MRIs.

Limitations

- Recall Bias: retrospective, self-report measures are subject to inaccurate recall.
- Selection Bias: lack of ethnocultural diversity within sample.
- Cross-Sectional Analysis: findings capture a snapshot of clinical symptoms at a singular point in time.

Acknowledgements

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