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NEWS

Adverse Association of Soccer Heading with Verbal Learning is Mediated by Microstructure of the Orbitofrontal Gray Matter-White Matter Interface

PURPOSE

Repetitive head impacts (RHI) from soccer heading are an integral part of the sport. High RHI exposure is associated with worse verbal learning (VL). Adverse associations of RHI with white matter (WM) microstructure have also been identified using diffusion tensor MRI (DTI). The orbitofrontal region and the gray matter (GM) - WM interface (GWI) are known predilection sites for head impact shear force trauma, but DTI investigations have been restricted to deeper WM regions. Moreover, studies have not yet tested the causal role of imaging findings in the pathway from RHI exposure to worse cognitive function. We tested the mediating role of orbitofrontal GWI microstructure in a known association of RHI with worse VL. We hypothesized the natural sharp transition from high WM fractional anisotropy (FA) to low GM FA is attenuated as a function of RHI and this attenuation mediates the association of RHI with VL.

METHODS AND MATERIALS

We analyzed RHI (12-month heading from HeadCount, a validated instrument), DTI (3.0T; 32 directions; b=800; voxel size 2mm) and VL (International Shopping List) from 353 amateur soccer players (18-53, 27% female). To overcome limitations (e.g., misregistration and partial volume effects) we interrogated the transition from low GM FA to high WM FA by computing the slope of FA orthogonal to the GWI (defined by FreeSurfer) over the entire orbitofrontal region, as follows: we binned all orbitofrontal voxels by distance to the GWI and computed average FA within each bin. Average FA was plotted vs. distance to the GWI and fit to a 7th order polynomial. FA slope across the GWI is defined as the maximum slope magnitude of the polynomial fit. To test mediation by GWI microstructure, we fitted linear models to test the associations of (1) RHI with VL, (2) RHI with FA slope and (3) RHI and FA slope with VL, with age and sex as covariates. Mediation by FA slope was calculated as the product of RHI effect size in model (2) and FA slope effect size in model (3). Mediation significance was tested using the Sobel test.

RESULTS

We confirmed an association of higher RHI with worse VL ($p=0.0305$). High RHI was associated with lower orbitofrontal GWI FA slope ($p= 0.00745$). The orbitofrontal GWI FA slope was a significant mediator ($p= 0.0186$) of the association of higher RHI with worse VL.

CONCLUSIONS

GWI microstructure integrity in the orbitofrontal region, as quantified by FA slope, mediates the association of RHI with VL. These results support a mechanistic role for juxtacortical white matter in adverse associations of soccer RHI with worse cognitive performance.

CLINICAL RELEVANCE/APPLICATIONS

GWI microstructure findings support a causal role in the adverse association of RHI with cognitive performance and may serve as a complementary biomarker of trauma-related brain pathology.