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Letter to the Editor

The Spurious Chicken and the Confounding Egg: Commentary on Cumulative Head Impact Exposure and Youth Football (Re: DOI: 10.1089/neu.2016.4413)

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Dear Editor:

In a previous issue of the *Journal of Neurotrauma,* Montenigro and coworkers[1] assert that repetitive head impacts obtained while playing football increases later-life neurological consequences. Although this is an important line of research inquiry that can be very fruitful, several faulty scientific premises undermine the veracity of the authors' claims. This letter outlines a few concerns about the basic research premise, arguing first and foremost that ''causality'' cannot be established given the research design. Also, the absence of authoritative controls for spurious relations and confounding variables weaken the argument that participation in contact sports like football is related to later clinical symptoms and even lasting neurological problems. This letter also discusses the requirements for establishing linkages between early adolescent or young adult activities and long-term neurological impairment. The basic premise that repetitive head impacts can contribute to later-life problems requires first establishing a scientific paradigm to examine these developmental relations beyond reproach. This letter concludes with several suggestions that have ramifications for future studies of this nature, utilizing more robust methodology and statistical techniques to clarify whether the chicken invariably preceded the egg.

Why the Chicken or the Egg

The basic argument proposed by Montenigro and coworkers rests on the supposition that football entails concussive events that jar the brain (i.e., shearing and tensile forces that disrupt axonal connections), a delicate organ protected by the skull. As they claim, repeated exposure to these events can be detrimental and can have long-term adverse clinical outcomes including ''neurodegenerative disease.'' To test this, Montenigro and colleagues first developed a psychometric tool to assess concussive forces associated with repetitive head impacts, the cumulative head impact index, and then evaluated its predictive significance with regard to specific clinical outcomes, controlling for other important metrics (e.g., duration of play, age of first exposure, and concussion history, to name a few). At first glance, this would seem an ideal opportunity to reveal whether repetitive head injury (RHI) is detrimental to future neurological functioning. However, careful analysis of the research design along with certain methodological weaknesses undermine the primary claim regarding causality.

Philosophically speaking, causality in science requires that no less than three conditions are met: (1) covariation such that when ''A'' occurs so does ''B,'' (2) temporal relations so that event ''A'' (i.e., RHI) precedes event ''B'' (neurological impairment), and (3) control for extraneous factors or what is termed ''spurious and confounding relations'' (third variable alternatives that can also cause ''B'')*. Montenigro and coworkers meet the requirement for covariation, specifically that ''A'' and ''B'' both occur within a reasonable time frame or that when ''A'' occurs ''B'' also is also present, so that a concussed football player shows clinical symptoms of neurological deficits at the time of the incident (and perhaps thereafter for a short duration). In addition, one must also contend with the issue of ruling out spuriousness and confounding in addition to meeting rigorous scientific requirements of causality.†

Medically speaking, concussions do not dissipate overnight, and in many cases, even in the National Football League (NFL), concussion protocols are quite extensive; for example, removing a player from any physical contact until he passes certain benchmark tests that reveal complete absence of symptoms. This is all good, if the deficits are temporary and can abate with time. The real issue is whether the damaging effects of RHI do not dissipate and are responsible for later neurological deficits.

Measuring RHI at an early age (adolescence or young adult) and then assessing neurological status at some reasonable follow-up 5 or 10 years later would appear to take care of the need for temporal relations. Importantly, baseline measures of neurological functioning are required to rule out prior existing conditions. This did not appear to be a formidable part of the study and the lack of statistical control for early measures of the consequent weakens the argument for causality. Related to this, there may be ''dormant instigators,'' which specifically reference early vulnerabilities in these youth that surface later in life, appearing as cognitive, mood, or neurological deficits. Dormant effects carry the risk of events later in life affecting neurological performance, separate and independent from football brain injuries.

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*Readers interested in exploring the philosophical basis for causal claims can read David Hume's Treatise on Human Nature[2], and also Mackie[3] addresses the logic behind causality in depth.

†van Stralen and coworkers[4] provide an excellent discussion of confounding in a medical context. For the purist, Christenfeld and coworkers[5] provide statistical definitions of confounding.

Confounders are the Culprit

It is well established that most people will develop a modicum of neurological problems with advancing age, irrespective of playing contact sports. This can take shape as natural memory loss,[6] and other manifestations of age-related cognitive decline.[7] One of the complications of aging is an increased deficit in cognitive functioning, including the ability to sort, retain, or process information. Invariably, we also encounter problems accessing certain ''heuristics'' that help us recover information. Various linguistic, grammatical, and lexical connections as well as reasoning skills show deficits with advancing age.[8] These instances of ''age-related cognitive decline'' parallel decrements in grip strength, loss of muscle tone (sarcopenia), diminished visual acuity, and other physical burdens (i.e., mobility) that are markers of aging. Recent evidence ties physical decline to inflammatory markers such as cytokines and C-reactive protein[9] as well as other pathophysiological and oxidative biochemical markers that can influence both mild cognitive impairment and physical aging.[10] There is also evidence that intensity of brain cortical activity is associated with rates of cognitive decline.[11] Overall, the inclusion of any one of these third-variable alternatives to control for confounding is an important ingredient in establishing causation.

Developmental psychopathology may also play a role in neurological outcomes, highlighting, in this case, family-related factors as third-variable alternatives responsible for negative outcomes.[12] For example, parents having trouble effectively managing their child's behavior could turn to sports and related activities as a way to smooth over child-rearing troubles and teach self-control.[13] This is becoming increasingly common in studies examining the effect of martial arts on youth behavior disorders.[14] Parents opting for these special activities expect to teach their child some form of personal discipline. Unfortunately, Montenigro and coworkers failed to assess any parenting or child rearing measures, leading to questions about spurious relations and confounding.[15] A host of additional family environment factors could possibly contribute to future neurological problems, and this fuels the argument that the usual suspect risk factors were not statistically controlled in the predictive models. It should therefore be no surprise that sample selection is a concern, as many youth attracted to sports are by their very nature, prone to behavioral problems.

Depression is both Genetic and Environmental

Much can be said about the role of early-life family factors in depression. Indeed, a considerable body of research shows that family (particularly maternal) psychological deficits affect a young child's development.[16] The underlying mechanisms can involve a range of factors including how mothers (or fathers) respond to their child, discipline practices, family dynamics (interactions with siblings), stress, and other social interactional processes.[17] There is also compelling evidence of genetic vulnerability to depression involving transmission from parent to child.[18] In the absence of randomized design (which is unethical in this situation), researchers must rely on clever naturalistic experiments (i.e., twins separated at birth) to tease apart genetic, familial, and environmental factors as competing explanations. Longitudinal prospective studies will demonstrate that some percent of the population will become depressed and that, in many cases, family dysfunction during childhood contributes to variation in depression.[19,20] Coupled with this is the observed stability of depression through the life course.[21] Life course theory, which relies on ''cumulative interactional continuity'' to explain consistency in behavior, reinforces that stable personality dispositions may create vulnerabilities to depression and other mental health conditions.[22] These vulnerabilities persist through the life course. All of this leaves us with a pressing question, ''How much of the later life depression results from head trauma versus the formative effect of early child rearing?'' Again, this points to the potential role of confounding variables that were not controlled in the current study.

Methodological Considerations

By any stretch of the imagination this was a very small study ($n = 93$), leading to questions as to whether it is considerably underpowered. This is certainly concerning if the goal was to conduct subgroup analyses (i.e., field position, younger vs. older) and further, to control for confounding (degrees of freedom change with the introduction of each control factor). Other methodological concerns involve splitting hairs over data management. For example, it has been well established among quantitative methodologists that dichotomization invariably biases parameter estimates.[23] Dichotomizing normally continuous measures loses meaningful variance. This grossly distorts relations for individuals far removed from the designated cut-point (i.e., median split), and assumes that these individuals are behaviorally similar to the individuals scoring closer to the cut-point (committing empirical gloss). As with any instrumental variable, sliding the cut-point along the underlying dimension in question (i.e., using an upper or lower quartile cut-point) could reveal a completely different set of results, arguably leading to flexible data analysis.[24] Because of the borrowing of data the from helmet accelerometer and related impact studies, it is unclear why Montenigro and coworkers did not use Bayesian statistical inference with informative priors to estimate parameters reflecting concussions.[25] As has been consistently demonstrated with developmental studies,[26] Bayes's theorem offers an alternative form of statistical inference, and the computational methods are relatively accessible and particularly useful for small sample studies. This would be a more formidable statistical approach ensuring that reliable (i.e., more precise) estimates of concussive events were used to provide weighted mean impacts per season. Filling in or imputing data requires that there is a reasonable and accurate frame of reference (i.e., the posterior distribution is more accurate given informative priors and observed data). This is especially warranted given the relatively small sample used in the current study (background knowledge for informative priors could be drawn from larger concussive or head trauma studies and the data stratified to comport with the current age and player distributions).

The various methodological and conceptual demands placed on a study of this nature require that these findings can be replicated. This involves both direct replication[27] that closely adheres to the study protocols (same measures, same time span, same protocols) and theoretical replication, the latter more attuned to examining whether sports in general with and without contact produce later life problems. More specifically, one needs to ask whether participation in a wide array of sports, all of which have the potential for brain injuries of the concussive type, produces neurological deficits. This includes, for example, studies of heading balls in soccer, playing ice hockey, wrestling, diving, or any contact sport (i.e., lacrosse). If both a direct and theoretical replication produce the same findings, we can increase our confidence in the hypotheses that link RHI with later neurocognitive deficits. Otherwise, there are too many competing explanations that have not been ruled out. These are the standards to which a single study must be held accountable. By testing an integrated model, one that includes family

factors and other baseline measures that are potential confounders, it will be possible to eliminate rival explanations and gain model precision. In the current context this means including measures of family dynamics, behavioral activity (risk taking, inhibition, and excitation), and measures of self-regulation/control, all of which should boost model precision. Importantly, failure to include relevant variables leads to model misspecification (biased parameters) and can foster erroneous conclusions. These are the required steps in normal science that can provide information as to whether repeated head trauma from contact sports like football is invariably associated with later neurological deficits.

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