Final publication is available from *Molecular Psychiatry* https://doi.org/10.1038/s41380-024-02859-0

Tempering an interpretation based on quality of data to make causal conclusions about race, inequities, and brain differences

Michael S. Scheeringa, MD

In volume 28 of this journal, Harnett et al. (2023) reported their effort to understand how structural inequities partially explain differences between racial groups on neurophysiology and brain connectivity (1). The authors' interpretation was that inequities are a form of chronic stress of structural racism which acts on human development to cause enduring brain differences. Given the strong interest in unequal treatment of races and government's history of intervening with a strong hand when justified by science, I believe this paper merits additional comment on how the findings were interpreted.

One concern is that the authors claimed that differences in baseline startle response and amygdala connectivity between Black and White participants were "race-related differences." The Black and White groups, however, were not equivalent, as Blacks were significantly worse off than Whites on four of the six measures of inequities (education, marital status, income, and a home address-based area deprivation index), and Whites scored higher than Blacks on a fifth

(total prior trauma). Because these were cross-sectional data, it is impossible to know if the brain differences in startle and connectivity were caused by race or inequities (or some other unmeasured factor). There was no effort to create subgroups that matched on inequities for a more unbiased test of race.

Another concern is that neurophysiology and connectivity differences between races were less common than the authors conveyed in the Discussion section. Hispanics, who also differed from Blacks and Whites on some of the inequity variables, failed to show differences on neurophysiology and connectivity in all seventeen tests with Blacks and all seventeen tests with Whites. This complete picture of results suggests that a causal relationship between inequities and brain differences, if there is one, is not only impossible to determine from these cross-sectional data, but appears unlikely by their own data.

Another concern is that the authors based their interpretation entirely on three tests that reached statistical significance showing inequities partially accounted for some of the brain differences, but downplayed the other thirteen tests that were non-significant. Further, the three significant tests represented only a partial accounting which was not close to being a full accounting; meaning that much, probably most, of the brain differences were not accounted for by inequities. When the overall pattern is that thirteen of sixteen tests (81%) involving inequities as explanatory variables were non-significant, and the three significant tests were weak effects, the more likely interpretation is that the three significant tests were spurious and will be nonreplicable.

Lastly, another concern is that the differences in amygdala connectivity found in Blacks compared to Whites eventually showed no functional significance in symptoms. Three months post-trauma, of the six connectivity patterns found between Blacks and Whites, only one

significantly associated with PTSD severity. At the six months assessment, this association had disappeared; further evidence that the authors' interpretation should have been more tempered.

The limitation that neurophysiology and connectivity data were cross-sectional, being collected once per subject, cannot be overemphasized. The authors did not mention this rather substantial weakness as a limitation. Instead, their interpretation was that they found evidence that the stress of chronic experiences of racism permanently changes brains. When pre-trauma prospective studies of the stress of life-threatening trauma experiences have been reviewed (and there are now more than two dozen such studies) the theory that stress changes brains has failed to find much support (2-4). There are no pre-inequity or pre-adversity prospective studies.

Overall, the types of data collected were incapable of finding race-related differences (i.e., racial groups were unequal on important variables) and were incapable of proving causal effects (i.e., cross-sectional data of neurobiology collected long after exposure events). I found it strange then when the authors only conclusion was that they had found a causal role for structural inequities to explain race-related differences. Their interpretation was not conditioned by either the potential sampling bias, or by the infrequency of significant tests, or by the cross-sectional nature of data. The authors are, of course, free to interpret their findings any way they like, but it creates the unfortunate situation that critics must bear some burden to rightly point out their absence of equipoise.

The authors did not prescribe government policies to intervene in the affairs of society, but it seems likely that their interpretation will be cited by others as evidence that inequities from structural racism cause brain damage. Similar claims about the unproven effects from other types of stress—adverse childhood experiences and toxic stress—have already been used by others as justification for misguided screening programs (5, 6) and widespread government interventions

(7). This is why we need to be rigorous in our scientific explanations of findings on this highly-charged topic. Greater effort is needed in the interpretation phase of scientific papers to convey responsibly all reasonable explanations of the data so that interventions that are implemented are the most likely to help individuals with problems.

Contributions

All contributions—conception, drafting, and editing—were from the single author MS.

Conflict of Interest Statement: Dr. Scheeringa receives royalties from Guilford Press and Central Recovery Press.

REFERENCES

1. Harnett NG, Fani N, Carter S, Sanchez LD, Rowland GE, Davie WM, et al. Structural inequities contribute to racial/ethnic differences in neurophysiological tone, but not threat reactivity, after trauma exposure. Mol Psychiatry. 2023;28:2975-84.
2. DiGangi JA, Gomez D, Mendoza L, Jason LA, Keys CB, Koenen KC. Pretrauma risk factors for posttraumatic stress disorder: A systematic review of the literature. Clin Psychol Rev. 2013;33:728-44.
3. Danese A, Moffitt TE, Arseneault L, Bleiberg BA, Dinardo PB, Gandelman SB, et al. The origins of cognitive deficits in victimized children: Implications for neuroscientists and clinicians. Am J Psychiatry. 2017;174:349-61.
4. Scheeringa MS. Reexamination of diathesis stress and neurotoxic stress theories: A qualitative review of pre-trauma neurobiology in relation to posttraumatic stress symptoms. Int J Methods Psychiatr Res. 2021;30:e1864.
5. Baldwin JR, Caspi A, Meehan AJ, Ambler A, Arseneault L, Fisher HL, et al. Population vs individual prediction of poor health from results of adverse childhood experiences screening. JAMA Pediatrics. 2023;175(4):385-93.
6. Malvaso CG, Cale J, Whitten T, Day A, singh S, Hacket L, et al. Associations between adverse childhood experiences and trauma among young people who offend: A systematic literature review. Trauma Violence Abuse. 2022;23(5):1677-94.
7. Kabir S. Gov. Josh Green declares Hawaii as a 'trauma-informed' state. Here's what that means. Island News [Internet]. 2024 February 21, 2024. Available from: https://www.kitv.com/news/local/gov-josh-green-declares-hawaii-as-a-trauma-informed-state-heres-what-that-means/article_6714c2e2-d05f-11ee-8c3e-4fb669eb737f.html.