Neurotoxicology and Teratology 52 (2015) 58–59

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Interpretation of prenatal drug exposure functional imaging data

Abbreviations:
PDE
Topic:
prenatal drug exposure

We appreciate Drs. McAllister and Hart's interest in our work examining brain imaging and behavioral functioning among adolescents who vary in prenatal drug exposure (PDE). The concerns they raised regarding the use of "pathological" terms and the comparable task performance between the two groups may reflect a misconception regarding methods used in functional neuroimaging studies. Their comments also suggest a pattern of misunderstanding regarding the role of comparison groups in studies versus the use of a standardized test for which there is a criterion for pathology (Payer et al., 2012; Richardson et al., 2015). There are several flaws in the authors' interpretation of our results and conclusions.

Most importantly, in block-design imaging studies, if the prenatally exposed and non-exposed groups demonstrate significant performance differences, it is not possible to interpret underlying neural activation differences because the groups are not similarly engaged when the imaging data are acquired. On the other hand, if the two groups have similar performances, differences in neural activation are thought to reflect neural differences in how the groups accomplish the task. In our study, we examined working memory, an area that has been identified as vulnerable among children with PDE. Performance between the groups on this relatively easy working memory task was equivalent, assuring that both groups were equally engaged and performing the task well during acquisition of the brain functioning data. We found that adolescents with PDE had altered neural functioning compared to adolescents with no PDE when performing a working memory task. Alterations in neural functioning are known to *sometimes* have functional significance and thus we referred to the differences as "altered" and commented that it may be valuable to recognize their presence in areas such as working memory, which is involved in multiple areas of daily functioning requiring learning (e.g., academics).

In our analyses of brain imaging data and behavioral functioning, we also found that the non-exposed comparison group demonstrated coupling between reaction time, intra-individual variability in reaction time, and accuracy; whereas the prenatal drug exposed group demonstrated no associations. We refer to these group level behavioral differences as "subtle" and suggest, when combined with the imaging results, that they may reflect processing differences related to PDE that should be investigated further.

Our experimental design employed a between-group contrast between a comparison group (adolescents from the same community, born in the same hospital, but who were not PDE) and those who were PDE. This design tests for differences between the groups rather than assessing for pathology. The point of the comparison group is to establish the range of variability in adolescents who are as similar as possible to the PDE group but lacking prenatal exposure to drugs of abuse.

As members of our group and others have shown (Ackerman et al., 2010; Buckingham-Howes et al., 2013), there are few performance differences that can be attributed to PDE. Thus, we stand by the language we used in our article as it reflects an appropriately cautious interpretation of the data with care taken not to consider our participants to be performing in a manner that would be described "in surprisingly pathological terms" (McAllister and Hart, 2015) for *we* do not consider their behavior to be pathological. There is emerging neuroscientific evidence from preclinical studies, along with brain imaging methods (e.g., Riggins et al., 2012) that enable investigators to examine how PDE relates to neural processing. Investigations such as ours will lead to a better understanding of how prenatal exposure relates to long-term functioning.

Finally, McAllister and Hart selected a title that is polemical in nature. We chose to reply to the scientific aspects of the comment, as is fitting for scientific discourse, rather than the provocative and inflammatory tone of the title and letter.

Funding and Disclosure

This research was funded by the National Institutes of Health grants R01 DA07432 (Nair) and R01 DA021059 (Black) and the Intramural Research Program of the NIH, NIDA. The funders had no involvement in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the manuscript for publication. The authors have no competing financial interests in relation to the work described.

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http://dx.doi.org/10.1016/j.ntt.2015.10.006

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19 September 2015