

**Prenatal androgen influences on the brain: A review, critique, and illustration of research on
congenital adrenal hyperplasia**

Beltz, Adriene; Demidenko, Michael; Wilson, Stephen; Berenbaum, Sheri

Review timeline:

Submission date: 8 December 2020

Editorial Decision: Minor Modification (14 April 2020)

Revision Received: 27 April 2021

Accepted: 20 May 2021

Editor 1: Sara Bulgheroni

Editor 2: Cristina Ghiani

Reviewer 1: Carlotta Cocchetti

1st Editorial Decision

Decision letter

Dear Dr Beltz:

Our apologies for the long wait and delay in reviewing your manuscript. We've now received the reviewer feedback and have appended those reviews below. The reviewer is overall very enthusiastic and supportive of the study, although some concerns were raised and some suggestions were made for clarification, but these points should be relatively straightforward to address. If there are any questions or points that are problematic, please feel free to contact me. I am glad to discuss.

We ask that you return your manuscript within 30 days. Please explain in your cover letter how you have changed the present version and submit a point-by-point response to the editors' and reviewers' comments. If you require longer than 30 days to make the revisions, please contact Dr Cristina Ghiani (cghiani@mednet.ucla.edu). To submit your revised manuscript: Log in by clicking on the link below <https://submission.wiley.com/submissionBoard/1/dc69810d-869a-4e55-a0a3-640d6f8ebffc/current>

(If the above link space is blank, it is because you submitted your original manuscript through our old submission site. Therefore, to return your revision, please go to our new submission site here (submission.wiley.com/jnr) and submit your revision as a new manuscript; answer yes to the question "Are you returning a revision for a manuscript originally submitted to our former submission site (ScholarOne Manuscripts)? If you indicate yes, please enter your original manuscript's Manuscript ID number in the space below" and including your original submission's Manuscript ID number (jnr-2020-Dec-9295) where indicated. This will help us to link your revision to your original submission.)

The journal has adopted the "Expects Data" data sharing policy, which states that all original articles and reviews must include a Data Availability Statement (DAS). Please see <https://authorservices.wiley.com/author-resources/Journal-Authors/open-access/data-sharing-citation/data-sharing-policy.html#standardtemplates> for examples of an appropriate DAS. Please include the DAS in the manuscript as well.

Thank you again for your submission to the Journal of Neuroscience Research; we look forward to reading your revised manuscript.

Best Wishes,

Dr Sara Bulgheroni
Associate Editor, Journal of Neuroscience Research

Dr Cristina Ghiani
Editor-in-Chief, Journal of Neuroscience Research

Editors Comments to the Author:

The review is over the word limit for a mini review, it would be best if the authors could just change the type of article to review.

Can you please explain what is the meaning of 'gendered behavior' in the first sentence of the introduction? Please make sure not to use gender and sex as interchangeable.

Reviewer: 1

Comments to the Author

Dear editors, thank you for offering me this great opportunity to be a reviewer of this paper named 'Prenatal hormone influences on the brain: a review, critique and illustration'. The manuscript describes how prenatal androgens exposure affects human behavior in the context of congenital adrenal hyperplasia (CAH) and illustrates pilot data on neural integration underlying reward processing in women with CAH vs. their sisters. The pilot study results are really interesting and the review is overall well written and easy to follow.

Based on my perception, the manuscript should be accepted after minor revision:

Comments:

Title

Since both the review part and the pilot data focus on CAH or – more generally – DSD, I think you should underline this aspect in the title.

General considerations

- The Authors should specify in the whole text/abstract that this is a narrative review
- Perhaps, considering that the review section represents a large part of the manuscript, Authors should consider adding a section on research methods.
- The review would benefit of a table summarizing evidence for prenatal androgen effects on brain structure, function and behavior.

Review part

Page 5 line 31 (and in the whole text): I don't like the term "natural experiments" very much. Maybe you could use "clinical models"

Page 6 line 6: delete "present"

Page 6 line 22: among those factors, you should at least cite social and cultural influences

Page 6 line 50: "measured" instead of "obtained"?

Page 7 "indirect indicators of prenatal hormones" subparagraph: I think you should at least cite otoacoustic emission

Page 7 lines 47-49: with regards to gender identity development, more recent manuscripts summarizing sex hormones role should be considered (i.e. doi: 10.3390/ijms21062123).

Page 8 line 29: there's a typo "studied" instead of "studies"

Page 8 line 31: maybe "apart from" could be better than "not"

Illustration part

- Which are the inclusion and exclusion criteria of the study? Please, specify.
- Limitations of the study need to be implemented in the text
- Page 20 lines 24-38: the sentence is too long, please modify

Authors' Response

Thank you to the editors for facilitating the review of our manuscript, and to the reviewer for their helpful comments. Below, we have responded to each comment (restated in *italics*), and we have indicated pages in the manuscript that reflect the corresponding changes, which are shown in **red font**. We are grateful for this feedback; it has improved our manuscript.

Editor

1. The review is over the word limit for a mini review, it would be best if the authors could just change the type of article to review.

Thank you for your flexibility concerning the word limit. We have selected the "review" article type when submitting our revision.

2. Can you please explain what is the meaning of 'gendered behavior' in the first sentence of the

introduction? Please make sure not to use gender and sex as interchangeable.

Thank you for this important question and recommendation. By “gendered behavior” we mean robust sex differences in behaviors that are linked to the nature of differences between males and females. We now clarify this in the text (p. 4). We also note that the manuscript does not follow a popular distinction between biological (i.e., “sex”) and sociocultural (i.e., “gender”) influences, as causes of many gendered behaviors are not yet known. Instead, we use “sex” when referring to male and female categories, and “gender” when referring to judgments about the nature of those categories (e.g., as in gender identity). We have modified the manuscript accordingly (e.g., Abstract and p. 4).

Reviewer 1

Dear editors, thank you for offering me this great opportunity to be a reviewer of this paper named ‘Prenatal hormone influences on the brain: a review, critique and illustration’. The manuscript describes how prenatal androgens exposure affects human behavior in the context of congenital adrenal hyperplasia (CAH) and illustrates pilot data on neural integration underlying reward processing in women with CAH vs. their sisters. The pilot study results are really interesting and the review is overall well written and easy to follow. Based on my perception, the manuscript should be accepted after minor revision.

Thank you for positive assessment of our work! We really appreciate all of your thoughtful recommendations, and we hope that the changes we have made improve the manuscript.

1. Since both the review part and the pilot data focus on CAH or – more generally – DSD, I think you should underline this aspect in the title.

Thank you for this suggestion. We have consequentially changed the title to “Prenatal androgen influences on the brain: A review, critique, and illustration of research on congenital adrenal hyperplasia.”

2. The Authors should specify in the whole text/abstract that this is a narrative review.

We now state this throughout the manuscript, including in the Abstract and Significance Statement (see pp. 5 & 21).

3. Perhaps, considering that the review section represents a large part of the manuscript, Authors should consider adding a section on research methods.

Thank you for this suggestion. Because this was not a systematic review of prenatal androgen influences on the brain, we do not describe study inclusion methods in detail. We do note, however, key limitations of our review (e.g., that we did not include many early studies with low statistical power or that used indicators of prenatal androgen exposure beyond CAH and CAIS diagnoses (p. 9). Thus, we appreciate your suggestions for conveying the scope of our paper to readers, by explicitly stating that we are conducting a narrative review (comment #2 above) and mentioning congenital adrenal hyperplasia in the title (comment #1 above).

4. The review would benefit of a table summarizing evidence for prenatal androgen effects on brain structure, function and behavior.

Thank you for this suggestion. We considered it carefully, and ultimately, decided to forgo a table or figure. The details that would be included in a table were already covered quite extensively in the manuscript text. Although a figure would succinctly summarize evidence for prenatal androgen effects on brain structure and function, the entire point of our paper is that most studies on this topic do not actually permit inferences about prenatal androgens due to disease or other (e.g., developmental or behavioral) confounds, and thus, a figure would likely be misleading.

5. Page 5 line 31 (and in the whole text): I don’t like the term “natural experiments” very

much. Maybe you could use “clinical models”.

We appreciate this point and spent considerable time and energy thinking about it. Scientifically, CAH is a natural experiment, and we would like to emphasize the importance of natural experiments in neuroscience, as we have done in other work on puberty, the menstrual cycle, hormonal contraceptive use, menopause, and menopausal hormone therapy (see Beltz & Moser, 2020 cited in text). We tried the term “clinical models” but that seemed to suggest the presence of some controlled manipulation. Our experience speaking with people with CAH and their families suggests that most understand our use of the term, but we have nonetheless, reworded some areas of the paper to reduce our mention of “experiments” (e.g., p. 6).

6. Page 6 line 6: delete “present”.

We changed “present” to “influences” to clarify our meaning (p. 6).

7. Page 6 line 22: among those factors, you should at least cite social and cultural influences.

Thank you for this comment. We now state that females with CAH and CAIS could differ from comparison groups for combined biological and sociocultural reasons (p. 6).

8. Page 6 line 50: “measured” instead of “obtained”?

Given how amniocentesis is performed, we elected to maintain our use of “obtained”.

9. Page 7 “indirect indicators of prenatal hormones” subparagraph: I think you should at least cite otoacoustic emission.

Thank you for this comment. We initially highlighted the two most widely-used indirect indicators of prenatal androgen exposure, but at your suggestion, we now mention others (with references) that have their own sets of limitations, including otoacoustic emissions and anogenital distance (pp. 7-8).

10. Page 7 lines 47-49: with regards to gender identity development, more recent manuscripts summarizing sex hormones role should be considered (i.e. doi: 10.3390/ijms21062123).

Thank you for this suggestion. This is an interesting article, but we ultimately elected not to cite it because some of the claims (e.g., regarding neural sexual dimorphism) are inconsistent with the extant literature and with the position we take in this paper (e.g., sex differences as averages that are influenced by prenatal androgen exposure).

11. Page 8 line 29: there’s a typo “studied” instead of “studies”.

Thank you for pointing this out. We have corrected this typo and carefully reviewed the manuscript for potential others (p. 9).

12. Page 8 line 31: maybe “apart from” could be better than “not”.

We have made this change (p. 9).

13. Which are the inclusion and exclusion criteria of the study? Please, specify.

Thank you for asking this important question. We now clarify that participants were drawn from a larger behavioral study of individuals with CAH and their siblings, and they were invited to enroll in neuroimaging if they were at least 18 years old and had a sibling who was also willing to participate (p. 16).

14. Limitations of the study need to be implemented in the text.

Thank you for highlighting this oversight. We now consider some limitations of the empirical illustration, such as the lack of a male subsample and *a priori* region of interest selection required by the network mapping approach (pp. 20-21).

15. Page 20 lines 24-38: the sentence is too long, please modify.

Thank you for this pointing this out. We have revised this section of the Conclusions (p. 21).

2nd Editorial Decision

Decision Letter

Dear Dr Beltz:

We are pleased to inform you that your manuscript has been accepted for publication. Thank you for submitting this excellent work to our journal.

In the coming weeks, the Production Department will contact you regarding a copyright transfer agreement and they will then send an electronic proof file of your article to you for your review and approval.

Please note that your article cannot be published until the publisher has received the appropriate signed license agreement. Within the next few days, the corresponding author will receive an email from Wiley's Author Services asking them to log in. There, they will be presented with the appropriate license for completion. Additional information can be found at <https://authorservices.wiley.com/author-resources/Journal-Authors/licensing-open-access/index.html>

Would you be interested in publishing your proven experimental method as a detailed step-by-step protocol? Current Protocols in Neuroscience welcomes proposals from prospective authors to disseminate their experimental methodology in the rapidly evolving field of neuroscience. Please submit your proposal here: <https://currentprotocols.onlinelibrary.wiley.com/hub/submitproposal>

Congratulations on your results, and thank you for choosing the Journal of Neuroscience Research for publishing your work. I hope you will consider us for the publication of your future manuscripts.

Sincerely,

Dr Sara Bulgheroni
Associate Editor, Journal of Neuroscience Research

Dr Cristina Ghiani
Editor-in-Chief, Journal of Neuroscience Research

Reviewer: 1

Comments to the Author

The Authors replied satisfactorily to my comments, thus in my opinion the manuscript should be accepted in its current form.

Authors' Response

3rd Editorial Decision

Decision Letter

Authors' Response

4th editorial decision

Decision Letter

Author response