Title: Neurodevelopmental profile of Fetal Alcohol Spectrum Disorder: A systematic review

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Version: 2 Date: 18 May 2017

Author’s response to reviews:

Response to Reviewers’ Comments

Reviewer reports:

Heather Carmichael Olson (Reviewer 1): This systematic review focuses on finding, evaluating and discussing the existing literature aimed at identifying a behavioral phenotype of the set of conditions termed FASD. This is a worthy goal. From a large number of peer-reviewed studies, the few studies that evaluated the classification function of an identified neurodevelopmental profile were included. Findings were that two approaches have been taken to this research question, including: (1) studies that used subsets of norm-referenced caregiver ratings of child behavior; and (2) selected subtest scores from standardized test batteries assessing wide-ranging neurodevelopmental domains. The authors deemed both approaches as promising, though the current reviewer notes that neither approach consistently pairs both good specificity with good sensitivity. Conclusions were that research in this area is limited and that a profile of FASD has not yet been established. The authors provide a set of recommendations for future research.

This manuscript is very well-written, leading the reader through an explanation of what is a complex scientific problem and relevant research findings in an understandable manner. The literature search was comprehensive (even including all publication languages and a manual review of content page in major journals covering neurodevelopmental disorders). A surprisingly small number of studies meeting criteria of the review protocol were identified (N=9), with only a few investigators attempting to accomplish this challenging research aim, which is an interesting finding in itself. Results of these fairly small but programmatic research efforts are described logically and with clarity, and study limitations are highlighted and explained. Table 2 is especially helpful in summarizing the NST data, and Tables 3 through 5 useful in summarizing test scores used in the test battery approach. The conclusion is drawn that
the NST should still be considered in the validation stage and is intended for screening purposes, a cautious interpretation which seems quite accurate. What is known about the use of the BRIEF for this classification purpose is interpreted as in the exploratory stages, again an appropriately cautious interpretation. Limitations of the several attempts so far to use standardized test batteries to define a neurodevelopmental profile are carefully pointed out.

Author's Response:

Thank you.

It is quite useful that the authors clearly point out the diagnostic systems or PAE criteria used in most of the studies. The systems utilized in the reviewed studies range from the 2005 version of the Canadian guidelines, the 4-Digit Diagnostic Code, a definition of PAE in the Nguyen et al. study, to an almost identical definition of PAE as that used by Nguyen coupled with subsequent physical characteristics criteria used by Mattson and colleagues. (To be complete, it is recommended that the authors also mention the diagnostic code or method used to define FASD in the Haynes et al. study.) The authors also mention the important point that the classification of individuals in the Mattson et al. programmatic research is not reflective of how FAS is classified elsewhere.

Author's Response:

Thank you. We have now specified that they children with FASD in were “diagnosed according to either the 2005 Canadian diagnostic guidelines [1] or the 4-Digit Diagnostic Code [25]” (pg.13).

But the authors do not raise and discuss the vital issue that the use of these different methods of diagnosing FAS, conditions under the umbrella term of FASD, or particular levels of PAE mean that the screening tools being evaluated are, de facto, aimed at classifying different groups of affected individuals. This means that the problem of identifying the neurodevelopmental profile of FASD goes well beyond the challenges of the sensitivity and specificity of different tools, or even the issues currently raised in the Discussion section. It seems crucial for the authors to comment on how their findings may be impacted by: (1) the recent Coles et al. findings that different FASD diagnostic systems may be identifying different groups of affected individuals; and (2) the fact that classifying individuals based on PAE alone, or on PAE plus physical characteristics, will generate different groups than classifying individuals based on a defined diagnostic system. In addition to commentary on this issue, a recommendation in the Discussion section about resolving this thorny issue seems necessary.

Author's Response:
We have now added the following paragraph to the Discussion section (pg. 20-21): “It should also be recognized that the studies reviewed used different diagnostic guidelines for ascertaining cases of FASD. Given that it was recently reported that existing FASD diagnostic guidelines lack convergent validity and are limited in their concordance with respect to the specific diagnostic entities [34], the consequence of this variation is that the profiles are essentially classifying different groups of affected individuals. Thus, the only conceivable way to resolve this issue is for a standardized common diagnostic approach to be developed and widely accepted. Only then will we be able to identify whether a neurodevelopmental profile of FASD exists, and truly assess its classification function.”

There are a few other issues that the authors might clarify to enhance the manuscript. The authors characterize lower levels of specificity or sensitivity as "varying," rather than pointing out that some of the levels found are quite low— for instance, the NST has been found in some studies to have a rather low level of probability of correctly identifying individuals who do not have the condition. The current reviewer is not a psychometrics expert… but might it be useful to compute the confidence intervals for sensitivity and specificity, at least for the programmatic research on the NST, to better characterize the state of the data?

Author's Response :

We have added the caveat that some estimates are “unfavorably low” (pg. 13). Further, we have now added that “In order to estimate the level of uncertainty surrounding the classification estimates, exact 95% confidence intervals (CI) were estimated using a binomial distribution” to the Methods (pg. 8). Accordingly, we have added the respective CI throughout the paper and in Table 2.

Besides the major missing recommendation about how to handle the use of different diagnostic systems/PAE criteria, the authors do a good job of making recommendations for improving the literature. A minor point is that the seventh recommendation in the Discussion section is unclear. What specifically do the authors mean by exploring the possible heritability of some of the neurodevelopmental symptoms attributed to PAE?

Author's Response :

We have now clarified this sentence (pg. 22): “Seventh is the possibility that some of the associated neurodevelopmental symptoms were inherited from parents (e.g., a math disability) and not strictly attributable to the prenatal alcohol exposure.”
Also, the eighth recommendation may beg the question of whether it is even possible to identify and validate a neurodevelopmental profile of FASD. If the authors believe that finding a behavioral phenotype (at least for screening purposes) is achievable, what practical steps do they suggest to accomplish this eighth goal (and the sixth goal)? Are the authors suggesting big data strategies, where very large groups of individuals are brought together and identified using a common diagnostic system (or at least with data available so they are classifiable according to several different, well-defined, reproducible diagnostic systems)... and then neurodevelopmental profiles are examined with statistical adjustment for adverse prenatal and postnatal experiences... and divided into subgroups depending on dosage and timing of exposure, and genetic factors/differences in fetal susceptibility? The current reviewer is very interested in the practical recommendations the authors would make for concrete steps to establish at least a usable screening tool for FASD.

Author's Response:

It is certainly possible that a pathognomonic neurodevelopmental profile of FASD does not exist. We have added the following sentence to the Discussion (pg. 22-23) to attest to this: “However, given that the outcomes of prenatal alcohol exposure depend on a number of factors (e.g., genetics, health, alcohol metabolism, polisubstance exposure, timing of exposure [39-41]), as well as the fact that FASD is associated with multiple comorbid mental disorders [42-44], it should be acknowledged that FASD may in fact have a complex phenotype and a pathognomonic neurodevelopmental profile of FASD may not exist. It is possible that FASD has a pleiotropic phenotype (i.e., one cause (prenatal alcohol exposure) results in many outcomes); if this is the case it will negate the existence of a neurodevelopmental profile unique to those with FASD.”

We have now also added the following practical recommendation for achieving the areas of future research on pg. 22: “It is likely that many of these areas of future research will only be achievable if and when large detailed datasets are developed containing data on individuals with FASD diagnosed using a common diagnostic guideline, which will allow for certain variables (e.g., experience of postnatal adversities) to be controlled for.”

Larry Burd (Reviewer 2): The manuscript examines existing data to determine if FASD has a signature neurocognitive presentation. This is an interesting idea since neurobehavioral impairments are the unifying criterion across all FASD categorical diagnoses. I exclude ARBD since it is almost never diagnosed.

Page 5, 36-46 this is commonly stated but it's unclear to me what this means. Dubowitz Syndrome is mistaken for FASD? This must be exceptionally rare since the conditions the authors list are uncommon. In my experience the opposite is much more common. FASD is
rarely diagnosed and is misdiagnosed in about 85% of cases. ARND is the most frequently misdiagnosed of the FASD. Lastly, why would a diagnosis of Cornelia de Lange exclude prenatal alcohol exposure and the neurocognitive effects of PAE supporting a diagnosis of FASD? So would not the most common diagnosis be both? PAE and FASD present similar problems for ADHD, ODD and CD. It seems likely the PAE/FASD are the most common causes of ADHD, ODD, psychosis etc in childhood. So it seems to me that again the issue is that FASD is the diagnosis that is most often missed. ADHD and ODD may be diagnosed but FASD is almost never diagnosed. As above it seems to me that it is not FASD or ADHD but very likely both. This is true for intellectual disability and several other common diagnoses as well. I am curious about the author's thoughts on these issues.

Author's Response:

The intention of this paragraph is to demonstrate that FASD is often misdiagnosed – we have now reworded this paragraph to make this point clearer (pg. 5): “Further, coupled with the fact that the signs of such things as traumatic head injury and intellectual disability where the etiological cause is not prenatal alcohol exposure are mimicked by FASD, the diagnostic criteria of FASD may also overlap with other neurodevelopmental disorders such as Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD) [15]. As a result, individuals with FASD often receive multiple diagnoses before actually being assessed for and diagnosed with FASD [16].”

Methods

The search expertise of this research group is state of the art. The inclusion and exclusion criteria are clear.

Author's Response:

Thank you.

Results

The breakdown of behavioral observations is very useful. We do not currently have biomarkers for most of these entities or diagnoses. So observational data is the best we have. We also utilize neuropsychological testing. This is an area with multiple problems:

1. Many of the measures were developed for another purpose and have no norms relates to PAE or FASD.

2. The differences between head injury and FASD etc often have significant overlap.
3. The population norms for many of these tools are inadequate. Caucasians in the normative sample are very often part Hispanic, African American or American Indian.

4. Similarly, the ethnic racial populations are also often mixed. This is one of the overlooked features of normative data for facial features lip/philtrum palpebral fissure length etc. If the child is 40% Caucasian and 50% African American and 10% Hispanic why do we suggest using a 100% norm for African Americans to determine the correct facial feature measures for a child.

5. The rating scales often do not result in a diagnosis.

Author's Response:

We have now added the following sentences to the Discussion (pg. 19-20): “Although a biomarker would be the most ideal method for diagnosing cases of FASD, at this time observational data and neurodevelopmental testing are the most appropriate tools.” And “Nevertheless, studies utilizing observational and/or neurodevelopmental data to identify the presence of a unique neurodevelopmental profile of FASD are not without their limitations (e.g., confounding, and a lack of normative data with respect to FASD and mixed racial groups).”

When calculating sensitivity and specificity we might want to begin with what we know. First PAE is underreported by 25 to 50%. Thus we classify these cases as unexposed. This dramatically effects calculations of sensitivity, specificity accuracy and positive and negative likelihood ratios. So it may be that PAE and FASD have much more robust adverse effects than we currently appreciate. Secondly, on page 14 heavy exposure to alcohol in one study is defined as 4 or more drinks per occasion etc. This seems to me to be very modest levels of exposure. If one looks at the minimum levels of cumulative exposure these criteria produce PAE is very toxic. I think most FASD clinics see mostly children with exposure levels many times higher than this.

Author's Response:

We have now added the following sentences to the Discussion (pg. 21) acknowledging that: “Further, given the stigmatization associated with alcohol use during pregnancy and the increased likelihood of underreporting [35], it is possible that the comparison groups of typically developing control children used in the studies reviewed may contain some children prenatally exposed to alcohol, which is possible for example in studies of Mattson and colleagues [29,30] given their definition of prenatal alcohol exposure. Consequently, the classification function of a particular profile could in fact be more robust than observed.”
On page 14, the definition of prenatal alcohol exposure is in fact “at least four drinks per occasion at least once per week or at least 14 drinks per week during pregnancy”, which is considered significant.

Page 16 lines 36-41. Is FASD a cause of ADHD? If somewhere around 50% of people with FASD have ADHD, it seems it must be a very common cause of ADHD. How does this analysis work if that is correct?

Author's Response:

We have now specified that the ADHD comparison group “were not exposed to alcohol prenatally (as per the definition of prenatal alcohol exposure used by the authors)” (pg. 17).

Discussion

I think the authors have an admirable goal here. What do we know about the expression of FASD? Does FASD have a phenotype(s) that are detectable?

Three studies might help. The first is by Burd et al. in 2003 in Neurotoxicology and Teratology, followed by a related study in 2010 in Alcohol also by Burd et al., and a third by Berg et al. These studies examined comparisons across FASD diagnostic schema. The results suggest very modest rates of agreement even for FAS and Partial FAS. The ARND numbers are very low so comparisons are difficult. However, what this suggests is that a narrow or distinctive phenotype for FASD has yet to be achieved.

Author's Response:

We have added the following sentence to the Discussion (pg. 22): “… as well as the fact that FASD is associated with multiple comorbid mental disorders [42-44], it should be acknowledged that FASD may in fact have a complex phenotype and a pathognomonic neurodevelopmental profile of FASD may not exist”

Two relevant points for the authors to consider. In previous publications by this group they demonstrated that prenatal alcohol exposure is associated with extremely broad phenotypic presentation comprised of several hundred comorbid conditions. Some might be due to chance alone. Some are almost certainly due to PAE (ADHD, intellectual disability, vision disorders etc). The key is if PAE is present these conditions are likely due to PAE. If no PAE is reported the conditions could be due to other causes. Even then misclassification of PAE is likely very common. What is the potential phenotypic signature from PAE or the presence of FASD? It's
difficult to imagine how this could be identified since the outcomes from PAE depend on maternal (genetics, health, alcohol metabolism, polysubstance exposure) and the fetal risk is from (generational effects of exposure, epigenetic factors from either the father or mother, fetal exposure(s), fetal susceptibility or protective factors, timing of exposure) and our ability to appreciate (detect and or diagnose) the consequences of exposure. It could be that if the brain can do it or suffer from it PAE might cause it, make it worse or lower the threshold for expression of the condition. If this is the case then FASD is a pleitropic phenotype (one cause (PAE) = many outcomes (growth impairment, abnormal facial features, visual impairments, ADHD, intellectual disability) etc. Conversely, if FASD is a canalized disorder every feature of FASD has many causes (ADHD is caused by genetics, PAE, smoking, postnatal environmental adversity) then the phenomic presentation is complex and a useful behavioral signature is less likely.

Author's Response:

We have now added the following paragraph to the Discussion (pg. 22-23): “However, given that the outcomes of prenatal alcohol exposure depend on a number of factors (e.g., genetics, health, alcohol metabolism, polysubstance exposure, timing of exposure [39-41]), as well as the fact that FASD is associated with multiple comorbid mental disorders [42-44], it should be acknowledged that FASD may in fact have a complex phenotype and a pathognomonic neurodevelopmental profile of FASD may not exist. It is possible that FASD has a pleiotropic phenotype (i.e., one cause (prenatal alcohol exposure) results in many outcomes); if this is the case it will negate the existence of a neurodevelopmental profile unique to those with FASD.”

Currently the data suggests that FASD has a mostly a pleotropic phenotype. Where PAE or FASD is present they are likely to be an important element of an epidemiological causal chain. And if they are removed from the causal chain the disorder is much less likely to be present.

I have provided a several discussion items the authors should feel free to include any that they feel are relevant and also to ignore any that are not relevant.

Author's Response:

Thank you. We have added a number of your suggested items to the Discussion (see above).

This work is currently identifying strengths and limitations and importantly offering guidance and methods to improve future research in this area. This is emerging science for a common condition as a result its important.

Author's Response:

Thank you.