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Journal of neuroscience research policy on addressing sex as a biological variable: Comments, clarifications, and elaborations

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Dear Dr. Prager,

We would like to offer constructive commentary on the recent announcement of the new editorial policy for JNR, “requiring all authors to ensure proper consideration of sex as a biological variable.” The requirement to justify any failure to use data from both sexes where appropriate (ref: policy point 1) is a welcome step forward from current practice. We wholeheartedly concur with the need to move away from the “still overriding reliance on the male as equal proxy for the female”. Similarly, clear indication of the cohort size for each group (ref: policy point 2) will enable informed assessment of the significance (statistical and otherwise) of the data reported, while a focus on “experiments involving both female and male subjects studied at the same time, and with sufficient sample size to ensure meaningful statistical comparisons” (ref: policy point 3) should ensure great improvements in the quality of the research canon in this field. We appreciate that this policy is in addition to the Transparent Science Questionnaire for Authors (TSQ) and the Original Research Questionnaire (ORQ) being developed in parallel.

There are, however, some caveats to which we would like to draw attention, as well as some additional steps that would strengthen the policy and could widen its impact. These provisos are particularly relevant where the focus of sex/gender research is on human participants.

In order for the proliferation of data derived from group-level comparisons (i.e., between females and males, ref. policy points 3 and 5) to be productive and not misleading, several insights and practices, from study design to reporting and interpretation of results, are critical:

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- a. Many variables correlate with sex category, from level of ‘sex’ hormones, through body weight and muscle mass, to human-specific variables such as socioeconomic and educational status or gender-typically reinforced skills in cognition and behaviour (e.g. mental rotation versus empathy). Thus, key variables or ‘influences’ that may be relevant for understanding the study’s dependent measures should be identified, recorded and analysed, in order to ensure control of co- or potentially confounding variables (Rippon et al. 2014; Joel & Fausto-Sterling, 2016). While this is a focus of both the TSQ (e.g. points 2 a, c; 3a) and the ORQ (e.g. Qs 5,6,7), these checklist items are mainly concerned with variables of relevance to the study of non-human animals, and may be more relevant to clinical trials and research. Where the research concerns the study of humans, the potential influences of wide-ranging sources of variation should be considered and assessed (Joel and McCarthy, 2016). Variation in these additional variables could be analysed using more complex statistical techniques (such as ANCOVA) in an attempt to unravel the direct effects of sex. Alternatively, the relations between these variables and the dependent measures may be studied via multiple regression techniques or equivalent, in order to assess the separate contributions of those variables correlating with sex category to the variability in the dependent measures. However, given the incompleteness of this exercise when it comes to humans, the potential role of unmeasured variables should be acknowledged in the discussion of research findings. We are pleased to see that, in response to this suggestion, the ORQ now incorporates a request to reviewers to include such commentary (Q.10).
- b. When reporting significant differences, effect sizes and confidence intervals should always be stated. Given potential issues of sample size of relevance to this

research sphere, a recommendation to report and depict in figures standard deviations rather than standard errors would be appropriate. It should be noted that this would be in addition to the reporting requirements re statistical analyses indicated in the ORQ (Q8) and the TRQ (Section 5). As indicated in a previous JNR Editorial on *Transparent Reporting for Reproducible Science*, detailed data reporting and depiction are key factors in scientific quality. With respect to the reporting of sex/gender differences, the issue of overlap between groups is core to better appreciation of the practical and theoretical significance of the results (Rippon et al, 2014; Fine & Fidler, 2015).

- c. Failure to find or replicate expected differences should be discussed, and similarities as well as differences should be reported (for a statistical tool for reporting similarities, see the Index of Similarity, Nelson 2015).
- d. In interpreting findings of sex differences, care should be taken *not* to make inferences about the differences being pre-programmed, context-independent, persistent, or generalizable to additional strains and species, unless the study explicitly included the relevant conditions/manipulations needed to make such claims (Joel & McCarthy, 2016). This would obviously intersect with point a) above. We note Point 7 in the TRQ, and are concerned that explicit requests to comment on ‘possible translational implications’ should be tempered by reference to consideration of correlated and/or confounding variables (perhaps by adapting Q.11b in the ORQ). Context and history is especially critical with respect to research with humans, and the need to reflect psychological and sociocultural factors should be an explicit consideration in research design and interpretation. Such issues have been addressed in published guidelines in neuroimaging research (Rippon et al, 2014) and, as a reflection of the timeliness of JNR’s policy

announcement, debated in a recent issue of the *Journal of Neuroscience* (Eliot & Richardson, 2016; Shanksy & Woolley, 2016).

We are also concerned by the encouragement of post-hoc exploratory analyses of “potential sex differences in studies not explicitly designed to study them” (ref: policy points 4 and 5). In such studies, it is unlikely that the participant cohort will have been selected to appropriately control other relevant co-variables (see comment in point a) above). Sample size may also be an issue, but, in any event, the issue of sufficient power would be secondary to the problems of cohort selection. For example, it is now possible to access large shared neuroimaging datasets to carry out exploratory analyses of sex differences but, in the absence of appropriate additional demographic information, conclusions about such differences should be viewed with caution (Biswal et al, 2010; Rippon, 2016). Thus the reliability and validity of the outcome of any post-hoc statistical comparison must be questionable. We also note that the policy itself rightly makes reference to the problem of false positive errors. As behavioural science is currently addressing a ‘replication crisis’ associated with methodological issues including post-hoc analyses (Simmons et al, 2011; OSC, 2012) and an increasingly popular solution to such issues is the pre-registration of protocols (Wagenmakers et al, 2012), the encouragement of post-hoc exploratory analyses seems contradictory to this important endeavour.

We also note that all of the above recommendations (a-d) are broadly based on the assumption that ‘sex’ can be considered a cleanly binary and independent variable. However, there is evidence that, from the fundamental biological level (Fausto-Sterling, 2000; Ainsworth, 2015; Richardson, 2013) to the brain (Joel et al, 2015) and behaviour (Reis and Carothers, 2014), it is a mistake to think of sex in this simple categorical fashion. Indeed, the

editor of the special issue explicitly makes reference to considering sex ‘influences’ rather than ‘differences’. This has the potential to change the whole landscape of design, analysis and interpretation in this area. Many other areas of science have moved on from simple difference analysis and offer much more nuanced insights into the interplay between different variables, with appropriate adjustments to the sophistication of their data analyses (Warner, 2012; Andrews and Baguley, 2013). Again, JNR could take the lead by noting this development and encouraging their authors to take a similar approach, designing, analysing and reporting their research accordingly, in order to maximise the gains and reduce the risk of a focus solely on sex category and the loss of information on the underlying sources of variability. Where it is felt that such high order multivariate analyses would be pragmatically difficult (perhaps because of the implications for sample sizes and experimental design changes) then this rationale should be clarified via the TRQ.

In addition we would like to note the following as an extension to JNR’s policy. The focus of the JNR policy is rightly on the design and analysis of sex-based research studies submitted to the journal for publication. However, an increasing concern is the inaccurate public dissemination of such research when published (Fine, 2010; Maney, 2014; O’Connor and Joffe, 2014). JNR could take the lead in this aspect of science communication by encouraging or even mandating the responsible use of language in the text itself and any associated press releases. Authors should be advised against the use of terms like ‘profound’, ‘fundamental’, and ‘essential’ in their titles and abstracts when the text reports findings of differences that are small and/or might only have been found in a minority of possible comparisons. Authors should also be encouraged to consider the appropriateness – and evidence for – inferences to function from structure (Fine, 2010), and the limits of generalizability between species (Eliot & Richardson, 2016). We acknowledge that such issues should generally be considered in the

normal course of review, but note that such scientifically unjustified language and claims have been particularly evidenced in this research sphere (O'Connor and Joffe, 2014).

We offer these comments on JNR's timely new policy in the spirit of ensuring that this 'zeitgeist shift' has the strong, powerful, and positive influence that is needed. As noted by the journal editor and the editor of the special issue, it is fundamentally important that research in this area is carried out; it is equally important that it is done well. We have referenced summaries of pitfalls to avoid (e.g. Maney et al 2016), suggested considerations for designs and research strategies (Rippon et al, 2014), conceptual tools for thinking about sex differences (Joel & McCarthy, 2016), and important issues relating to interpretation, particularly in press releases (Maney et al, 2014). We are delighted to note that, in response to submission of this letter, some of the above suggestions have already been incorporated into this particular editorial policy and we hope that the publication of this letter will encourage further steps to improve and strengthen the research and publication practices associated with the investigation of "sex as a biological variable."

Sincerely,

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