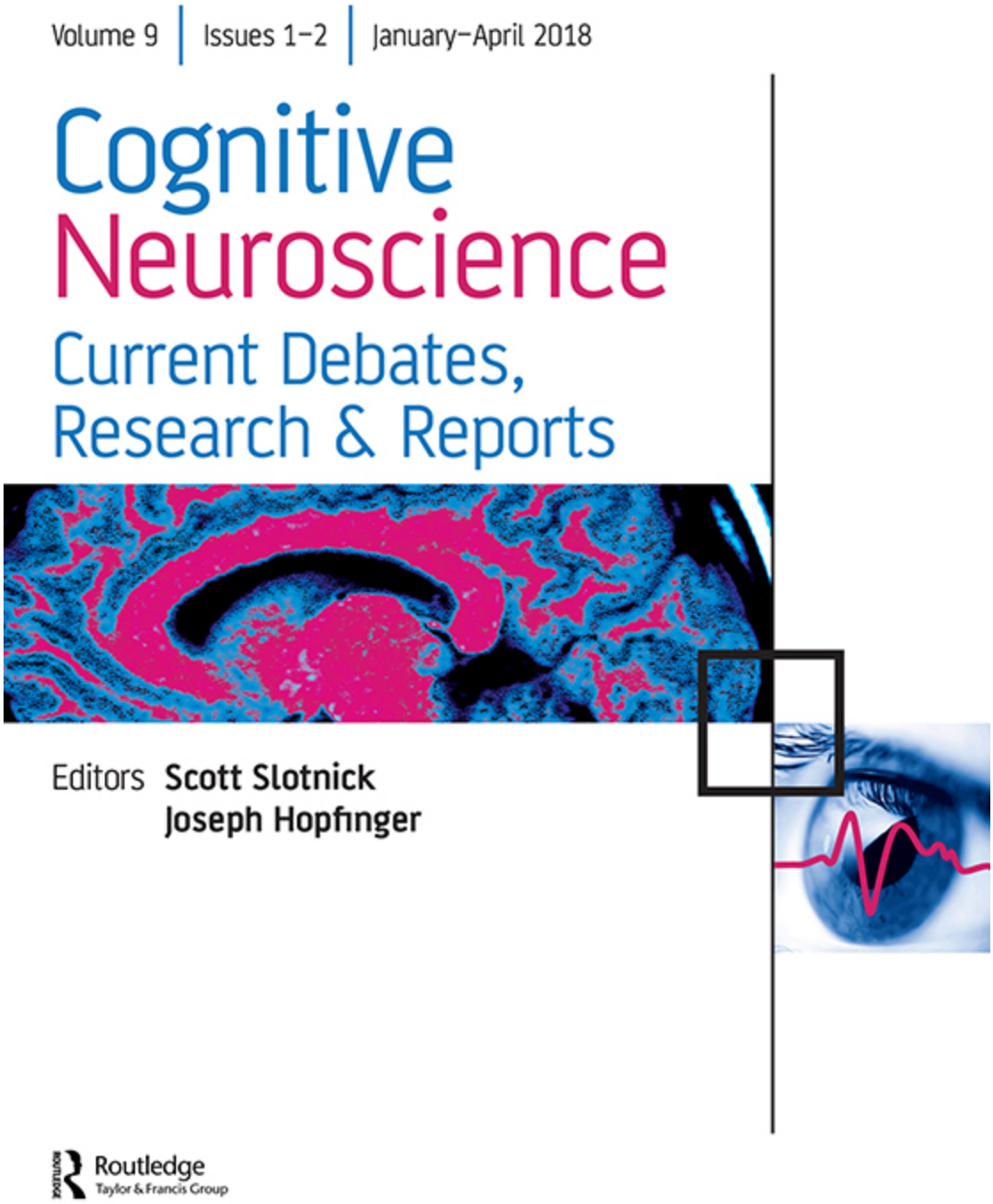

Sex differences in the brain: More than just male or female

Journal:	*Cognitive Neuroscience*

Manuscript ID	Draft
Manuscript Type:	Commentary
Date Submitted by the Author:	n/a
Complete List of Authors:	Wiersch, Lisa; Research Centre Jülich, INM-7 Weis, Susanne; Research Centre Jülich, INM-7
Keywords:	sex differences, functional MRI, ALE

Sex differences in the brain: More than just male or female

Commentary on: "Are there sex differences in brain activity during long-term memory?" by Dylan Spets and Scott Slotnick.

Lisa Wiersch[1,2] & Susanne Weis[1,2]

[1]Institute of Systems Neuroscience, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.

[2]Institute of Neuroscience and Medicine, Brain & Behaviour (INM-7), Research Centre Jülich, Jülich, Germany.

Corresponding author:

Susanne Weis

Institute of Systems Neuroscience
Medical Faculty
Heinrich Heine University Düsseldorf
Düsseldorf, Germany

Institute of Neuroscience and Medicine
Brain & Behaviour (INM-7)
Research Centre Jülich
Jülich, Germany

Tel: +49 2461 61 8609
Fax: +49 2461 61-1880
Email: S.Weis@fz-juelich.de
ORCID: https://orcid.org/0000-0001-7726-6470

Sex differences in the brain are widely studied, but results are often inconsistent and it is assumed that many negative findings are not even being reported. The lack of consistent findings might be based on the highly questionable assumption of a clear-cut sexual dimorphism in brain structure and function, that underlies commonly used group comparisons between males and females. Without having to rely on this assumption, state of the art statistical learning methods based on large neuroimaging data sets might offer the tools necessary to disentangle the complex pattern of sex related variations in brain structure and organization.

Employing a qualitative review and an activation likelihood estimation (ALE) meta-analysis of eight functional magnetic resonance imaging (fMRI) papers, Spets and Slotnick claim to have identified compelling evidence for substantial sex differences in brain activity during long-term memory retrieval. Unfortunately, their methodological approach is questionable. In an era of very large-scale neuroimaging (e.g. > 5000 subjects in [1]), all studies included in their meta-analysis comprise (much) less than 50 subjects. Small participant numbers have been shown to impact the reliability of cognitive neuroscience studies [2], a problem that can, in principle, be circumvented by proper use of meta-analyses. However, the present ALE analysis ignores the clear recommendation – based on a simulation study by the authors of the ALE approach [3] - to include at least 17 experiments. When even including less than ten experiments, ALE scores of a single experiment may already be close to significance relative to the overall null-distribution and results of the meta-analysis might simply reflect results of a single experiment [4, 5].

Furthermore, considering that sex differences as well as long term memory are highly researched topics, the inclusion of only eight studies in the meta-analysis in itself might point towards a file drawer problem, where negative findings on differences between the sexes are

simply not reported. This assumption is supported by results of a large meta-analysis involving 179 studies, which indicates an excess of false positives as well as a strong publication bias in the sex differences literature [6].

Looking beyond the present study, the above considerations point to a much more fundamental problem in sex differences research in neuroimaging (and in general): The commonly adopted group comparison approach simply is not sufficient to capture the complex nature of sex differences in the brain. Still, the vast majority of sex differences research is based on the highly questionable assumption of a clear-cut sexual dimorphism in the brain, which would only be justified if male and female brain features could be assumed to cluster distinctively and consistently at opposite ends of a single gender continuum [7].

On the contrary, recent research [8, 9] based on big data sets indicates that it is time to move away from considering sex differences in the brain as fixed, in-variant over time or binary with sharply defined category boundaries [7]. Rather, most brain features appear to be highly overlapping between the sexes [9], indicating that sex differences in the brain are not defined by biological sex alone but rather modulated by a variety of factors, some of which might even be dynamically changing over relative short time frames (e.g. the female menstrual cycle).

In an era of very large-scale neuroimaging, new methodological approaches like statistical learning are needed to understand the complex nature of sex differences in the brain. In fact, the actual question that should be asked is not whether or not sex differences exist in the brain, but rather how large and meaningful such differences are in relation to variation within each sex as well as sex-independent inter- and intra-individual variance. While we agree with the authors in that we should "question the widespread practice of collapsing across sex in the field

of cognitive neuroscience", much more detailed research is needed to actually understand sex differences in the brain to an extend that is transferable to real life and clinical applications. Almost inevitably, such studies will have to rely on very large neuroimaging data sets [1] in combination with appropriate statistical learning approaches [8].

1. Ritchie, S.J., et al., Cereb Cortex, 2018. **28**(8): p. 2959-2975.
2. Thirion, B., et al., Neuroimage, 2007. **35**(1): p. 105-20.
3. Eickhoff, S.B., et al., Neuroimage, 2016. **137**: p. 70-85.
4. Muller, V.I., et al., Neurosci Biobehav Rev, 2018. **84**: p. 151-161.
5. Eickhoff, S.B., et al., Hum Brain Mapp, 2009. **30**(9): p. 2907-26.
6. David, S.P., et al., Sci Rep, 2018. **8**(1): p. 6082.
7. Rippon, G., et al., Front Hum Neurosci, 2014. **8**: p. 650.
8. Weis, S., et al., Cereb Cortex, 2020. **30**(2): p. 824-835.
9. Joel, D., et al., Proc Natl Acad Sci U S A, 2015. **112**(50): p. 15468-73.