

Sex Influences on the Brain: An Issue Whose Time Has Come

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The issue of sex influences on the brain is rapidly moving center stage, driven by abundant results proving that subject sex can and regularly does alter, negate, and even reverse neuroscientific findings and conclusions down to the molecular level and thus can no longer be justifiably marginalized or ignored.

Early in 2013, the US Food and Drug Administration (FDA) ordered the makers of the sleep aid Ambien to cut their recommended dose in half—but only for women. In essence, the FDA was acknowledging that millions of women had been overdosing on the drug since its approval. In 2014, the Director of the National Institutes of Health, Francis Collins, and the Director of the NIH Office of Research on Women's Health, Janine Clayton, published a game-changing article stating that all NIH-funded research—for the first time ever—will be required to actively consider sex influences (Clayton and Collins, 2014).

What lies behind these remarkable developments? The answer to this question is the rapidly burgeoning weight of evidence proving that sex matters in different kinds of ways, from the level of the intact human down to the level of ion-channel function, and everywhere in between. Numerous excellent reviews document this striking development (Cockroft et al., 2007; Jazin and Cahill, 2010; McCarthy et al., 2009). As a recent example, the laboratory of one of us (D.A.) made the serendipitous discovery that endogenous levels of phosphorylation of synapsin I (a major regulator of synaptic transmission throughout the CNS) differ dramatically between male and female mice (Qin et al., 2013). This was highly unexpected because (1) there is no difference between the sexes in total levels of either synapsin I or the kinase that phosphorylates it, and (2) the phosphorylation of synapsin in rodents has been investigated by several researchers over the past 36 years, but in each case,

only one sex was used—either males (Strömbom et al., 1979; Yamagata et al., 1995) or females (Iwata et al., 1996).

There are many examples like this across the neuroscience spectrum. Sex influences on brain function have been reported regarding the neural/genetic underpinnings of addiction (Barker et al., 2010), stress responses (Bangasser, 2013), genetic changes with human aging (Berchtold et al., 2008), human brain connectivity (Ingalhalikar et al., 2014), schizophrenia (Abazyan et al., 2014), pre-natal nicotine exposure (Cao et al., 2013), drug responses (Reilly et al., 1990), ischemia (Lang and McCullough, 2008), microcephaly (Rimol et al., 2010), microglia function (Crain et al., 2013), and pain perception (Sorge et al., 2015) to name only a tiny fraction of the extant findings. For a review of sex differences in molecular neuroscience, see Jazin and Cahill (2010).

The immense power of carefully attending to potential sex effects, and conversely the confusion caused by assuming they do not exist, is nicely exemplified by the work of Rimol et al. (2010) concerning the genetic control of human brain size. Humans are distinguished by the dramatic and relatively recent evolutionary growth of their brains relative to body size. As one approach to understanding how this happened, Rimol et al. (2010) examined loss-of-function mutations in genes associated with congenital primary recessive microcephaly. They did so by correlating SNPs from four such genes with brain morphometry obtained with MRI. Critically, they note that previous attempts to link common variants in this gene family

to variation in human brain morphology were both largely unsuccessful, and generally assumed that sex differences would not exist. However, Rimol et al. (2010) detected sex-specific associations between the SNPs and brain morphometry in two separate cohorts: SNPs of the gene CDK5RAP2 significantly related to brain phenotype only in men, whereas SNPs of the genes MCPH1 and ASPM significantly related to brain phenotype only in women. They note that these findings “are unique in their demonstration of an association between common variants of any of the MCPH genes and brain structure in humans.” Had they assumed that sex would not matter, they would almost certainly have missed this discovery.

Another recent paper highlights the fact that sex influences not only brain function, but also interactions between the brain and other systems. Sorge et al. (2015) examined interactions between neural and immune function in pain perception. Using multiple approaches, they found that, unlike what they and others had previously found using males, pain hypersensitivity in females does not involve a contribution from microglia. In contrast to male mice, female mice achieve similar levels of pain hypersensitivity using adaptive immune cells, likely T lymphocytes. These results provide yet more evidence that the neural mechanisms of pain differ substantially in males and females. Despite the evidence, Sorge et al. (2015) note that male-only studies remain “standard” in the pain field, as in most of neuroscience, with results extrapolated freely to females. We fail to see how such an approach at this juncture is even scientifically defensible.

The converging evidence of the influence of sex on brain function across the entire spectrum of brain science raises the question, “If sex matters so much to brain function at essentially all levels, how did we miss this fact for so long?” A complete answer is beyond the scope of this short review, but we offer two thoughts. First, and simplest, neuroscience to this day studies male animals almost exclusively (Beery and Zucker, 2011), meaning sex differences have no chance of ever being discovered, much less missed, in the vast majority of neuroscience studies. And second, even when sex differences are present, conceptual blinders can easily block them from view. An example concerns the original investigations of the well-known sleep aid Ambien (zolpidem), which clearly showed that the drug was being metabolized much more slowly in females than in males. Yet investigators at the time appear to have simply dismissed the result as being unimportant. It was not until some 20 years later—after the deaths of women killed while driving the morning after they took the drug, but while still unexpectedly under its influence—that the FDA finally mandated that the recommended dosage in women be cut in half. No one knows how many “Ambiens” are out there now or will be generated in the future if neuroscience clings to its very widespread, long-standing view of sex influences as mildly important at best, a nuisance at worst.

Importantly, the National Institute of Health is finally recognizing the profound importance of exploring sex influences and recently announced a new policy stating in part that, starting with FY2016, research applications “will include accounting for sex as a biological variable in the Research Strategy section” and that “strong justification...must be provided for applications proposing to study

one sex.” Such justification cannot include the fact that little or no extant literature on a specific topic exists (see http://orwh.od.nih.gov/sexinscience/overview/pdf/NOT-OD-15-102_Guidance.pdf).

A previous commentary on the issue of sex influences in this journal (Eliot, 2011) referred to “the trouble with sex differences.” Eliot focused on the issue of sex difference findings being misconstrued by the general public and encouraged neuroscientists to help convey appropriate messages to the public. We agree, but add that neuroscientists cannot do this until they themselves understand what the essential right message is, namely that the issue of sex influences is clearly very important at all levels of brain function yet remains massively understudied. The “trouble” with sex differences at present in our view is the continuing reluctance of so many neuroscientists to pursue the issue despite the evidence.

The French novelist Victor Hugo famously said, “There is one thing more powerful than all the armies in the world, and that is an idea whose time has come.” We think that the idea that “sex matters” for brain science is an idea whose time has come. The health of both men and women now requires research scientists to recognize this fact and to start adjusting their science accordingly.

REFERENCES

- Abazyan, B., Dziedzic, J., Hua, K., Abazyan, S., Yang, C., Mori, S., Pletnikov, M.V., and Guilarte, T.R. (2014). *Schizophr Bull.* **40**, 575–584.
- Bangasser, D.A. (2013). *Biol. Sex Differ.* **4**, 2.
- Barker, J.M., Torregrossa, M.M., Arnold, A.P., and Taylor, J.R. (2010). *J. Neurosci.* **30**, 9140–9144.
- Beery, A.K., and Zucker, I. (2011). *Neurosci. Bio-behav. Rev.* **35**, 565–572.
- Berchtold, N.C., Cribbs, D.H., Coleman, P.D., Rogers, J., Head, E., Kim, R., Beach, T., Miller, C., Troncoso, J., Trojanowski, J.Q., et al. (2008). *Proc. Natl. Acad. Sci. USA* **105**, 15605–15610.
- Cao, J., Wang, J., Dwyer, J.B., Gautier, N.M., Wang, S., Leslie, F.M., and Li, M.D. (2013). *Transl Psychiatry* **3**, e247.
- Clayton, J.A., and Collins, F.S. (2014). *Nature* **509**, 282–283.
- Cosgrove, K.P., Mazure, C.M., and Staley, J.K. (2007). *Biol. Psychiatry* **62**, 847–855.
- Crain, J.M., Nikodemova, M., and Watters, J.J. (2013). *J. Neurosci. Res.* **91**, 1143–1151.
- Eliot, L. (2011). *Neuron* **72**, 895–898.
- Ingalhalikar, M., Smith, A., Parker, D., Satterthwaite, T.D., Elliott, M.A., Ruparel, K., Hakonarson, H., Gur, R.E., Gur, R.C., and Verma, R. (2014). *Proc. Natl. Acad. Sci. USA* **111**, 823–828.
- Iwata, S., Hewlett, G.H., Ferrell, S.T., Czernik, A.J., Meiri, K.F., and Gnegy, M.E. (1996). *J. Pharmacol. Exp. Ther.* **278**, 1428–1434.
- Jazin, E., and Cahill, L. (2010). *Nat. Rev. Neurosci.* **11**, 9–17.
- Lang, J.T., and McCullough, L.D. (2008). *J. Transl. Med.* **6**, 33.
- McCarthy, M.M., Auger, A.P., Bale, T.L., De Vries, G.J., Dunn, G.A., Forger, N.G., Murray, E.K., Nugent, B.M., Schwarz, J.M., and Wilson, M.E. (2009). *J. Neurosci.* **29**, 12815–12823.
- Qin, Z., Kaufman, R.S., Khoury, R.N., Khoury, M.K., and Aswad, D.W. (2013). *PLoS ONE* **8**, e80758.
- Reilly, P.E., Thompson, D.A., Mason, S.R., and Hooper, W.D. (1990). *Mol. Pharmacol.* **37**, 767–774.
- Rimol, L.M., Agartz, I., Djurovic, S., Brown, A.A., Roddey, J.C., Kähler, A.K., Mattingsdal, M., Athanasios, L., Joyner, A.H., Schork, N.J., et al.; Alzheimer’s Disease Neuroimaging Initiative (2010). *Proc. Natl. Acad. Sci. USA* **107**, 384–388.
- Sorge, R.E., Mapplebeck, J.C., Rosen, S., Beggs, S., Taves, S., Alexander, J.K., Martin, L.J., Austin, J.S., Sotocinal, S.G., Chen, D., et al. (2015). *Nat. Neurosci.* **18**, 1081–1083.
- Strömbom, U., Forn, J., Dolphin, A.C., and Greengard, P. (1979). *Proc. Natl. Acad. Sci. USA* **76**, 4687–4690.
- Yamagata, Y., Obata, K., Greengard, P., and Czernik, A.J. (1995). *Neuroscience* **64**, 1–4.