Practical guidelines for the consideration of the link between sex and gender in medical research and health: Neuroimaging

Jennifer Merchant, Catherine Vidal

Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

Practical guidelines for the consideration of the link between sex and gender in medical research and health

NEUROIMAGING

The Inserm Ethics Committee

"Gender and Health Research" Group

Juin
2016

Practical guidelines for considering the interactions between sex and gender in medical research and health

NEUROIMAGING

In 2014, the Inserm Ethics Committee set up a "Gender and Health Research" group (http://www.inserm.fr/qu-est-ce-que-l-inserm/l-ethique-a-l-inserm/les-groupes-de-reflexion-thematique-du-comite-d-ethique). As gender is often overlooked in biomedical research in France (unlike in Anglo-American and other European countries), one of the group's goals is to reflect on the ethical issues concerning the influence of social and cultural factors on the differences and inequalities between men and women when it comes to health and medical research practices.

It is important to encourage researchers to consider the differences between men and women - not just as a simple dichotomy between male and female, but as an interaction between sex and gender (Fausto-Sterling, 2000, 2012; Springer Krieger 2003). Such an approach provides a framework for improved research practices, and consequently increases knowledge about the origins of differences between women and men in health.

Recommendations for neuroimaging research

Principles and consequences of the design, analysis and interpretation of experiments in medical research.

In neuroimaging research on brain functions and cognitive skills, studies that question the impact of education and sociocultural environment on gender differences in men and women are still rare (Rippon 2014). Neuroscientists are still relatively unfamiliar with the concept of gender. A better awareness of gender can only enrich research on cognitive and behavioral disorders, which often vary according to sex and environment (Dussauge 2012; Fausto-Sterling 2000, 2012; Fine 2014).

In this paper, we will present some principles that may be useful when considering the relationship between sex and gender, and give examples of how this approach is likely to improve the practices of MRI brain research on both women and men. We will also propose recommendations for the design, analysis and interpretation of experiments (see Rippon 2014 for a detailed review of theoretical and practical issues in MRI research comparing female and male subjects).

The interaction between sex and gender

For over 10 years, MRI studies on brain plasticity have shown how experience and learning shape the brains of both children and adults (May 2011; Vidal 2009). The concept of brain plasticity provides a fundamental neurobiological insight into the social and cultural construction of sexual identity. Sex and gender are not separate variables, but interact in a process of embodiment, a term that describes the relationship between biological sex and the physical, emotional, social, and cultural environment (Fausto-Sterling 2000, 2012, Fine 2013). Gender influences biology, and biology affects gender.

These interactions result in a wide range of personalities, as well as cognitive and social behaviors, which reveal both differences and similarities between women and men (Hyde 2014). This diversity is reflected in the brain, and can be detected by neuroimaging studies (Kaiser 2009; Bluhm 2013; Mueller 2013; Joel 2015). Several principles therefore arise in MRI studies on both men and women that need to be taken into account.

1) There is great diversity in the anatomy and functioning of brains, regardless of sex.

Meta-analyses comparing the brains of both men and women show that there is no strict dimorphism that differentiates male brains from female brains (MacCarthy 2011; Joël 2015; Giedd 2012; Ruigrok 2014).

The brain volume of men is indeed more (about 10% on average) than that of women, even after taking into account the difference in body size (Cosgrove, 2007). Women also have on average slightly more gray matter, and men slightly more white matter (Hanggi, 2014). These differences, however, are related to brain size, and not sex (Hanggi 2014; Jancke 2015). If we compare the brains of men and women of the same volume (around 15-20% of cases in the population), we no longer see differences in gray and white matter ratios (Luders, 2014). The few studies that have shown differences after taking the size factor into account are rare, and need to be replicated (Luders, 2009; Raznahana 2014).

On a functional level, meta-analyses also indicate significant diversity in brain activity (Wallentin 2009; Bluhm 2013; Mueller 2013; Miller 2014). An overview of the studies on the language areas of the brain that were published from 1995 to 2009 (which together included 2000 subjects), shows that interindividual variability is such that no statistical difference between the sexes can be detected (Kaiser, 2009).

It is important to note that there is a certain degree of bias in the interpretation and media coverage of the results of some scientific studies (Guo, 2014; Ionnidis, 2014;

Kriegeskorte, 2010). When comparing the brains of women and men in studies with a large number of subjects, differences that are sometimes observed on a smaller scale go largely undetected. However, it is the studies that show differences that are cited the most often! When going through recent MRI studies on cognitive function, one finds that out of the approximately 16.000 articles published from 1992 to 2008, only 2.6% reported gender differences (Kaiser, 2009).

Finally, and contrary to popular belief, the brains of women and men show no distinct differences, at least to the degree that they can be easily identified. Meta-analyses reveal that brain diversity is so rich that there is significant overlap (effect size) in the anatomy and function of the brains of males and females. There is just as much variety in psychological traits, cognitive skills and social behaviors, all of which reflect both similarities and differences between men and women (Petersen 2011; Miller 2014; Hyde 2014).

Recommendations 1:

Statistics and data analysis

Given the diversity, differences and overlap between the anatomical and functional traits in male and female brains, the following measures are recommended in statistical analysis:

- Use a sample that is large enough to avoid false positives and negatives.

- If the samples are small, as is frequent in MRI studies, the results need to be replicated before they are considered valid. Use non-parametric statistical tests.

- Estimate effect sizes and conduct meta-analyses

Illustrations

MRI results for each sex often undergo separate statistical analyses that are illustrated with distinct images. If these images are different, their *qualitative* comparison is insufficient. It is important to instead make a *quantitative* statistical comparison in which the differences between men and women are represented by a single image.

Publications

It is important to report the absence as well as the presence of gender differences in studies. This should lead to more efficient methods of collecting information as well as more thorough results in online databases, whose keywords currently only take the differences between the sexes into account.

2) Brain and cognitive characteristics are not fixed, and evolve with time and according to environment due to the brain's plasticity.

MRI research has amply demonstrated that learning and experiences alter both the structure (thickness of the cortex, amount of white matter, etc.) and functioning of the brain (May 2011; Fine 2013). When an MRI scan shows differences between men and women, it does not mean that these differences have been engraved in the brain since birth, nor that they will persist. MRI scans only give a snapshot of the state of a person's brain in a given moment.

Differences between men and women in cognitive abilities are not set in stone. For example, spatial orientation test scores, which often reflect better performances from boys, become the same when the girls being tested are first trained to play video games, or do not fall victim to stereotype threats (Spencer 1999; Spelke 2005; Wraga 2006; Feng 2007). Epidemiological surveys show that differences in performance between boys and girls in math and language tests vary by country and socioeconomic status (Guiso 2008; Hyde 2009; Else-Quest 2010).

In conclusion, the differences between men and women that are linked to education, socialization and life experience are reflected in the functional structure of the brain, and therefore in behavior as well. These gender differences are not fixed, and can be modified, neutralized or even reversed depending on personal experience and sociocultural, economic and political environment.

Recommendations 2:

Image Interpretation

- Recognize the immediate and impermanent nature of MRI images, and keep the brain's capacity for plasticity in mind when analyzing MRI scans.
- Question the possible *origins* of the presence or absence of gender differences

Take variables other than biological sex into account when comparing the brains of women and men.

- Collect bibliographical information other than sex, such as age, education, hobbies and interests (such as sports or games), occupation, ethnicity, family history, social status, and economic status.
- Incorporate these different variables when selecting subject groups, in order to form groups that could be more relevant than those which are simply classified by sex.

Writing Articles

Use "sex/gender" rather than the term "sex" to acknowledge the complex relationships between sex and gender.

General conclusion

Categorization by sex is a general practice that implies that biological sex is a significant factor when studying the neurobiological bases of cognitive function in women and men. Neuroimaging studies often interpret brain-related differences between men and women as the result of genetic and/or hormonal determinism (Jordan-Young 2010; Bluhm 2013). When a region of the brain appears to be different between men and women, it is often seen as reflecting a difference in cognitive skills or social behavior – an interpretation which is often heavily influenced by gender stereotypes.

It is clear that despite current knowledge about brain plasticity, essentialist conceptions of the origins of gender differences persist in many scientific publications. Reflection on the ethical issues has to be undertaken in order to create the intellectual and methodological conditions needed to encourage researchers to integrate gender into neuroimaging research practices (Illes 2006; Dussauge 2012; Vidal 2012). It is important to question the normal and the pathological through the lens of gender, and thus move past the simple biological dichotomy between men and women. This approach will allow us to develop new models that articulate the biological and social mechanisms that may explain the differences and inequalities between women and men in the field of health. Taking gender into account in neuroscience also has a social impact when transmitting scientific research to a large public. Explaining that societal roles assigned to women and men are not determined by a biological law hardwired into their brains will help fight against conservative prejudices and sexist stereotypes.

Catherine Vidal and Jennifer Merchant

Members of the “Gender and Health Research" Group of the Inserm Ethics Committee

Bibliography

Bluhm R, 2013. “New research, old problems: methodological and ethical issues in fMRI research examining sex/gender differences in emotion processing”, *Neuroethics*, 6: 319-330

Cosgrove KP, Mazure CM, Staley JK., 2007. “Evolving knowledge of sex differences in brain structure, function, and chemistry”, *Biol Psychiatry*, 62 :847-55.

Dussauge I and Kaiser A (eds) 2012. “Special issue : Neuroscience and sex/gender”, *Neuroethics*, 5 : 211-215

Else-Quest NM, Hyde JS, Linn MC. 2010. Cross-national patterns of gender differences in mathematics: a meta-analysis., *Psychol Bull*. 136:103-27.

Fausto-Sterling, A. 2000. *Sexing the Body. Gender Politics and the Construction of Sexuality*, Basic Books, NewYork.

Fausto-Sterling A, Garcia C and Lamarre M, 2012. “Sexing the baby: Part 1. What do we really know about sex differentiation in the first three years of life?”, *Social Science & Medicine*, 74 : 1684-92.

Feng J, Spence I, Pratt J. 2007. Playing an action video game reduces gender differences in spatial cognition. *Psychol Sci*., 18 :850-855.

Fillod O,2014. “Le connectome et la circulation circulaire des stéréotypes de genre”, http://allodoxia.blog.lemonde.fr/ .

Fine C, 2014. “His Brain, her brain?”, *Science*, 346 : 915-916.

Fine C, Jordan-Young R, Kaiser A, Rippon G. 2013 .Plasticity, plasticity, plasticity…and the rigid problem of sex., *Trends Cogn Sci*., 17:550-551.

Giedd J et al. 2012. "Magnetic resonance imaging of male/female differences in human adolescent brain anatomy", *Biol.Sex Differ*. 3:19.

Guiso, L, Monte, F, Sapienza P and Zingales L, 2008. "Culture, Gender, and Maths", *Science*, 320 : 1164-1165.

Guo Q et al. 2014. A systematic review of the reporting of sample size calculations and corresponding data components in observational functional magnetic resonance imaging studies. *Neuroimage*. 1:172-81.

Hänggi J et al. 2014. "The hypothesis of neuronal interconnectivity as a function of brain size—a general organization principle of the human connectome", *Frontiers in human neuroscience*, 8 : 3-16

Hyde JS. 2014. Gender similarities and differences., *Annu Rev Psychol*. 65:373-98.

Hyde JS and Mertz JE. 2009. Gender, culture, and mathematics performance., *Proc Natl Acad Sci U S A*.106:8801-7

Illes J et al. 2006. "ELSI priorities for brain imaging", *American Journal of Bioethics*, 6 : 24-31.

Ingalhalikar M. et al. 2014. "Sex differences in the structural connectome of the human brain", *Proc Natl Acad Sci U S A*, 111: 823-8.

Ioannidis JP et al. 2014.Publication and other reporting biases in cognitive sciences: detection, prevalence, and prevention.*Trends Cogn Sci*, 18:235-41.

Jancke L et al., 2015. "Brain size, sex, and the aging brain", *Human Brain Mapping*, 36, 1:150-169

Joel Daphna et al. 2015 "Sex Beyond the Genitalia: The Human Brain Mosaic", *Proceedings of the National Academy of Sciences*.

Jordan-Young RM, 2010. *Brain Storm: The Flaws in the Science of Sex Differences*, Cambridge, Harvard University Press.

Kaiser A *et al*., 2009. "On sex/gender related similarities and differences in fMRI language research", *Brain Research Reviews*, 61 : 49-59

Kriegeskorte N et al. 2010. Everything you never wanted to know about circular analysis, but were afraid to ask., *J Cereb Blood Flow Metab*, 30:1551-7.

Krieger N, 2003. Genders, sexes, and health: What are the connections—and why does it matter?, *International Journal of Epidemiology*, 32, 652-657.

Luders E, Gaser C, Narr KL and Toga AW. 2009. "Why sex matters: brain size independent differences in gray matter distributions between men and women", *J Neurosci*. 29:14265-70.

Luders E, Toga AW and Thompson PM, 2014. "Why size matters: Differences in brain volume account for apparent sex differences in callosal anatomy", *NeuroImage*, 84 : 820-824.

May A, 2011. "Experience-dependent structural plasticity in the adult human brain", *Trends in Cognitive Sciences*, 15: 475-82.

Miller D and Halpern DF, 2014. "The new science of cognitive sex differences", *Trends in Cognitive Sciences*, 18 : 37-45

Mueller S et al. 2013. "Individual Variability in Functional Connectivity Architecture of the Human Brain", *Neuron*, 77: 586–595.

McCarthy MM and Arnold AP, 2011. Reframing sexual differentiation of the brain. *Nature Neurosci*. 14:677-83.

Petersen JL and Hyde JS. 2011. Gender differences in sexual attitudes and behaviors: a review of meta-analytic results and large datasets. *J Sex Res*. , 48:149-65

Raznahana A et al., 2014. "Longitudinal four-dimensional mapping of subcortical anatomy in human development", *PNAS 111* : 1592–1597

Rippon, G, Jordan-Young R, Kaiser A and Fine C, 2014. "Recommendations for sex/gender neuroimaging research: key principles and implications for research design, analysis, and interpretation", *Frontiers in Human Neuroscience*, 8 : 1-1

Ruigrok A et al., 2014. "A meta-analysis of sex differences in human brain structure", *Neuroscience and Behavioral Reviews*, 39 : 34-50

Spencer SJ, Steele CM and Quinn DM, 1999. "Stereotype threat and women's math performance", *J. Exp.Soc.Psychol*. 35 : 4-28

Spelke E, 2005. "Sex differences in intrinsic aptitudes for mathematics and science ? A critical review", *American Psychologist*, 60 : 950-958.

Springer K, Mager Stellman J and Jordan-Young R, 2012. "Beyond a catalogue of differences: A theoretical frame and good practice guidelines for researching sex/gender in human health", *Social Science & Medicine*, 74 : 1817-1824.

Vidal C, 2009. *Le cerveau évolue-t-il au cours de la vie ?* Paris, Le Pommier.

Vidal C, 2012. "The Sexed Brain: Between Science and Ideology", *Neuroethics*, 5: 295-303.

Wallentin M, 2009. Putative sex differences in verbal abilities and language cortex: a critical review. *Brain Lang*.108:175-83.

Wraga M, Helt M, Jacobs E *et al*., 2006. "Neural basis of stereotype-induced shifts in women's mental rotation performance", *SCAN*, 2 : 12– 19.