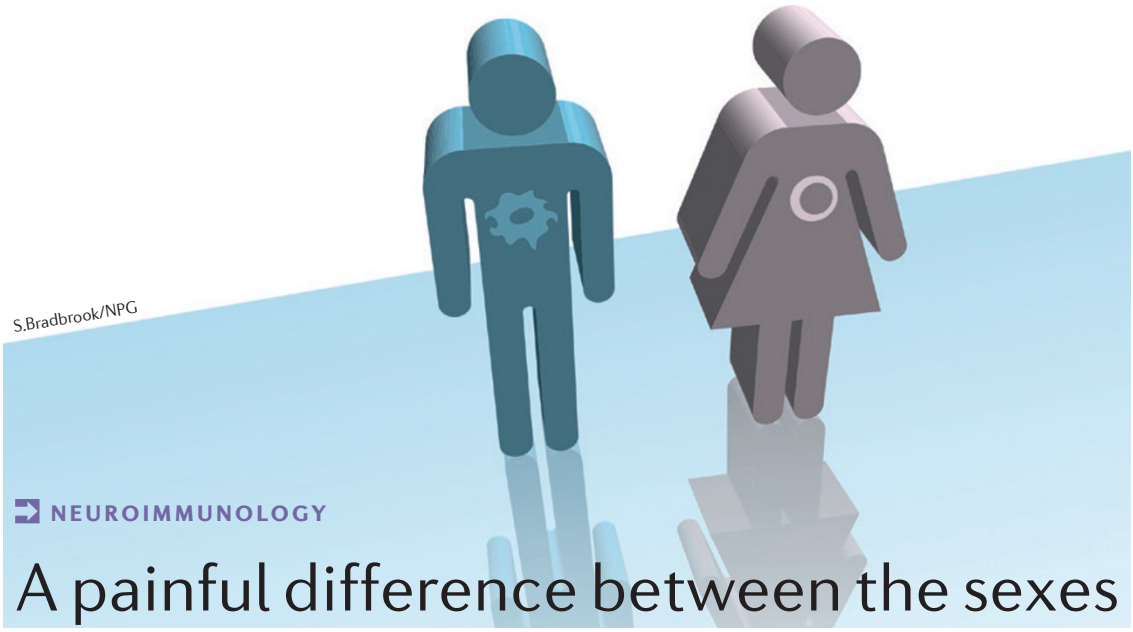
Nature Reviews Immunology | AOP, published online 17 July 2015; doi:10.1038/nri3892



NEUROIMMUNOLOGY

A painful difference between the sexes

There is a growing appreciation of how immune pathways interact with the nervous system to shape the pain response. A study in *Nature Neuroscience* now describes a key sex difference in the neuroimmune mechanisms involved in pain perception. The authors report that microglia are essential for mechanical pain hypersensitivity in male mice, whereas lymphocytes seem to fulfil this role in female mice.

A number of studies have suggested a crucial role for microglia in pain processing. However, previous work by some of the researchers involved in this study had shown that Toll-like receptor 4 (TLR4) is necessary for mechanical pain hypersensitivity (allodynia) in male mice but not in females. As TLR4 is expressed by microglia, this prompted the authors to explore whether pain may be processed in female mice through a pathway that is independent of microglia.

They induced mechanical allodynia in mice of both sexes (using the spared nerve injury model of neuropathic pain or a model of inflammatory pain induced by complete Freund's adjuvant) and found that intrathecal injection of glial inhibitors reversed allodynia in male mice but not in female mice. Similarly, the transient depletion of microglia blocked allodynia in male mice but not in females. In addition, blocking several signalling mediators previously shown to participate in the microglia–neuron pain pathway — specifically $P2X_4$ receptor, p38 MAP kinase or brain-derived neurotrophic factor — also reversed allodynia in male, but not in female, mice. These findings suggest that microglia have an essential role in mechanical pain perception in male mice, but that an alternative pathway is used in females.

To test whether adaptive immune cells might be involved, the authors studied allodynia in nude or recombination-activating gene 1-knockout (*Rag1*$^{-/-}$) mice, which lack T cells and B cells. Notably, the administration of glial inhibitors reversed allodynia in both male and female nude or *Rag1*$^{-/-}$ mice. By contrast, in female *Rag1*$^{-/-}$ mice that had received an adoptive transfer of splenocytes, allodynia could not be blocked by glial inhibitors. Therefore, female mice process mechanical pain via lymphocyte-dependent mechanisms but can use a microglia-dependent pathway when lymphocytes are not present.

Sex hormones are known to regulate the expression of peroxisome proliferator-activated receptors (PPARs), which in turn can regulate the expression of cytokines associated with pain responses. This led the authors to examine whether the sexually dimorphic expression of PPARs might account for their observations. Indeed, they found that a PPARα agonist reversed allodynia in males, but not in females or castrated males, whereas a PPARγ agonist reversed allodynia in females but not in males or testosterone-treated females.

These findings have important implications for research in this field, as they indicate that male and female mice cannot be used interchangeably in future studies. Moreover, the data suggest that distinct clinical strategies could be needed in order to optimize pain management in male and female patients.

Yvonne Bordon

> “a key sex difference in the neuroimmune mechanisms involved in pain perception”

ORIGINAL RESEARCH PAPER Sorge, R. E. *et al.* Different immune cells mediate mechanical pain hypersensitivity in male and female mice. *Nat. Neurosci.* http://dx.doi.org/10.1038/nn.4053 (2015)

FURTHER READING Grace, P. M. *et al.* Pathological pain and the neuroimmune interface. *Nat. Rev. Immunol.* **14**, 217–231 (2014)