A rat is not a monkey is not a human: comment on Mogil (*Nature Rev. Neurosci.* 10, 283–294 (2009))

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The March issue of *Nature Reviews Neuroscience* contains an article by Jeff Mogil (Animal models of pain: progress and challenges. *Nature Rev. Neurosci.* 10, 283–294 (2009))¹ on the progress and challenges in animal models of pain. One major reason why pain models in rodents have had little translational success that needs to be added to those mentioned in the article is that — in addition to the numerous genetic and neurochemical differences between rodents and humans, even in the spinal dorsal horn — rats and mice simply do not have the neuroanatomical pathway to the forebrain that is crucial for pain sensation in humans. A recent article promoting human pain studies² also does not mention this important difference between rodents and humans.

To be specific, the lamina I spinothalamicocortical pathway to the dorsal posterior insula by way of the posterior part of the ventromedial nucleus (VMpo) is crucial for pain in humans^{3,4}. A lesion of the ascending lamina I fibres in the middle of the lateral funiculus, a lesion of the VMpo or a lesion of dorsal posterior insula (dpIns) can cause the complete and permanent loss of pain and temperature sensation in a contralateral region of the body^{5–8}. Conversely, microstimulation in either the VMpo or the dpIns in awake humans can cause a well-localized report of either sensation^{9,10}. The existence of this pathway has generated debate (for example, see REFS 11–14), but there is no comparable evidence in rodents — rodents do not have either of these forebrain structures.

Paradoxically, post-stroke central pain can emerge after a lesion of either the VMpo

or the dpIns^{7,8}. However, rather than disproving that pain is a specific sensation, as Wall proclaimed¹³, this phenomenon instead reveals the disinhibition (unmasking) of another pathway (lamina I to medial dorsal thalamus to anterior cingulate cortex) that is again present only in primates⁴ (see also REF. 15), as presciently conjectured by Head and Holmes⁷. Because these structures are present only in primates there can never be a rodent model of post-stroke central pain.

Finally, and perhaps of the utmost significance, the re-representation of this pathway in the anterior insular cortex is crucial for subjective feelings of pain (or any other feeling) in humans^{15–19}, and neither rodents nor monkeys seem to have a homologous structure. The inescapable truth is that pain in humans is indeed a subjective experience. The available evidence indicates that neither rodents nor monkeys can experience feelings in the same way that humans do.

So, a rat is not a monkey is not a human. Studying the behaviour of rodents is valid ethological and neurobiological work, and animal welfare is certainly important. However, it is the pain of fellow humans that urgently needs to be addressed. In contrast to the situation for lamina I neurons, which can be studied in rodents (for example, see REF. 20) because there are strong similarities (and also strong differences!) between rat and primate dorsal horns, the forebrain and the feelings of humans in pain cannot be studied in species that do not have the same neuroanatomical substrates. I submit that these points strongly recommend greater emphasis on studies of pain in humans.

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1. Mogil, J. S. Animal models of pain: progress and challenges. *Nature Rev. Neurosci.* 10, 283–294 (2009).
2. Langley, C. K. *et al.* Volunteer studies in pain research — opportunities and challenges to replace animal experiments: the report and recommendations of a Focus on Alternatives workshop. *Neuroimage* 42, 467–473 (2008).
3. Craig, A. D., Bushnell, M. C., Zhang, E.-T. & Blomqvist, A. A thalamic nucleus specific for pain and temperature sensation. *Nature* 372, 770–773 (1994).
4. Craig, A. D. Distribution of trigeminothalamic and spinothalamic lamina I terminations in the macaque monkey. *J. Comp. Neurol.* 477, 119–148 (2004).
5. Birklein, F., Rolke, R. & Müller-Forell, W. Isolated insular infarction eliminates contralateral cold, cold pain, and pinprick perception. *Neurology* 65, 1381 (2005).
6. Craig, A. D., Zhang, E. T. & Blomqvist, A. Association of spinothalamic lamina I neurons and their ascending axons with calbindin-immunoreactivity in monkey and human. *Pain* 97, 105–115 (2002).
7. Head, H. & Holmes, G. Sensory disturbances from cerebral lesions. *Brain* 34, 102–254 (1911).
8. Schmähmann, J. D. & Leifer, D. Parietal pseudothalamic pain syndrome: clinical features and anatomic correlates. *Arch. Neurol.* 49, 1032–1037 (1992).
9. Davis, K. D. *et al.* Thalamic relay site for cold perception in humans. *J. Neurophysiol.* 81, 1970–1973 (1999).
10. Ostrowsky, K. *et al.* Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cereb. Cortex* 12, 376–385 (2002).
11. Davidson, S., Zhang, X., Khasabov, S. G., Simone, D. A. & Giesler, G. J. Jr. Termination zones of functionally characterized spinothalamic tract neurons within the primate posterior thalamus. *J. Neurophysiol.* 100, 2026–2037 (2008).
12. Graziano, A. & Jones, E. G. Widespread thalamic terminations of fibers arising in the superficial medullary dorsal horn of monkeys and their relation to calbindin immunoreactivity. *J. Neurosci.* 24, 248–256 (2004).
13. Wall, P. D. Pain in the brain and lower parts of the anatomy. *Pain* 62, 389–391 (1995).
14. Willis, W. D. Jr, Zhang, X., Honda, C. N. & Giesler, G. J. Jr. A critical review of the role of the proposed VMpo nucleus in pain. *J. Pain* 3, 79–94 (2002).
15. Craig, A. D. How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Rev. Neurosci.* 3, 655–666 (2002).
16. Berthier, M. L., Starkstein, S. E. & Leiguarda, R. C. Asymbolia for pain: a sensory-limbic disconnection syndrome. *Ann. Neurol.* 24, 41–49 (1988).
17. Brooks, J. C., Nurmikko, T. J., Bimson, W. E., Singh, K. D. & Roberts, N. fMRI of thermal pain: effects of stimulus laterality and attention. *Neuroimage* 15, 293–301 (2002).
18. Craig, A. D. How do you feel — now? The anterior insula and human awareness. *Nature Rev. Neurosci.* 10, 59–70 (2009).
19. Kong, J. *et al.* Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. *Hum. Brain Mapp.* 27, 715–721 (2006).
20. Coull, J. A. M. *et al.* BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature* 438, 1017–1021 (2005).