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Editorial comment

Looking at visceral pain: New vistas

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The usefulness of visceral pain is not immediately apparent. Sherrington defined pain as *the psychical adjunct of a protective reflex*, implying that pain has a protective and useful role. But what is the usefulness of the pain of childbirth, of a bladder infection, of a renal colic or even of a simple gastroenteritis? Many of these events are related to normal functions of the body and some – like childbirth – are intrinsic to the perpetuation of our species, which should be the most powerful drive of evolution. Human beings have puzzled about the meaning of visceral pain since the beginning of time: *In pain thou shalt bring forth children*, says the Bible: so, at least for the pain of childbirth, it must be God's curse to women for their sins.

The more we know about the mechanisms of visceral pain the more we find important differences in the neurobiological processes that mediate this form of pain when compared to those responsible for somatic pain [1]. Some internal organs do not have sensors capable of generating conscious perceptions. Afferent signals from viscera such as the liver, the spleen or the kidneys never reach consciousness, rendering these organs incapable of producing pain. Visceral nociceptors innervating other organs include many that encode the full range of stimulus intensities from innocuous to noxious and are probably responsible for the transition of the sensation of distension in the bladder and rectum from fullness to pain.

Visceral pain is the most common form of pain in the clinic, experienced by all of us and often inadequately treated as just a symptom of an underlying disease. We need to know more about the mechanisms of visceral pain and it is important that we develop ways of studying how the brain processes the signals from our internal organs that eventually produce pain. One novel method is to literally look at the pain, identifying which regions of the brain are more active while we feel visceral pain and how the activity in these brain areas is modulated over time in parallel with changes in the intensity and quality of the painful sensations. This issue of the *Scandinavian Journal of Pain* includes a comprehensive review of the techniques for imaging visceral pain [2], the very procedures that allow us to probe the basic mechanisms underlying visceral pain in conscious humans. This is especially important for visceral pain, because developing clinically relevant models of visceral pain in preclinical species, particularly rodents, is very challenging [1].

Animal models of visceral pain have focused on reproducing conditions known to cause visceral pain in man, for example experimentally induced bladder inflammation or kidney stones or on the acute activation of visceral nociceptors with capsaicin, mustard oil or other such compounds. These models are often complex, difficult to mass-produce and therefore not easily adaptable to a drug discovery environment. Imaging visceral pain in humans offers an alternative and particularly useful way of studying visceral pain sensations in both normal subjects and patients. Recent developments in non-invasive assessment of brain activity, as described by Frokjaer and colleagues in their review paper, have opened new avenues to address the questions of the slow time course of many forms of visceral pain, the many different regions of the brain activated by these stimuli and the identification of the key areas that mediate visceral pain sensations. Their review highlights some of the challenges of approaching visceral pain using imaging techniques. However, the study of visceral pain in humans also provides a unique insight that can shed light on the mechanisms of pain in general.

Somatic pain has a clear protective component, best expressed by the withdrawal reflex triggered by a noxious stimulus. We touch something hot and immediately we withdraw our hand. The very fast time course of such events illustrates the survival value of somatic pain as part of our defense against the dangers of our environment. In marked contrast, one of the most distinct features of visceral pain is the difference in its temporal course, such that responses to painful visceral stimuli are much slower and longer lasting than responses to somatic injury. There is no equivalent in the visceral world to the rapid limb withdrawal reflex of the somatic system and as a consequence, no visceral equivalent of a tail-flick or hot-plate test, to cite two standard animal behavioral assays of somatic pain. Painful visceral sensations triggered by internal stimuli are slow to occur, take time to develop and are always accompanied by complex reflex responses that are much more than a simple withdrawal from a stimulus. This likely reflects the slower nature of the events occurring in visceral organs in general as compared to those of the somatic system.

Visceral pain is very often much more intense and widespread and engages multiple CNS pathways, perhaps as a result of the fact that it is always more prolonged than normal or *protective* somatic

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pain responses. Visceral pain is also very often accompanied by general sensations like malaise and nausea which further extends the brain areas activated by a visceral stimulus perceived as painful. This feature of visceral pain has the advantage for the investigator that non-harmful, experimental manipulations capable of evoking visceral pain in normal humans are directly relevant to the study of clinical pain states both visceral and somatic. Experimental stimuli that evoke visceral pain have a longer temporal course and evoke much stronger affective responses than their short-lived somatic counterparts. Imaging visceral pain processing in normal volunteers has the obvious advantage of activating components of pain processing that are only engaged by much more chronic and painful somatic conditions.

Another characteristic feature of the time course of visceral pain is that it is often intermittent in nature with acute episodes of intense pain interspersed with periods of less pain or relatively pain free periods, as for example the colicky pain of kidney stones. In some of these types of visceral pain conditions, episodes of pain can be reliably triggered by acute manipulations, for example migraine, angina or esophageal pain, or occur predictably, for example dysmenorrhea. This feature lends itself very well to a direct comparison of imaging activity during a baseline period or condition with the activity during an episode of pain in the same subject. In contrast, studies comparing *pain* and *no-pain* states for the same subject in somatic clinical conditions are much more difficult to perform and the only practical study design is often a between-subject comparison protocol.

We can also take advantage of the fact that there are no private pathways in the spinal cord and brain for visceral sensory information. Signals from internal organs are forced to hitch rides on somatosensory pathways. This results in the referral to the surface of the body of pain of visceral origin. The area of the body where visceral pain is perceived may also develop tenderness or increased responsiveness to external stimuli, the visceral equivalent of secondary hyperalgesia known in the visceral field as *referred hyperalgesia*. Referred hyperalgesia, like somatic secondary hyperalgesia, is the result of changes in central processing triggered and maintained by a persistent nociceptive input. A key difference from somatic secondary hyperalgesia is that referred hyperalgesia on the body surface is spatially separated from the initiating nociceptive input originating in the viscera. This unique property allows the study of the mechanisms of centrally mediated hyperalgesia in an imaging paradigm without risk of contamination by peripheral sensitization mechanisms.

Frokjaer and colleagues review in detail the methodology of PET imaging and its advantages and limitations. PET techniques allow measurement of the density, locations and occupancy by endogenous ligands of cell surface markers, for example neurotransmitter receptors in man. PET has been used to monitor opioid receptor occupancy in human experimental pain models and clinical pain states [3]. Differences in receptor density have also been found to be associated with several psychiatric disease states [4] but this is an avenue that has yet to be explored specifically for visceral pain.

Publications in the area of visceral pain imaging have to date largely focused on functional studies examining the activity of different brain regions and of the connections between these regions, as carefully reviewed by Frokjaer and colleagues. However, recent studies in the pain area have also examined structural changes in the brain, like increases in the size and density of grey matter, in different brain regions. The results suggest that pain, particularly chronic pain states, may be associated with reduction in cortical thickness and perhaps even neurodegeneration. While there have been multiple studies in many clinical pain conditions, there have been very few studies specifically addressing visceral pain conditions

While pain perception is obviously a brain function and imaging studies can offer direct insight into pain processing by the brain we do not want to end this brief commentary without pointing out that peripheral mechanisms can play a key role in the early stages of visceral pain signaling. Unlike somatic nociceptors, visceral sensors are intimately integrated with the peripheral tissue that they innervate, with some non-neural cells of internal organs having a quasi-sensory role [5]. This has been best studied in the bladder with the startling demonstration of sensory transduction elements in bladder urothelial cells, which offers the possibility of therapeutic interventions for visceral pain directly aimed at a peripheral target [6,7]. Once again, visceral pain shows unique properties that challenge our dogmas and shed light on how the brain, and the internal organs, deal with this enigmatic, but very prevalent and clinically relevant, form of pain.

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