

A new approach to pain

Professor Anthony Jones, head of the Pain Research Group at Hope Hospital, Salford, explains how he and his team are getting to grips with the causes of chronic pain.

We were awarded a five-year **arc** programme grant in 2001 to study brain mechanisms of pain perception in musculoskeletal disorders, and their modulation by drugs. The purpose of this research programme was to bring together knowledge and skills to discover new pain mechanisms, and to lead to new methods of treatment for arthritic pain. We studied patients whose pain was mainly from long-term damage of the joints (e.g. rheumatoid arthritis and osteoarthritis) compared to patients with conditions where the pain is thought to be mainly driven by psychological factors, such as chronic widespread pain (fibromyalgia). We used a combination of experimental techniques to identify how different aspects of pain are experienced by an individual. Our other aim was to establish how certain features of pain are processed in different areas of the brain, and how these are affected when the attention patients give to the pain is altered by distraction.

During this period we developed techniques for measuring the different components of how the brain detects and interprets pain stimulation, and how these components contribute to normal and abnormal pain perception. Within the brain there are two main systems, the medial (within the centre) and the lateral (to the side of the brain) pain systems. Using this information, we conducted brain imaging studies in normal volunteers and established the role of the two main pain systems in the brain. The medial pain system was found to be concerned mainly with processing emotional aspects of pain (how unpleasant it is), and the lateral pain system is concerned mainly with sensory-discriminative processing (where it is). This provides us with the potential to reduce unpleasantness without necessarily decreasing the awareness of pain location, by modifying activity only within the medial system. This is particularly important to patients with arthritis who need to have an awareness of joint damage and pain to protect their joints, but who will not benefit from the effects of the unpleasantness of the pain.

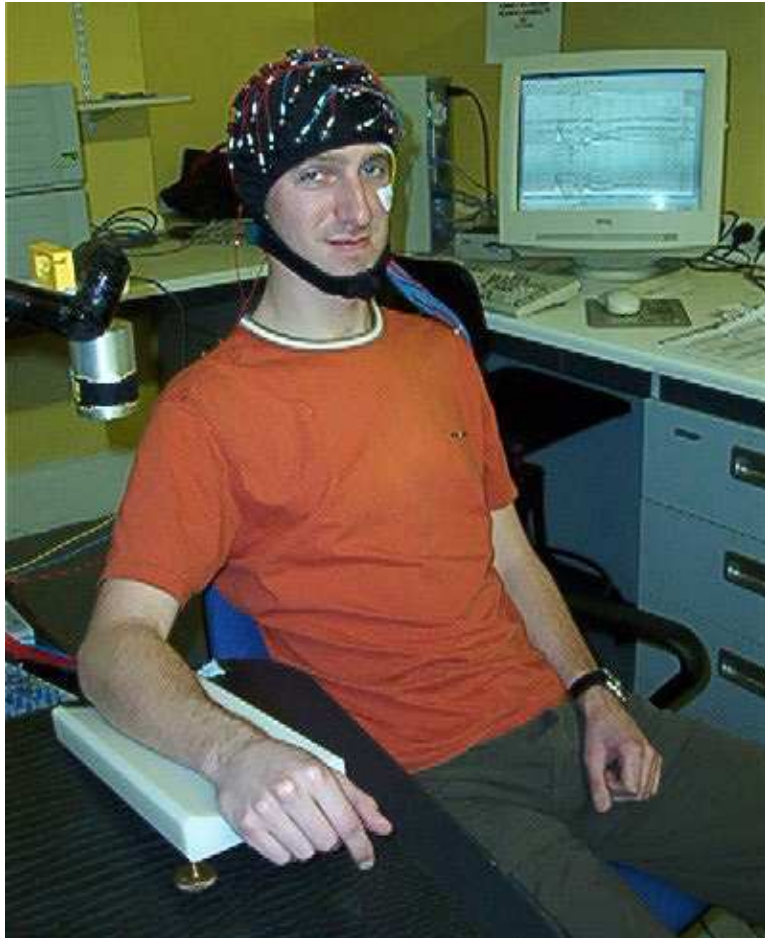
We have also for the first time investigated within the brain the patterns of response to arthritic pain, and compared these to experimentally induced pain. Osteoarthritic pain and acute experimental thermal pain were found to be both processed within the medial and lateral pain systems, but osteoarthritic pain was processed more within the medial pain system than the lateral pain system. This verified that osteoarthritic pain had greater emotional significance, and indicates that potential benefit may occur with treatment that modulates the medial pain system.

Patients with fibromyalgia.... tend to stay focussed on the unpleasant aspects of pain

We have also shown for the first time that there are abnormalities of attention in patients with fibromyalgia, providing a potential brain mechanism for this unpleasant condition. We have identified that patients with fibromyalgia have a problem with the way they deal with pain, in that they tend to stay focused on the unpleasant aspects of pain (processed within the medial pain system) compared to pain-free controls. This is a potential mechanism for the continuation of fibromyalgia and may be a consequence of a failure of internal control mechanisms. If this is the case, its correction by cognitive (psychological therapies) and drug interventions should alleviate or even prevent the symptoms.

We have developed a number of ways to measure how well people can alter the way they deal with different aspects of pain, such as how they manage and anticipate the pain. Anticipation of pain and its modulation has a major role in chronic pain, and we have demonstrated that

consistent measures of the anticipation of pain can be made using EEG (electroencephalography; see picture).



A volunteer undergoing an EEG recording using an electrode cap.

These EEG measures correlated well with the anticipated level of pain from an experimental laser stimulus. We also showed that the sources of these anticipatory responses in the medial (emotional) pain system are enhanced by certain types of anticipation, whereas sources within the lateral (discriminatory) system are decreased. Evidence from questionnaires we have conducted suggests that abnormal anticipation may contribute to the maintenance of chronic pain. These studies will allow us to measure the contribution of anticipation to the maintenance of chronic pain and to develop more refined talking therapies to modulate this aspect of pain perception. Other studies that we have conducted have found that noise reduces the unpleasantness of experimental pain. We think this might be why disgruntled teenagers like loud music, and it might also provide an excuse for more patients with chronic pain to go clubbing!

A strong association between pain and depression

We have also conducted research on the depletion of the neurotransmitter serotonin (a natural chemical produced by the body which regulates functions such as mood, appetite and sleep), and have demonstrated a reduction in the pain threshold (minimum pain stimulus that produces a response) and tolerance (the amount of pain an individual can endure) in serotonin depleted pain-free volunteers. Although there is indirect evidence for serotonin being important in pain perception, based on the pain-relieving effects of prescribed antidepressants that enhance

serotonin's effects, this is the first direct evidence for this in humans. It provides an explanation for the strong association between pain and depression and a potential explanation of the change of pain perception in some patients with depression.

It has been widely reported that the medial pain system contains many brain cells with regions (receptors) on their surface which respond to synthetic opiates like morphine. People who have had morphine for pain may have continued to feel the pain, but have no longer suffered with the unpleasantness of it. Positron emission tomography (PET) studies have shown that drugs such as morphine switch off large parts of the medial pain system. Morphine is now used in small doses taken by mouth to alleviate the pain of arthritis. Interestingly when these drugs are given for pain they have a low risk of addiction, whereas when they are taken for recreational purposes, in the absence of pain, they have a high risk of addiction.

PET studies have also shown that during acute and chronic pain a lot of natural morphine-like peptides called endorphins are released mainly into the medial pain system. We think that this is one of the brain's natural defence mechanisms to limit the unpleasantness of pain and to allow useful activity, such as escape from danger, to occur. They are probably also released during pleasurable activity and exercise, so we probably need to know more about how to keep releasing these endorphins. Interestingly, there are also chemicals being developed that may be able to prevent the breakdown of endorphins and enhance our natural defences against the suffering aspects of pain.

Pain is the main reason that arthritis patients consult a doctor

We have expanded our understanding of the brain mechanisms involved in the perception and processing of pain in osteoarthritis, and this will enable us to continue our research into new and exciting areas. Pain is the main reason that arthritis patients consult a doctor and the main cause of immobility, but treatment options are limited. We have shown that arthritic pain has an important emotional component in the brain. Our ultimate goal is to reduce this emotional component, in order to reduce the unpleasantness of pain and increase mobility. We want to investigate how levels of distress (anxiety and depression), which affect this emotional component, can also alter treatment outcome by studying the brain chemicals (opiates) which control this component. This will include studies into the effect of modulating the medial pain system by endogenous (produced in the body) and exogenous (manufactured) opiates, and the prediction of therapeutic outcome within the different physiological characteristics (phenotypes) that we are beginning to establish.

In order to complete some of these studies we will make use of a newly established imaging facility, the Wolfson Molecular Imaging Centre (WMIC). This centre, based in Manchester, employs experts from around the globe who are skilled in conducting cutting-edge research.

Lastly, in addition to the **arc**-funded research conducted by the group, I have been asked by the British Society for Rheumatology to co-ordinate a national group of clinicians, pharmacists, psychologists and physiotherapists to produce guidelines for doctors on the management of musculoskeletal pain. These guidelines will eventually be adopted nationally and introduced into practice in 2007.