DEVELOPMENTS in neuroimaging over the past 2 decades have given us remarkable insight into the living human central nervous system. Whether the information is neurochemical, structural, or functional, a range of central nervous system disorders will undoubtedly benefit from an improved scientific understanding of the mechanistic changes that occur \textit{in vivo} and over time as the condition develops or improves. The next challenge for neuroimaging is to deliver statistically robust information at an individual level, rather than group-averaging neural responses. This allows identified mechanisms with their concomitant neuroimaging markers to be related to your patient and their particular set of symptoms, possibly even providing measures that predict treatment response. The study in this month’s issue by Harris \textit{et al.} moves us forward in understanding individual patient responses to analgesics and highlights how brain imaging can be used to distinguish drug from placebo effects in patients.

Acute and chronic pain is one area where dramatic strides in our understanding of mechanisms have occurred. Functional imaging is a powerful tool that allows us to measure how the brain is processing and modulating nociceptive inputs to produce pain perceptions—a “behind the scenes” measure distinct from but obviously related to subjective descriptions of pain—a process that occurs subsequently. The relationship between the underlying neuroimaging measures and subsequent ratings and behavior is by no means a simple one. Many factors contribute to pain ratings, which irrespective of the nociceptive input or even the presence of strong analgesics mean divergences, and more complex relationships can occur between what subjects report and measured regional brain activity. This has tremendous value if you are careful with interpretation and do not consider or limit brain imaging as simply a surrogate measure of rating, as is sometimes purported. Other measures, say structural or neurochemical, might also provide clues as to the underlying mechanisms sustaining a chronic pain state or how the condition itself is changing the brain—all have value. One approach to test the clinical relevance of any of these measures is to treat the patient, say pharmacologically, and see how they change relative to definitive-standard clinical measures. However, given the differences in sensitivity of behavioral and neuroimaging measures alongside the complex relationship between brain processing of nociceptive inputs and subjective pain ratings, it is possible that a treatment can change structure, function, or neurochemistry in the absence of a significantly altered pain rating. That likelihood is why I find the study by Harris \textit{et al.} published here so fascinating. Alongside identifying neuroimaging markers that correlate with baseline clinical pain scores and that are modulated by drug but not placebo, they also show results where the scenario just described occurs: that observation raises some interesting questions.

Using a small cohort of female patients with fibromyalgia (14 and 17 for different neuroimaging measures) and a double-blind two-period cross-over study of pregabalin (dose escalation to 450 mg/day for 14 days, with maintained fixed dose of 450 mg/day for last 3 days) and placebo (using same regime), neurochemical, brain functional connectivity, and brain activity to pressure pain were collected in four separate imaging visits (pre- and posttreatment for the two arms) to...
determine which measures were modulated in the drug but not placebo arm.

Proton magnetic resonance spectroscopy (1H-MRS) was used to determine the resting free glutamate and combined glutamate + glutamine (Glx) concentration within the brain. This Glx measure likely reflects the brain's excitatory "tone," based on recent observations linking resting variances in γ-aminobutyric acid and Glx levels to neural activity and decision making. Also, previous observations that show Glx is increased within the posterior insular cortex of patients with fibromyalgia and decreases with successful treatment support its relevance in pain. The insular cortex is a prime candidate to monitor and target in pain studies aimed at assessing longitudinal treatment effects. Data from a wide array of studies support a pivotal role for the posterior insula/inner operculum in encoding and in certain circumstances generating pain experiences—the anterior insula is more involved with modulation, interpretation, and awareness of the pain. Harris et al.’s second measure linked activity within the insula to a core neural network that is fundamental to brain function: the Default Mode Network (DMN). This network, active at rest and comprising the medial temporal lobe, medial prefrontal cortex, posterior cingulate cortex, precuneus, and medial, lateral, and inferior parietal lobules, is thought to be involved in introspection/self-referential thinking and memory retrieval. Increased connectivity to this network from the insula has been reported in patients with fibromyalgia, and this connectivity normalizes with successful treatment. The third measure examined DMN deactivation (a normal response to all stimuli as we move from introspection to response to a new stimulus) to stimulus evoked pressure pain. Combined, these three complementary measures were examined for their utility as potential "pathological" markers of the chronic pain state that might be modified by pregabalin but not placebo, and how they relate to each other and to pain ratings. The ability to take meaningful biological measures that relate to the pain condition and in vivo assess the impact of drug or placebo treatment on them provides indirect support of their potential relevance and insight into how analgesics influence pain mechanisms at a systems level. Other neuroimaging data highlight the impact of unmanaged chronic pain on the brain. Whether these are adaptive or maladaptive influences is debatable, and this uncertainty raises an interesting question as to whether quelling and attempting to normalize aberrant brain activity to minimize their impact, irrespective of any analgesic effect, is a good thing. What the authors showed is that all three measures, Glx (right posterior insula only), connectivity of anterior and posterior insula to a key region of the DMN, and deactivation of some DMN regions to evoked pressure pain, were altered (decreased for first two, increased deactivation for last) by pregabalin but not placebo. For the 17 patients who contributed to the Glx data, there were no changes in clinical pain ratings whether on pregabalin or placebo, but a significant effect of pregabalin on pressure pain ratings. For the 14 patients who contributed to the DMN analyses, there was a significant reduction in clinical pain on pregabalin but not placebo. Of note, many of the pretreatment baseline levels of these measures correlated with the magnitude of clinical pain at that time, supporting earlier work and their potential relevance as pathological "markers." Harris et al. show also that clinical pain changes were predicted by resting connectivity and evoked neural activity (deactivation) in the DMN, whereas Glx within the posterior insula predict behavioral changes in evoked pain only. This observation tantalisingly suggests that the personalized medicine and stratification goals we so desperately want for our patients might be realized using neuroimaging alongside other measures being tested. Finally, it should be noted that the authors did not statistically and directly compare the changes pre- to posttreatment between drug and placebo arms. Group averaging pain-rating changes and comparing drug versus placebo is the norm; however, the assumption of additivity is currently being called into question. A brain "on-drug" might not necessarily be capable of mounting the same mechanistic placebo analgesic effects as a brain "off-drug," and so it might not be the case that subtracting behavioral data on the placebo from the drug arm is always valid. This concern is the basis of their rationale. Despite this (yet to be confirmed) issue, the data here show distinguishable mechanistic-based brain activity changes during pregabalin administration that are not present during placebo. It will be important to ascertain how generalizable these results are across chronic pain conditions treated with pregabalin. Seeing how our drugs work—as done here—not only confirms the utility of neuroimaging-based measures in translational pain studies but also raises important questions for future treatment strategies and debate.

Irene Tracey, M.A. (Oxon), Ph.D., F.R.C.A., FMRIB Centre, Nuffield Division Anaesthetics, Nuffield Department Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom. irene.tracey@ndcn.ox.ac.uk

References