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Technology for Chronic Pain

Minireview

Suyi Zhang¹ and Ben Seymour^{1,2}

Technology developed for chronic pain management has been fast evolving and offers new stand-alone prospects for the diagnosis and treatment of pain, rather than simply addressing the limitations of pharmacology-based approaches. There are two central challenges to be tackled: developing objective measures that capture the subjectivity of pain experience, and providing technology-based interventions that offer new approaches for pain management. Here we highlight recent developments that hold promise in addressing both of these challenges.

Chronic pain is the greatest cause of disability worldwide [1]. Tension-type headache, migraine, low back and neck pain, along with other musculoskeletal pain conditions, are among the most prevalent neurological causes of disability. In western societies, chronic pain is by far the most costly, in economic terms, of all neurological and psychiatric conditions as a result of its associated impact on the working population and its care requirements in the elderly. This enormous societal burden is fed in no small way by the inadequacy of current pharmacology-based treatments, especially for severe pain. In light of its fast-evolving nature and its contribution to many areas of medicine, medical technology has the capacity to become an integral part of the diagnosis and treatment of pain. In this minireview, we consider whether technology can offer a new direction in chronic pain management by addressing two central challenges — developing new objective measures that capture the subjectivity of pain experience, and providing technology-based treatments that offer new avenues of pain management.

Sensors and Biomarkers

Thomas Lewis, a Welsh neurologist, once wrote: “Pain is known to us by experience and described by illusion.” Indeed, the lack of any adequately objective, measurable index of pain is at the heart of clinical frustration regarding its management. On account of its fundamentally subjective nature, pain is currently measured almost solely by self-reporting, through either clinical questionnaires or visual analogue scale (VAS). Whilst simple and quantifiable, these approaches can be criticised for being idiosyncratic, lacking in consistency within or concordance between individuals, reactive to suggestions, and perhaps more importantly, pervious to deception and impression management [2]. Moreover, self-reporting may not always be available, for example, in the case of the very young, the elderly, and those otherwise unable to communicate effectively.

An objective pain measure could be used for three distinct classes of applications. First, it could be used in a clinical setting as a diagnostic and prognostic biomarker, to help classify and quantify patients, and to predict comorbidities and response to treatment. Second, in a domestic setting,

it could be used to evaluate and monitor patients in their daily life, and to understand the dynamics and impact of treatments on pain. Third, in a clinical engineering context, it could be used either to directly control treatment delivery, such as drug delivery or brain stimulation, or in communication devices. Accordingly, significant efforts continue to be made to try to devise objective indices of pain using behavioural, physiological, and brain activity measures (Figure 1).

Analysing Behaviour

Non-verbal pain behaviours may be as communicative as verbal self-reporting and, at an individual level, these are often easy to interpret from observation. Vocalisations of distress, abnormal posturing and facial expressions, and impaired functioning and movement all convey distress. However, although the information is clearly present, their usefulness as pain indices has been difficult to exploit because of the subjectivity inherent in human observers, and the difficulty in quantification of relevant data.

Recently, advances in computer vision have inspired the possibility of automatic recognition of facial expressions of pain without the need for human assessors. Fully automated computer vision systems code facial muscular movements according to a facial action database (based on Gabor filter decomposition of video frames — a feature extraction process (based on orientation selectivity of the filter) similar to that of the mammalian visual system) and measure their magnitudes in real time. The resulting set of component action units is then used as temporal features for classifiers. In previous studies, such detection systems have been used to discriminate pain from non-pain [3], and to classify real from faked pain expressions [4]. In both cases, computer vision outperforms human observers with significantly higher accuracy; it is also superior in capturing miniscule changes otherwise undetectable to human experts, and in continuously monitoring streams of video data. However, facial recognition methods cannot quantify pain directly, and different contexts or cultural background of the subject may influence the sensitivity of these methods, making them unlikely to become stand-alone pain assessments.

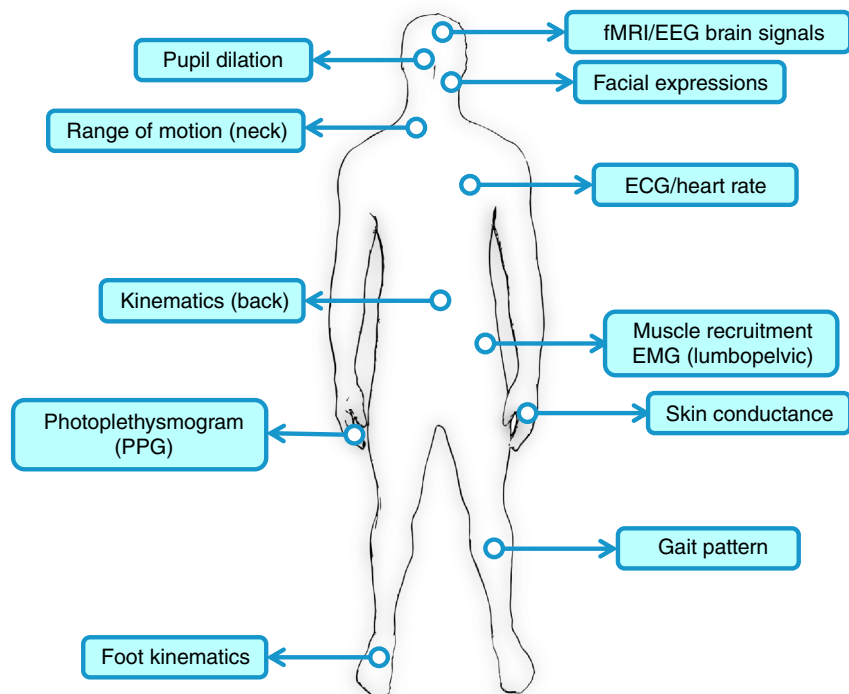
In addition to facial expression, many pain disorders will have motor manifestations in other domains, such as posture, gait and movement. Technologies such as the measurement of electrical activity produced by muscles (electromyography, EMG), body-attached movement sensors (accelerometry), foot or floor-plate pressure sensors, and environmental motion-capture systems (such as ‘Kinect’), can in principle capture impaired or altered musculoskeletal function as a result of pain. Surface EMG activities can inform muscle recruitment pattern, such as onset timing and symmetry, which may be significantly altered in patients who adopt different movement strategies because of pain [5]. Another approach is to measure alterations in the range of motion and related kinematic features (such as movement smoothness and jerk), using 3D orientation/motion sensors [6] and ground reaction force plates [7]. Wireless and wearable sensors facilitate remote (e.g. domestic) data collection, together with software/applications in mobile devices, they can be used for self-monitoring or preventative purposes in pain management [8]. At present, movement sensing is better suited to be part of the diagnostic investigation rather

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Figure 1. Behavioral, physiological, and direct brain signals that can be sensed as pain biomarkers. fMRI, functional magnetic resonance imaging; EEG, electroencephalogram; ECG, electrocardiogram; EMG, electromyogram.



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than solely as a pain indicator because of its required specificity in muscle groups and/or tasks; its high-false positive rate (e.g. interpreting non-painful movement as painful) and high inter-individual variability are also potentially problematic.

Analysing Physiological Signals

Pain may not always elicit externally perceivable pain behaviour, but its role in homeostasis is manifest by efferent responses in the autonomic nervous system [9]. Therefore, physiological signals that act as indices of autonomic regulation, including heart rate variability recorded via an electrocardiogram (ECG), skin conductance, also known as the galvanic skin response (GSR), blood volume fluctuations measured via photoplethysmography (PPG), and pupillary dilation, are potential pain indices. It has been demonstrated that a linear combination of multiple autonomic parameters can differentiate various intensities of acute heat pain that cannot be accomplished by a single parameter: the variability within sympathetic/parasympathetic outflows to different end organs can permit different autonomic parameters to generate a multi-dimensional model for pain intensity classification [10]. A recent study further supported this idea, as it showed that combined skin conductance and pupillary signals could predict pain intensity with high accuracy [11].

Autonomic indices, especially when used in isolation, face several weaknesses, however. First, these indices are not specific to pain compared with other salient and alerting stimuli. Second, they may be less useful in chronic compared with acute pain assessments. Third, autonomic parameters can vary significantly across individuals, according to trait differences such as gender, genotype, fear of pain, and level of pain catastrophising [12]. Although this last issue may be overcome by careful calibration or the use of extensive databases, the first two weaknesses may prove problematic in attempts to use physiological pain markers in clinical settings. With a number of wearable autonomic sensors being commercially developed, in addition to the greater application of multivariate methods [13–15], the validity of using combined physiological signals as a pain indicator could be substantially enhanced.

Analysing Brain Activity

The ability to identify acute pain with sensitivity and specificity is now well established with functional magnetic resonance imaging (fMRI) [13–15]. Using multivariate pattern analysis (MVPA) of voxel-based blood oxygen level dependent (BOLD) responses, it is possible to predict intensity

and even spatial location of acute pain, in a manner that is both specific to pain versus other salient stimuli and generalises across individuals. This convincingly demonstrates the existence of information-rich, measurable signals for pain in the brain. However, to be useful for applications, two important challenges need to be met. First, clinical diagnostic biomarkers require classifiers to be developed for chronic pain, not acute pain. Second, monitoring devices and neural engineering applications require implantable or wearable sensors, since portable fMRI is impossible.

Two approaches have been proposed for the development of fMRI-based MVPA clinical biomarkers. The first is to use voxel-based BOLD responses to acute phasic pain, e.g. electrical stimulation of the back, in patients with chronic back pain and compare with healthy controls; recent studies have demonstrated the feasibility of this strategy [14,16]. The second is to look at brain connectivity during resting-state brain activity. This latter approach has perhaps the most promise, since there is now substantial evidence that chronic pain and many other neurological and psychiatric brain disorders (such as depression, autism, and obsessive compulsive disorder) display abnormal brain connectivity, which in principle can be used for both univariate and multivariate pattern-based classification and prediction. In particular, the recent use of network theoretic approaches (graph theory) [17] to try to characterise the nature of connectivity disruption offers the hope of mapping data-driven biomarkers to the underlying biology.

fMRI cannot be used as an ambulant sensor, and although functional near-infrared spectroscopy (NIRS), which also measures blood flow, can be measured with wireless portable detectors, it is currently too cumbersome to be practical. Electroencephalogram (EEG), electrocorticogram (ECoG) and implanted deep brain electrode local field potential (LFP) signals may offer an alternative. In addition to eliciting spatially specific evoked responses in experimental

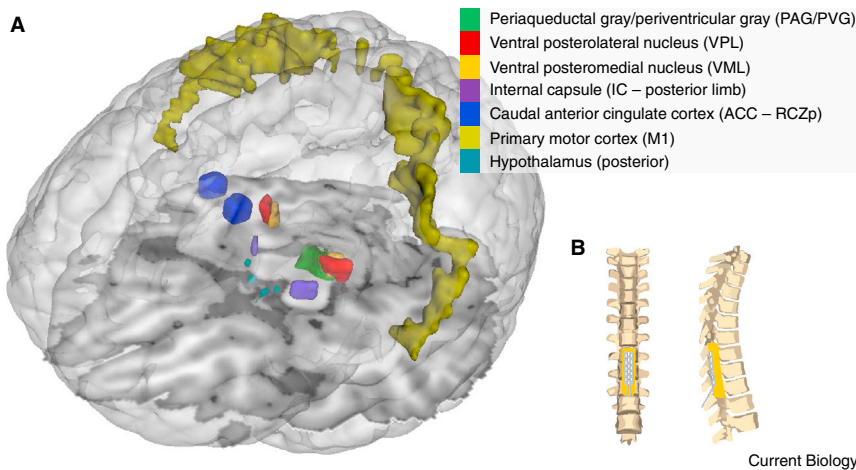


Figure 2. Demonstration of current neuromodulation targets.

(A) Major stimulation sites in the brain used in deep brain stimulation (DBS), motor cortex stimulation (MCS), and transcranial magnetic stimulation (TMS). (B) Schematic drawing of multi-electrode spinal cord stimulation (SCS) arrays.

settings, pain has more persistent disruptive effects on thalamocortical synchrony that may be useful in ambulant settings [18]. Similar event-related desynchronisation has also been identified in human subdural ECoG recordings [19]. In particular, persistent pain induces clear changes in oscillatory power in both theta and alpha frequency bands [20,21]. In a minority of chronic pain patients with implanted deep brain stimulation electrodes, LFP recordings have also shown a site-specific, time-frequency-dependent correlation with reported pain scores [22]. In summary, whilst fMRI will likely to become a valuable tool for clinical diagnosis, ambulant monitoring of pain may require the integration of sensing from multiple domains (neural, physiological and behavioural), which can capitalise on rapidly advancing sensor, network, and decoding technologies.

Ultimately, any behavioural or physiological method for pain detection or diagnosis must meet quite stringent criteria for specificity and sensitivity in order for it to be clinically useful. It also needs to be practical, robust (across environments and time), generalisable across patients and sites, and inexpensive. Thus, the emphasis of current research is on improving both sensor technology and analysis methodology.

Technology-based Interventions

Recent years have seen a growing interest in technology-based interventions in the management of neurological and psychiatric diseases. The first record of pain treatment using electrical stimulation dates back to about 15 AD: a Roman court physician, Scribonius, observed accidental contact with torpedo fish was able to relieve gout pain and recommended applying torpedo fish to painful regions as a general treatment [23]. Unlike conventional pharmacology, neuromodulation has the advantages of immediate delivery, reversibility and programmability, and a potentially lower risk of adverse effects. Recent clinical studies and trials have demonstrated the safety and efficacy of various neuromodulation modalities in chronic pain treatment (Figure 2).

Spinal Cord Stimulation

First proposed by Shealy and colleagues in 1967, implantable spinal cord stimulation (SCS) was initially utilised for cancer pain relief as an alternative to neuro-ablation. The first model consisted of platinum plate electrodes implantable in the spinal subarachnoid space, with external power

supply through needles passing through the skin [24]. The electrical stimulation in the dorsal columns creates non-painful, tingling paraesthesia, which attenuates the sensation of pain in the affected area. Although it is not especially well understood how SCS produces analgesic effects, several

mechanisms have been proposed for certain types of pain, including through both neural and vascular effects. Overall, SCS has gained acceptance (FDA approval) in the treatment of various chronic pain conditions of the limbs and trunk, amongst which mixed-pain syndromes, such as failed back surgery syndrome (FBSS), and inoperable ischemic limb pain, are the most common indications [25].

Current SCS systems are often equipped with implanted multi-electrode arrays, conductive leads, and a controllable pulse generator. Multi-electrode, paddle-type arrays offer more contact points, which lower surgical revision rate and the incidence of lead fracture, and allow more complex programming to stimulate specific dorsal column fibres [24]. Implanted pulse generators with rechargeable batteries, or radio-frequency receivers driven externally via antenna are both in use, with the latter aimed for use in patients requiring high-power stimulations [25]. Recently, high-frequency SCS systems at 5–10 kHz, a huge departure from the conventional range of 20–120 Hz, showed consistent pain relief in patients while inducing no perception of paraesthesia [26]. While its mechanism remains unknown, a recent animal study showed SCS at kHz level provided earlier inhibition of mechanical hypersensitivity [27], which suggests that other peripheral mechanisms may be responsible for satisfactory pain relief in some high-frequency SCS patients who previously failed conventional SCS trials because of inadequate paraesthesia coverage.

Other technological improvements include position-adaptive SCS driven by acceleration sensors that deal with the problem of under/overstimulation during a shift in body positions (and hence relative electrode–cord contact position) [28]. However, SCS is only effective in about 50–70% of cases and the causes of this remain unclear, meaning that a reasonable number of patients will end up seeking alternative treatments.

Deep Brain and Motor Cortex Stimulation

The first attempts using deep brain stimulation (DBS) for treating refractory pain date back to over 50 years ago, preceding both the gate control theory and SCS [29]. DBS involves surgical implantation of electrodes for electrical stimulation in pre-identified target sites located in deep brain structures — most commonly, the periaqueductal and/or periventricular gray matter (PAG/PVG), the sensory thalamus (the ventroposterolateral/ventroposteromedial

nucleus, VPL/VPM), the internal capsule, and the posterior hypothalamus [30,31]. The exact mechanism behind DBS-induced analgesia is not yet fully understood. It is assumed that stimulating PAG/PVG activates the descending pain modulatory systems and/or increases the release of endogenous opioids, while the stimulation of the sensory thalamus acts by modulating the integration or propagation of the transmitted sensory information, independent of opioid release [32]. It is also proposed that multiple mechanisms may be involved simultaneously [33].

As a result of the limited number of patients treated and a few, less-successful, earlier clinical studies, DBS for chronic pain treatment has yet to gain FDA approval, at the same time facing competition from cheaper, less invasive, and more easily implementable alternatives. The development of DBS has also been limited by the lack of consensus regarding the targeted stimulation sites and by patient selection, which contributed greatly to variability in efficacy [32,34]. The reported long-term success rate of DBS varied from 19% to 79%, and appeared to be higher for the treatment of certain pain states than others [31]. Fortunately, recent studies of DBS using neuroimaging and neuroelectrophysiology techniques may help in elucidating these issues. For example, magnetoencephalography (MEG) allows for a comparison of DBS-induced functional brain changes in the long- and short-term [35]. Also, local recordings from deep brain electrodes may contain neural ‘signatures’ of pathologies that might act as predictors of treatment efficacy or as feedback signals in new generation modulators [29].

Motor cortex stimulation (MCS) for pain relief originated from epidural brain stimulation, a less invasive alternative to DBS. In early exploratory research of neuropathic pain, Tsubokawa *et al.* [36] first demonstrated that stimulating the motor cortex using dural electrodes showed excellent pain reduction in post-stroke patients with thalamic pain, in cases where SCS and DBS had shown limited efficacy. The mechanism behind MCS pain modulation remains elusive; it is speculated that the excitation of the motor cortex may induce inhibition of nociceptive neurons in somatosensory areas, possibly also extending to the spinal cord [34,37]. According to an efficacy study, 55% of patients who had undergone MCS and 45% of those in 1-year post-operative follow-ups reported significant (i.e. more than 40%) pain relief [38].

Transcranial Magnetic Stimulation

Compared with SCS and DBS, transcranial magnetic stimulation (TMS) has the innate advantage of being non-invasive and hence safer with respect to the adverse events that may come with surgery. TMS is thought to achieve the same effect as MCS, but in a non-invasive manner through brief alternating magnetic fields on the scalp over the target; this stimulation induces electrical currents in the neurons of the cortex. Low-frequency stimulation (around 10 Hz) applied to the motor cortex within the somatotopic representation of the painful area in M1 has shown lasting pain relief in various neuropathic pain conditions [39]. In most cases, modest analgesic effects are reported after one or two weeks of daily repetitive TMS sessions [40,41]. In a study where a reduced number of weekly sessions were conducted after initial daily stimulations, some patients showed residual pain relief lasting for up to four weeks after stimulation stopped [40]. Additionally, the fact that the motor cortex is the targeted stimulation site enables the use of evoked

motor responses, or EMG, for target localisation. Recent development of MRI-navigated TMS allows more precise anatomical targeting over repetitive sessions [39].

In a similar vein to TMS, transcranial electrical stimulation (TES) — comprising transcranial direct or alternating current stimulation (tDCS/tACS) — stimulates the cortex using weak electrical current. tDCS of the motor cortex has shown effective reduction of neuropathic pain over sham controls [42]. As electrode positions and sizes in tDCS determine its therapeutic outcomes, engineering techniques, such as finite-element modelling, can optimise results by modelling cortical current distribution. Theoretically the main advantage of tDCS lies in its suitability for home use, since the stimulators are much smaller and logistically practical for domestic environments. However, a recent Cochrane systematic review pointed out that most current studies on non-invasive brain stimulations should be interpreted with caution due to suboptimal sham conditions and inadequate sample size [43].

Virtual/Augmented Reality

Virtual reality (VR) and augmented reality (AR) environments are technologies aiming to form a relatively believable simulation of reality by creating sensory illusions. While VR works to promote behavioural engagement in a virtual environment analogous to the real world, AR augments the real world by the addition of digital information [44]. Commonly used sensory stimulation in these systems include visual (e.g. display helmets), auditory (e.g. headphones), and tactile (e.g. vibrating actuators) feedback, usually with sensors incorporated to change stimulation settings according to user responses; in this way, users achieve a psychological sense of ‘presence’ in VR/AR environments through sensorimotor immersion.

Pain management through VR/AR employs two principal strategies: distraction and feedback. Distraction usually involves using active cognitive processing to shift the user’s attention, such as that required by interactive gaming, resulting in increased pain threshold and/or tolerance. Whilst it is effective in reducing experimental pain and burn-injury-related discomfort, its results in other pain conditions have been less consistent [45].

Feedback-based VR/AR strategies are principally aimed at phantom limb and deafferentation pain syndromes and related disorders in which central representations of pain are abnormal (such as complex regional pain syndrome). Founded on Ramachandran’s famous observation that a mirror illusion of an intact arm in the position of an amputated arm reduces phantom limb pain, the principle behind VR/AR pain relief is to simulate multimodal sensorimotor feedback as realistically as possible, for example, by incorporating location sensors on the limb stump to generate a more accurate kinaesthetic and visual feedback [46], or by using surface EMG to guide movements of virtual limbs to enable restoration of perceptual representation of the missing limb [47]. The growing affordability and portability of VR/AR systems will likely facilitate the development of standardised feedback therapy systems applicable to various chronic pain conditions.

Along the lines of VR/AR, robotic prostheses also show particular promise in alleviating phantom limb pain through partial restoration of motor and sensory functions. In a recent pioneering study, a patient suffering from phantom limb pain experienced a reduction of symptoms after implantation of

electrodes at the intraneural interface to efferently control an upper limb prosthesis and to afferently receive electrical stimulation corresponding to hand/finger sensation. The residual sensory presence of the missing limb and reduced pain rating lasted a week after implant removal, before eventually reverting to pre-implant level after 3 months [48]. Rapid advances in hand prostheses allowing bidirectional sensorimotor control in real time are likely to further enhance its naturalistic feeling [49]. The complete package offers substantial promise towards the long-term goal of near-natural functional restoration.

Future Directions

Despite the relative potential of present decoding and analysis applications for probing pain, it is not clear to what extent they are informative of the mechanisms or neurobiology behind chronic pain. A clearer theoretical and computational framework of pain processing is likely to be a critical pre-requisite in the further development of future therapeutic technologies; that is, it is the combination of data-driven and hypothesis-driven experiments that will be important in identifying new targets for technology-based interventions.

The difficulty of managing chronic pain is predominantly a result of its complex neurobiology: its symptomology is pervasive but subjective, and stems from the complex brain-wide network processing about which we understand very little. For this reason, it has benefitted less from medical technological approaches than other areas of medicine, but arguably stands to gain more. Below we consider three areas that are likely to see real advances in the next decade.

First, parallel advances in non-invasive wireless sensor technology, network technology, and big-data decoding mean that the ability to realise continuous domestic pain monitoring is feasible ('smart sensing'). This will allow pain communication systems for those with communication deficits, clinical monitoring of patients for diagnostic and treatment evaluation, and quantification for clinical trials.

Second, 'smart sensing' may allow for the development of novel neural engineering-based therapeutic devices that use feedback control in some manner. By using techniques such as fMRI, for example, it may be possible to develop new types of decoded neural feedback device that provide improved control over brain activity using conscious control strategies [50], as an adjunct to standard behavioural and cognitive therapy. This idea can also be extended to feedback-regulated neuromodulation systems, to yield 'closed-loop' control systems that adjust intervention using the measured pain intensity being experienced as feedback, in order to achieve continuous pain relief. The benefits of delivering stimulation at the required dose at the required time include reducing the probability of habituation to stimulation, the incidence of side effects, and battery usage.

Finally, more sophisticated stimulation methods are needed, and the advent of optogenetics has the potential of transforming the efficacy of pain neuromodulation. Optogenetics offers anatomical, cellular and temporal specificity, and should hold remarkable potential to open a new era in brain-stimulation technology. Direct manipulation of a specified population of cells can help elucidate their roles in a complex physiological process, such as pain, and potentially identify more refined stimulation targets for treatment purposes. This includes combined excitation and silencing methods, spinal cord stimulation, multi-fibre stimulation to drive changes in brain dynamics, targeting neuromodulator

and neuropeptide pathways, glial optogenetics, and other methods. Aside from the methodological challenge of safely transfecting opsins in humans, its success will likely depend on a better understanding of the basic neuronal physiology of pain information processing that it promises.

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