SECTION II

Pain in the brain

CHAPTER 8

Brain imaging in experimental pain

Massieh Moayedi and Tim V. Salomons

Traditional theories of pain have depicted pain as a 'bottom-up' phenomenon: a direct reflection of peripheral injury or pathology. Descartes, often considered the father of Specificity theory (but see Moayedi and Davis, 2013), posited that the pain system runs on a direct line from the skin to a pain centre in the brain. Activation of this line was viewed as necessary and sufficient for the experience of pain, with the implication of a one-to-one correspondence between peripheral stimulation and the pain experience. Such theories allow only a minimal role for the brain, viewing it largely as a relay centre for messages from the periphery, as evidenced by Descartes' metaphor of the brain as a bell to be rung by tugging on a string in the periphery (Descartes, 1664).

The Specificity account of pain was advanced by the discovery of nociceptors: these are nerve endings in the periphery that respond exclusively to stimulation that is strong enough to signal potential damage. Sherrington (1903) used the term 'nocicipient' to describe cutaneous end organs specific to noxious stimuli – a framework that was validated by Perl's discovery of primary afferents responsive only to mechanical noxious stimulation (Burgess and Perl, 1967), as well as of polymodal nociceptors and high-threshold mechanoreceptors (Bessou and Perl, 1969). These discoveries supported one aspect of the bottom-up account, namely that pain is associated with the activation of specialised receptors in the periphery. It is critical to note, however, that pain and nociception are not synonymous. Nociception, according to the 2011 taxonomy of the International Association for the Study of Pain (IASP), is 'the neural process of encoding noxious stimuli' (Merskey and Bogduk, 1994: 209) – a process that is initiated by activation of nociceptors through noxious stimulation. In contrast to nociception, however, pain requires a conscious perception.

The clinical literature provides multiple examples of what Melzack and Wall (2004) referred to as the 'variable link' between nociception and the conscious perception of pain. Beecher (1946) famously documented soldiers who sustained grave injuries on the battlefield but experienced no pain until they were safe from direct threat, highlighting the fact that nociception is not sufficient for the experience of pain. Furthermore, many chronic pain disorders occur without apparent injury or measurable pathology, or persist long after an initial injury has healed; this suggests that the relationship between nociception and pain might be less exclusive than

An Introduction to Pain and its Relation to Nervous System Disorders, First Edition. Edited by Anna A. Battaglia.

depicted by early theorists. Observation of the centrally mediated facilitation of pain in many of these chronic pain disorders (Edwards, 2005; Arendt-Nielsen and Yarnitsky, 2009) suggests that one explanation for the complex relationship between nociception and pain is that the brain plays a far more prominent role than that initially hypothesised by Descartes.

Even in the presence of nociceptive input, the experience of pain can be transformed by the cognitive and emotional context in which nociception occurs. Pain that is believed to signal a grave health risk is experienced differently from a similar level of pain that is believed to be innocuous. Cognitive and affective responses to pain are critical to clinical presentation, as belief-based schemas such as catastrophising are repeatedly shown to affect outcomes in chronic pain (Campbell and Edwards, 2009). These top-down modulatory influences provide further demonstration of the 'variable link' between nociception and pain perception.

As our understanding of the peripheral events that give rise to nociception develops, it is clear that the depiction of specific channels or 'labelled lines' for pain was prescient. Nevertheless, it is equally clear that nociception alone cannot account for the entirety of pain experience. The brain plays an active role in modulating the conscious perception of pain in response to the sensory, emotional and cognitive context in which nociception occurs. Understanding how the brain instantiates this active role, however, remains a challenge. While work in non-human species continues to provide insight into key processes, it has one critical limitation: pain is inherently a subjective experience and impossible to fully understand without subjective report. Thus, while work in non-human species allows for more invasive and directly interventional studies, understanding how the brain shapes the human experience of pain requires techniques that can combine the direct *in vivo* examination of neural processes with self-report. Modern brain-imaging techniques provide this opportunity and therefore represent a critical tool for understanding the brain's contribution to human pain experience. Now, more than twenty years after the first neuroimaging studies were used to investigate pain (Jones et al., 1991; Talbot et al., 1991) the field of pain neuroimaging has expanded exponentially – but how far has it advanced our understanding of how the brain contributes to the pain experience? This chapter reviews the contribution of neuroimaging to our understanding of the brain's role in this experience and assesses some of the methodological and inferential challenges that have limited progress.

Brain-imaging methods

Functional brain imaging

There are various imaging modalities that can be used to investigate brain mechanisms of pain. As indicated in Figure 8.1, methodologies for examining brain function differ in their temporal and spatial specificity. Additionally, imaging techniques vary in terms of their suitability for examining evoked or basal states or in terms of their ability to capture specific aspects of pain transmission or response. Electroencephalography (EEG) is a non-invasive brain-imaging technique for measuring the brain's intrinsic electrical activity through the skull with a single or an array of electrodes. It offers high temporal resolution, allowing for the measurement of spontaneous neural activity related to spontaneous pain or for event-related neural activity (stimulus-evoked potentials like pulsed laser heat stimuli) on a millisecond time scale. However, the spatial resolution of these techniques is comparatively low, because each electrode records

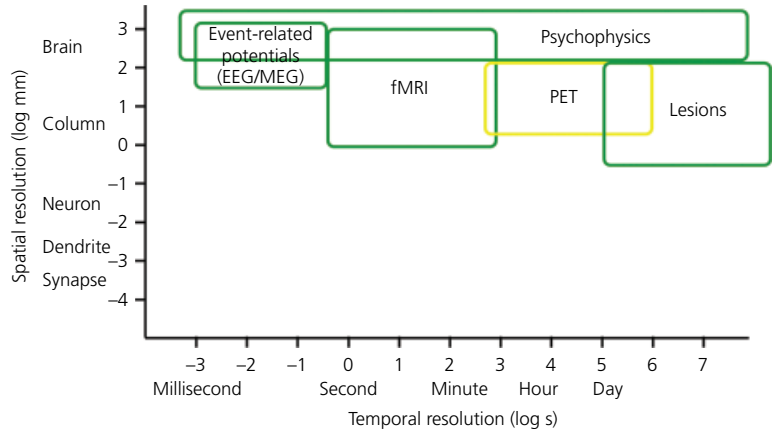

Figure 8.1 Schematic of the spatial and temporal resolution of different techniques to elucidate brain functions. The y-axis represents the spatial resolution, and the x-axis represents the temporal resolution. The colour of the boxes represent the invasiveness of the technique: yellow is invasive, and green is non-invasive.

the sum of activities from large swathes of brain (large, that is, by comparison to the size of individual neurons). Positron emission tomography (PET) imaging is based on the spatial distribution of radioactivity emitted by radioactive isotopes (injected into the subject as part of a molecule) that emit positrons as they decay. The system investigated relies on the radionuclide used. While PET offers relatively poor temporal resolution, it (along with a similar but more recent method, arterial spin labelling) provides quantitative images, making it possible to study basal states. A further advantage of PET is the ability to use radiolabelled molecules in order to target the activity of specific neurotransmitter systems during a given paradigm. Therefore PET can be used to investigate the role of neurotransmitters like dopamine, serotonin and opiates in nociceptive processing and in pain modulation.

While other functional techniques offer advantages in terms of temporal resolution, receptor specificity or the ability to provide quantitative (rather than relative) measures, functional magnetic resonance imaging has been the most widely used measure, primarily because it is non-invasive and is perceived to have a good balance of temporal and spatial resolution relative to other imaging modalities (see Figure 8.1). This chapter will therefore focus primarily on fMRI.

Functional Magenetic Resonance Imaging

Functional magnetic resonance imaging measures a hemodynamic response, usually the blood oxygenation level-dependent (BOLD) signal. The hemodynamic response is used as a proxy for neuronal activity, on the assumption that oxygenated blood flows preferentially to regions where neuronal populations are more active. This variation can be detected by the MRI scanner due to differences in the magnetic properties of oxygenated and deoxygenated blood.

There are several ways to exploit blood oxygenation level-dependent (BOLD) fMRI so as to glean information on brain function. The first is to investigate brain function in response to a stimulus or a task or related to a perception. Another method is to investigate brain regions that are temporally synchronised in the absence of a task – in other words, to investigate resting-state functional connectivity.

Stimulus-evoked fMRI

Most fMRI studies evaluate brain responses related to an experimental stimulus by comparing them to a baseline or control stimulus. This method can be used to assess brain regions related to noxious stimuli and individual differences in painful perception. It allows the investigation of brain mechanisms underlying acute pain, and also stimulus-evoked pains (such as pain induced through topical capsaicin application) in experimental models of sensitisation.

The BOLD hemodynamic response function (HRF) has a delay with respect to the stimulus onset: it is maximal at about 4–6 seconds after the stimulus onset and lasts between 10 and 14 seconds. Furthermore, the time to scan the full brain (and thus to return to re-sampling the activation change in a given region) tends to be in the 2–3-second range. Given these temporal constraints, fMRI studies are largely focused on global changes in signal that occur over longer periods, rather than changes that might occur over short periods (e.g., through the activation of different nociceptors). Studies that have investigated brain responses to nociceptive stimulation in this way have identified a set of brain regions – the so-called 'pain matrix' – that are consistently activated. The findings related to these regions will be described in fuller detail below.

Percept-related fMRI

Sensation and perception are dynamic processes: the intensity of a sensation can fluctuate in the absence of changes to the stimulus. These changes are due to bottom-up and top-down modulation related to various physiological and psychological factors. For example, some acute pain qualities can vary over time (Davis and Pope, 2002), either attenuating or increasing during a tonic stimulation (Hashmi and Davis, 2008). Given the temporal constraints mentioned above, fluctuations in pain percepts over time may not be captured in traditional stimulus-fMRI.

Therefore, to identify the neural basis of these temporal fluctuations in perception, several groups developed percept-related fMRI. This method relies on the selection of a clear, definable percept that the subject is experiencing, the precise timing when s/he is experiencing it, and the temporal profile of the intensity of percept. These measurements are acquired through some method of continuous online perceptual ratings during fMRI acquisition. The BOLD response recorded during the fMRI session is correlated to the online ratings provided by the subject.

Percept-related fMRI has been used to identify and dissect brain responses linked to various pain-related percepts, such as noxious tonic chemically induced stinging and burning pain (Porro et al., 1998), noxious heat (Apkarian et al., 1999; Gelnar et al., 1999; Chen et al., 2002), cold-evoked prickle sensations (Davis et al., 2002), and noxious cold-evoked paradoxical heat sensation (Davis et al., 2004). Importantly, some of the studies compared these pain-related brain activity to innocuous stimuli and control tasks (e.g., Apkarian et al., 1999; Gelnar et al., 1999; Chen et al., 2002).

Functional connectivity

In addition to traditional, evoked-response approaches that identify brain regions commonly co-activated during a task, it is possible to investigate 'functional connectivity' – that is, the degree to which these brain regions are meaningfully linked during a task or at rest. There are several types of functional connectivity methods during task that can be used for the purpose of assessing hierarchical processing in the brain (in other words the order of processing) – for

example effective connectivity, mediation analysis, regional coherence – or to determine how connectivity is moderated by a particular behavioural or psychophysical condition (e.g. reaction time or pain intensity), using a psychophysiological interaction (PPI) analysis. These methods are covered in detail elsewhere (see Friston et al., 1997; Friston, 2002; Friston, 2011; Smith, 2012). This chapter will focus on resting state functional connectivity. Resting state fMRI (rs-fMRI) data are collected in the absence of any task – the subject is instructed not to think of anything in particular. Rs-fMRI data consist of activity with ultra-low frequency (<0.1 Hz) oscillations between brain regions (Friston, 1994). The 'connectivity' measured with rs-fMRI includes brain regions that are connected through direct connections, indirection connections, or a common input.

Rs-fMRI has been used to examine intrinsic brain networks that putatively reflect brain architecture. The first intrinsic brain network identified to be functionally connected was the so-called 'default mode network' (DMN) (Gusnard and Raichle, 2001; Mazoyer et al., 2001; Raichle et al., 2001). In addition to the DMN, various networks have been identified on the basis of the spatial pattern of regions that are functionally connected (Smith et al., 2009), and their co-activation during a task (Fox et al., 2005; De Luca et al., 2006; Weissman-Fogel et al., 2010); such networks include the salience, executive control, sensorimotor, cognitive and emotional networks. New theories are now incorporating the role of these networks in pain perception and modulation (Farmer, Baliki and Apkarian, 2012; Kucyi and Davis, 2014).

Brain imaging of experimental acute pain

Imaging acute pain

The first two brain-imaging studies to investigate brain regions involved in nociception and pain perception and modulation in healthy subjects were performed using PET (Jones et al., 1991; Talbot et al., 1991). One study reported that heat pain, when compared to an innocuous warm stimulus, evoked an increase in regional cerebral blood flow (rCBF) in the contralateral thalamus, in the lentiform nucleus and in the cingulate cortex (ACC) – or rather in the mid-cingulate cortex (MCC), with the current nomenclature (Jones et al., 1991). The other study reported increased rCBF in S1, S2 and the MCC (Talbot et al., 1991). The first fMRI study to investigate the neural correlates of pain perception found that painful electrical stimulation increased the BOLD signal in S1 and MCC (Davis et al., 1995). Many studies have since investigated pain-related brain activation, and some have specifically attempted to identify the neural correlates of the different dimensions of pain. Several reviews and meta-analyses have summarised these findings (Treede et al., 1999; Casey, 2000; Davis, 2000; Peyron, Laurent and Garcia-Larrea, 2000; Price, 2000; Rainville, 2002; Apkarian et al., 2005; Farrell, Laird and Egan, 2005; Bingel and Tracey, 2008; Duerden and Albanese, 2011). In general, brain-imaging studies of pain have reported the activation of S1, S2, MCC, insula, prefrontal and motor regions. As mentioned above, these regions have collectively been referred to as the 'pain matrix' – a putative network that has been supposed to integrate nociceptive signals into the experience of pain. The putative roles of these regions in pain-related processing, as determined by neuroimaging studies, are described below.

S1

It is well known, from classic brain stimulation studies in humans and from animal electrophysiology studies, that S1 is somatotopically organised (Penfield and Boldrey, 1937). This S1 tactile homunculus has been largely confirmed in human brain-imaging studies (for a review, see Apkarian et al., 2005). It generally shows an inverted organisation: the face is represented ventrolaterally, the upper limb is represented more dorsolaterally, and the lower limb is represented within the medial wall. Furthermore, it is noteworthy that nociresponsive cells have been identified in the primate S1 (Kenshalo and Isensee, 1983; Kenshalo et al., 1988; Chudler et al., 1990; Kenshalo et al., 2000).

Although nearly all neuroimaging studies have confirmed that S1 responds to innocuous A-beta fibre stimulation, these methods have not provided a clear role for S1 responses to A-delta (nociceptive) stimulation (Bushnell et al., 1999). Therefore, on the basis of neuroimaging findings, it remains unclear whether S1 is implicated in pain perception.

Furthermore, imaging studies have obtained vastly different findings in S1 activation in pain paradigms. Specifically, some studies have identified significant contralateral S1 activation to the stimulation of the arm (e.g., Talbot et al., 1991), whereas others did not find S1 activity in response to noxious stimulation (e.g., Jones et al., 1991). In a later study, Apkarian and colleagues (1992) found that S1 actually showed deactivation in response to noxious thermal stimuli. However, in a meta-analysis, Apkarian and colleagues (2005) reported that 69 per cent of PET, 76 per cent of fMRI, 10 per cent of EEG and 70 per cent of magnetoencephalography (MEG) studies reported an S1 activation in acute pain paradigms. More recently, MEG (Timmermann et al., 2001; Ploner et al., 2006), EEG (Valentini et al., 2012; Hu et al., 2014) and diffuse optical tomography (Becerra et al., 2009) studies have reported S1 responses evoked by painful stimuli. Also, a recent meta-analysis identified S1 as a region that is activated across 140 neuroimaging studies of acute experimental heat and cold pain (Duerden and Albanese, 2011). Several human neuroimaging studies have found graded responses in S1 (and other cortical areas) (Derbyshire et al., 1997; Porro et al., 1998; Coghill et al., 1999; Moulton et al., 2005). Further evidence for a role for S1 in pain perception comes from a study that used hypnotic suggestion to dissociate pain intensity from pain unpleasantness (Rainville et al., 1999) and found that S1 and possibly S2 responses correlated with pain intensity, whereas responses in the ACC correlated with pain unpleasantness. In sum, while a large number of neuroimaging studies have supported a role for S1 in nociception and pain processing, there is considerable inconsistency.

These inconsistencies may be related to the sensory stimuli used in eliciting pain. Specifically, there is a clear role for the activation of S1 to innocuous tactile stimulation, and thus it is possible that noxious stimuli become contaminated by tactile stimuli; for example, when a heat probe is used to stimulate the arm, the probe places some pressure on the arm, and fibres that encode innocuous warm temperatures or touch may also be firing. Many of the studies use stimulators that activate both A-delta and A-beta fibres; and they do not control for these inputs. The use of a laser to elicit noxious stimuli gets around this potential confound, as it specifically activates nociceptors – and not tactile sensory afferent. More recent and more sensitive methods have clearly identified, in S1, activity specific to laser-evoked potential (LEP), and have clearly demonstrated that S1 processes

nociceptive information at early stages and at the latest stages of nociceptive processing (Lee, Mouraux and Iannetti, 2009; Valentini et al., 2012; Hu et al., 2014) and that LEP-specific gamma-band activity in S1 is a direct and obligatory correlate of pain intensity (Zhang et al., 2012). Therefore the combination of LEPs, study designs that could parse nociceptive activity from general, salience-related brain activity, and novel analysis methods has demonstrated that S1 does indeed process nociceptive information – encoding pain magnitude and location.

Further evidence for the role of S1 in localising nociceptive stimuli on the body comes from the identification of pain somatotopic maps in this brain region. The first functional investigations in humans revealed a gross somatotopy of nociceptive responses in S1 (Lamour, Willer and Guilbaud, 1983; Andersson et al., 1997; Kenshalo et al., 2000; Bingel et al., 2004). Recent advances in functional neuroimaging techniques allow for the detection of surprisingly finer somatotopic maps of nociceptive signals. For example, phase-encoded MRI analysis was used to reveal that nociceptive somatotopic maps in S1 are fine-grained (Mancini et al., 2012). Furthermore, body regions where spatial acuity is very high, such as fingers (Weinstein, 1968; Mancini et al., 2014), are magnified in S1 independently of their intra-epidermal innervation density (Mancini et al., 2013). In addition, somatotopic maps for nociceptive inputs in S1 are co-aligned to maps of tactile, innocuous mechanical input to the same body part (Mancini et al., 2012).

Therefore neuroimaging studies have replicated many of the previous findings from electrophysiological and brain stimulation about the role of S1 in nociception and pain perception. Specifically, neuroimaging studies have confirmed the somatotopic organisation of S1 and have shown that S1 responses are graded to noxious stimulus intensity. Together, these findings suggest that S1 is implicated in the sensory–discriminative dimension of pain, as it encodes the location and intensity of a noxious stimulus.

S2/parietal operculum

Although many imaging studies report that S2 is activated during painful stimuli, the findings have not clarified the role of S2 in pain processing. According to Apkarian et al. (2005), 68 per cent of PET, 81 per cent of fMRI, 60 per cent of EEG and 95 per cent of MEG studies reported S2 activation in investigations of the neural correlates of acute pain in healthy controls. Also, Duerden and Albanese's (2011) meta-analysis identified S2 as one of the regions that are most commonly activated in neuroimaging studies of experimental pain. However, it is not clear how S2 activations reflect various aspects of the pain experience. It is also unclear whether S2 receives nociceptive information from the thalamus via a relay through S1 (i.e., serial processing) (Allison et al., 1989; Hari et al., 1993), or directly, in parallel to information being sent to S1 (Pons, Garraghty and Mishkin, 1992; Ploner et al., 2006; Liang, Mouraux and Iannetti, 2011). Furthermore, evidence from LEP studies has demonstrated that the early electrophysiological nociceptive response (N2) is caused by activity in S2/the posterior insular cortex (e.g., Frot et al., 2007), which suggests that there is parallel processing in S1 and S2. This is based on the timing of the observed electrophysiological responses – serial activity would lead to waveforms that occur serially, whereas parallel activity would result in a waveform with activity from both S1 and S2. This latter possibility can be resolved through source localisation

methods. Using these methods, recent findings have opposed a parallel processing model with regard to the sensory–discriminative dimension of pain (Valentini et al., 2012).

One study that investigates painful LEP with subdural electrodes has demonstrated somatotopic organisation along the anterior–posterior axis, the foot being anterior to the face, within S2 (Vogel et al., 2003). This organisation is different from that of tactile input, and it has been suggested that there may be a pain somatotopic map independent of the tactile somatotopic map (Apkarian et al., 2005).

The insula

The insula is a large brain area consisting of three subregions: the anterior, the mid and the posterior insula. The insula has been consistently activated in most experimental studies of pain. Apkarian et al. (2005) reported that 88 per cent of PET, 100 per cent of fMRI, 30 per cent of EEG and 20 per cent of MEG studies of acute pain in healthy volunteers reported insular activation. A more recent meta-analysis of 140 experimental pain neuroimaging studies also identified the insula as one of the regions most likely to be activated (Duerden and Albanese, 2011).

Given the ubiquity of insula activation in imaging studies, many groups have postulated a central role for the insula in pain perception. For example, the insula responds in a graded fashion to increasing intensity of noxious stimuli (Coghill et al., 1999). In line with this, Garcia-Larrea has posited that the posterior insula is akin to the tertiary somatosensory cortex (S3), which receives direct input from the spinothalamic system and produces pain through network interaction with other brain regions (Garcia-Larrea, 2012). Similarly, Craig has suggested that the posterior insula is the site of sensory–discriminative nociceptive processing (Craig, 2002). Support for this hypothesis comes from the presence of somatotopic maps in the insula (Brooks et al., 2005; Hua et al., 2005; Henderson et al., 2007); in fact there are several somatotopic maps for different noxious stimuli and within different subregions (Baumgartner et al., 2010). In these somatotopic maps, the face is anterior to the foot.

Brooks and Tracey (2007) have suggested that the insula is a multidimensional integration site for pain. This hypothesis is based on the convergence of the afferent pathways underlying the sensory–discriminative and the cognitive–affective dimensions of pain (the lateral and the medial spinothalamic tracts, respectively) at the insula (Treede et al., 1999); on the fact that electrophysiological stimulation of the insula elicits painful percepts (Ostrowsky et al., 2002); and on the fact that lesions to this region are related to abnormal pain percepts (Greenspan et al., 1999; Starr et al., 2009). In contrast, Baliki and colleagues (2009) have advanced the hypothesis that, in addition to integrating the dimensions of pain perception, the insula is a central, multimodal magnitude estimator and a nociceptive-specific magnitude estimator. However, Craig (2003b, 2003a, 2009, 2010) and others (Devinsky, Morrell and Vogt, 1995; Critchley, 2004; Critchley et al., 2004; Pollatos et al., 2005; Pollatos et al., 2007) have proposed that the insula is involved in integrating multimodal information important for sensorimotor, emotional, allostatic/homeostatic and cognitive functions and should be called a limbic sensory cortex. In fact Craig reclassifies pain as a homeostatic emotion rather than regarding it as a submodality of the somatosensory system.

The insula has also been implicated in a network responsible for encoding, evaluating and responding to salient sensory stimuli (Downar et al., 2001; Downar et al., 2002; Downar et al., 2003; Mouraux and Iannetti, 2009; Iannetti and Mouraux, 2010; Legrain et al., 2011; Mouraux et al., 2011). In a meta-analysis of the function of the insula, Kurth and colleagues (2010) investigated 79 studies that showed insular activation in imaging studies of acute pain stimulation paradigms in healthy controls, and found that all of the subregions of the insula were activated. It is, however, noteworthy that this same study identified different subregions of the insula that showed responses to paradigms that tested the neural correlates of processes related to pain, such as somatosensation, motor output, attention, interoception, and emotion, and that these activations generally overlapped with that of pain, underscoring the more general function of the insula in processing salient stimuli.

In sum, because the insula receives multimodal input, it is an ideal site for integrating information from the various dimensions of pain. However, it is activated in many other paradigms and across different modalities (Downar et al., 2003; Yarkoni et al., 2011). Therefore the insula may best be considered as a region that encodes behaviourally salient stimuli, including pain.

The cingulate cortex

The cingulate cortex is a large, heterogeneous brain region that can be subdivided into several subregions. There are many classification systems that are used in order to differentiate between these subregions, and this adds to the complexity of comparing studies that use different species or different nomenclatures. In this chapter, the nomenclature developed by Vogt and colleagues (2005) will be used whenever possible. It is noteworthy that the region previously referred to as the ACC has now been divided into two regions: the MCC and the ACC. The ACC can be further subdivided into the subgenual ACC (sgACC) and the perigenual ACC (pgACC). The MCC can be further subdivided into the anterior MCC (aMCC) and the posterior MCC (pMCC). Various regions of the cingulate cortex are involved in nociceptive processing and pain modulation (for a review, see Vogt and Sikes, 2000; Bushnell, Ceko and Low, 2013), although this chapter will largely focus on the roles of the MCC, as this is the cingulate region most consistently activated in neuroimaging studies of pain (Shackman et al., 2011). Brain-imaging studies have consistently shown MCC activity during noxious stimulation. For example, the MCC showed graded responses to the increasing intensity of noxious stimuli (Coghill et al., 1999). Furthermore, according to Apkarian et al. (2005), 94 per cent of PET, 81 per cent of fMRI, 100 per cent of EEG and 25 per cent of MEG studies reported cingulate activation in imaging studies of acute pain in healthy volunteers.

On the basis of converging evidence across domains, the aMCC has often been considered the seat of the affective dimension of pain (or unpleasantness, as opposed to pain discriminability) (Vogt, Sikes and Vogt, 1993). For example, tracing studies have shown that the spinothalamic tract projects directly to the MCC (Dum, Levinthal and Strick, 2009); electrophysiological studies have demonstrated the presence of neurons with increased activity during pain anticipation and escape from a noxious stimulus (Hutchison et al., 1999; Koyama et al., 2001; Iwata et al., 2005); and cingulotomy and cingulectomy – that is, the surgical ablation and disruption of the cingulate cortex in cases of intractable pain – have been somewhat

effective in reducing the affective dimension of pain in patients (for a review, see Fuchs et al., 2014, and also Davis et al., 1994).

Early neuroimaging evidence for the role of the ACC/MCC in the processing of the affective dimension of pain came from an influential study where hypnotic suggestion was used in order to manipulate the perception of pain intensity and unpleasantness. In this study, Rainville and colleagues (1997) found that the modulation of pain unpleasantness (but not of its intensity) affected the CBF in the ACC.

More recent evidence has demonstrated that the MCC may be something more complex than a node in the limbic circuit. It has been proposed that, rather than simply encode affect, the cingulate may serve as a hub between the affective processing and the motor planning involved in processing and planning affectively motivated motor outputs (Vogt and Sikes, 2009; Shackman et al., 2011). Support for the affective premotor cingulate concept comes from studies that have shown that the stimulation of a region analogous to aMCC is related to the urge to escape a threatening stimulus (Iwata et al., 2005) and has direct projections to primary motor regions, as well as corticobulbar/corticospinal projections (Dum and Strick, 1992).

In addition to the role of the cingulate cortex as an affective–motor interface, the aMCC's role in cognitive processing has been well documented; influential early models even suggest that this region is specialised for cognition, as affective processing occurs in more ventral and anterior regions (Devinsky et al., 1995; Bush, Luu and Posner, 2000). It is noteworthy that the evidence cited above in support of a role for the aMCC in pain-related affect was a key piece of evidence against this segregated model of cingulate function (Shackman et al., 2011). Indeed, there is ample evidence that, in addition to its role in affective and motor responses, the MCC is involved in the cognitive–evaluative processing of pain (for a comprehensive review, see Seminowicz and Davis, 2007; Bushnell et al., 2013).

Like the insula in nociceptive processing and pain integration, the MCC is well situated to integrate the cognitive–evaluative and affective dimensions of pain. Its connectivity with motor regions suggests that it is a hub for mounting an appropriate motor response to pain (Morrison, Perini and Dunham, 2013). Therefore a working model for the role of the cingulate cortex is that of a hub for the integration of cognitive and affective information towards the initiation of appropriate defensive actions.

Other brain regions

A set of other brain regions are also often – but less consistently – activated in acute pain-imaging paradigms, for example the prefrontal cortex (PFC) and the cortical and subcortical motor regions. Given the size and heterogeneity of the PFC, its role in pain modulation is beyond the scope of this chapter. Briefly, there is no evidence suggesting that the PFC receives nociceptive information directly from the thalamus. In contrast to tract tracing studies, PET and fMRI studies often identified PFC regions activated through noxious stimulation (Apkarian et al., 2005). Interestingly, no EEG or MEG studies reported PFC activation. The PFC does, however, have reciprocal connections with a number of nociresponsive brain regions such as the cingulate cortex, the insula, and the somatosensory cortex (Nieuwenhuys, Voogd and van Huijzen, 2008; for more in-depth reviews, see Bushnell et al., 2013; Colloca et al., 2013).

Motor regions are activated in acute pain paradigms in healthy controls, but less reliably than the aforementioned brain regions (Apkarian et al., 2005). In the context of pain, it is believed that motor regions serve two purposes: to orient the body toward the source of pain and to initiate nocifensive behaviour (e.g., to avoid the stimulus). Similarly, another study reported that hypertonic saline injection into the masseter muscle, an experimental acute pain model, was related to deactivation in the face region of M1, as measured by fMRI (Nash et al., 2010). It is, however, noteworthy that some studies have not observed activation in M1 during noxious stimulation (Romaniello et al., 2000; Halkjaer et al., 2006).

The basal ganglia are a set of subcortical nuclei that have been associated with motor function. However, it is noteworthy that the basal ganglia do receive input from many cortical and subcortical regions and form several functional loops (Nieuwenhuys et al., 2008). It has been proposed that this extensive wiring to the brain suggests that the basal ganglia may be implicated in more than just motor functions (Haber and Knutson, 2009). For instance, the basal ganglia are often activated in neuroimaging studies of experimental pain (Borsook et al., 2010). It has been suggested that the cortico-thalamo-basal ganglia–cortical loops may provide a unique anatomical substrate for the integration of the various dimensions of pain (Borsook et al., 2010). However, more work is required to further investigate this possibility.

Other motor regions, including the primary motor cortex (PMC) and the supplementary motor area (SMA), are also commonly activated in brain-imaging studies of experimental pain in healthy volunteers (Apkarian et al., 2005; Duerden and Albanese, 2011). The PMC has been implicated in the cognitive modulation of motor output, and the SMA has been implicated in motor planning and in the temporal organisation of movements (Picard and Strick, 2001). Therefore their activation during experimental pain is probably related to the cognitive and motivational dimensions of pain with regard to nocifensive behaviours.

In sum, many studies have found that acute pain stimuli evoke activities in widespread brain regions such as the S1, the S2, the ACC, the MCC, and the insula (Apkarian et al., 2005). Some fMRI studies have also reported that noxious stimuli elicit activity in additional brain areas such as the PFC, the motor cortex and the SMA, and also subcortically – in the basal ganglia, thalamus and brainstem (Apkarian et al., 2005; Duerden and Albanese, 2011). In line with the concept that pain is multidimensional, these findings demonstrate that pain is associated with activity not only in regions that are traditional parts of pain pathways, but also in areas implicated in innocuous somatosensory, cognitive and motor functions.

Salience, pain and specificity

Neuroimaging provides a unique window for viewing how the human brain processes pain in real time. After more than twenty years of compiling functional neuroimaging data, it is worth assessing the utility of these data in terms of furthering our understanding of how the brain processes pain. As reviewed above, fMRI studies consistently identify a pattern of activation (referred to as the "pain matrix") commonly involving the ACC, the insula, the thalamus and the somatosensory cortices.

A key assumption underlying the term 'pain matrix' is that this pattern of activation is specific to pain. Given how consistent this spatial pattern is while subjects are experiencing pain, it is unsurprising that it has been considered as a potential objective marker or 'neurosignature' for pain. Furthermore, the activation of 'pain matrix' regions has been used as evidence of perceptual similarity between pain and social isolation (Eisenberger, Lieberman and Williams, 2003; Macdonald and Leary, 2005), The notion that pain matrix activation in these studies indicates that these aversive psychological states are experienced as physically painful has pervaded both the scientific literature and popular press. A 2005 review article claimed that psychological distress is 'experienced as painful because reactions to rejection are mediated by aspects of the physical pain system' (Macdonald and Leary, 2005: 202), and a recent article in the *New York Times* stated that 'being socially rejected doesn't just feel bad, it hurts' (Paul, 2011). In the wake of these studies, a host of others have inferred that other evoked negative affective states (including distress from completing mathematical problems: Lyons and Beilock, 2012) are experienced as painful, on the basis of observed activation in the pain matrix.

The argument that underlies these studies relies on the assumption that the pattern of brain activity elicited by a nociceptive stimulus actually reflects the neural mechanism that gives rise to pain. Judging the presence of physical pain to be based on a pattern of neural activity relies on *reverse inference*. This argument takes the following form:

- If Tom is feeling pain, the pain matrix is activated.
- The pain matrix is activated.
- Therefore Tom is feeling pain.

Given the consistency of pain matrix activation during pain, the ubiquity of this type of argument is unsurprising. The logical fallacy becomes more apparent, however, if we apply the same inferential structure to a different example:

- If Tom is in Moscow, he is in Russia.
- Tom is in Russia.
- Therefore Tom is in Moscow.

The latter example exposes the logical flaw of reverse inference. There are many places in Russia that Tom could be other than Moscow, so the fact he is in Russia is not sufficient for inferring that he is in Moscow. Poldrack (2006) has argued that, while reverse inferences are logically flawed, they should be treated probabilistically, as the likelihood of the inference being true depends on the degree of exclusivity between the antecedent and the consequent. In the above example, the reverse inference is unlikely to be true, since Moscow is a relatively small part of Russia. The inference would be far more likely in the case of Singapore, where the relationship between city and state is exclusive (one can't be in the country without being in the state). To apply a similar logic in the case of neuroimaging, we would have higher confidence in a reverse inference if a given pattern of activation were exclusively associated with a given mental state. Thus, to evaluate the reverse inference that pain matrix activation signals the presence of pain, we must evaluate whether pain matrix activation is exclusively associated with the experience of pain.

In an early series of fMRI experiments, Downar and colleagues (2000, 2001, 2002) called the specificity of these responses into question by demonstrating that a network of regions largely overlapping the pain matrix were associated with the relevance and novelty of

environmental stimuli rather than with their painfulness. Similarly. Mouraux and colleagues (Moraux and Iannetti, 2009; Moraux et al., 2011) have shown that salient (but non-painful) stimuli in other sensory modalities (visual, auditory, non-painfully tactile) can elicit patterns of activation remarkably similar to those generated in response to nociceptive stimuli. These studies demonstrate that pain matrix activation is not sufficient for the experience of pain; and we have recently demonstrated that it is not necessary for it either. Using cold-pressor and nociceptive heat, we demonstrated intact sensory and emotional pain responses in an individual with extensive damage to the pain matrix (including near-complete ablation of the cingulate and insular cortices) (Feinstein et al., 2015).

On the basis of these studies, it has been concluded that the 'pain matrix' is better characterised as a 'salience matrix' associated with detecting, processing and reacting to salient sensory events (Iannetti et al., 2013; Uddin, 2015). Clearly this interpretation (and the empirical findings that give rise to it) indicates that observed activation in this matrix of regions is not sufficiently specific to pain to justify reverse inferences. This non-specificity calls into question the conclusion of experiential similarity between pain and other negative affective states (e.g., social isolation), which is based on nothing more than overlapping neuroimaging findings.

Perhaps more importantly from the perspective of basic pain research, however, are the implications for neuroimaging's ability to elucidate the brain's role in pain. If, on the one hand, the neural response to pain really is no more than an acknowledgement by the brain that incoming nociceptive input is salient and requires appropriate defensive routines, then Descartes' original conceptualisation of the brain as a bell to be rung by a string in the periphery might be an accurate characterisation of the brain's limited role in the perceptual experience of pain. If, on the other hand, the brain plays a far more active role in shaping the unique perceptual experience of pain (as seems almost certain, given the wide variety of pain experiences and the relative lack of variety of the nociceptive input), then the non-specificity of the 'pain matrix' suggests that neuroimaging research on pain has failed in identifying neural responses that make pain perceptually distinct from other salient sensory and emotional experiences.

One possible explanation for the lack of specificity is that technical limitations make fMRI poorly suited to detect responses specific to pain. As previously discussed, the temporal resolution is of the order of seconds, far below the timescale of the nociceptive input. Furthermore, fMRI relies on oxygenated blood flow as a proxy for neuronal activation, and this introduces temporal delays and further measurement imprecision. Finally, while the spatial resolution (in cubic millimetres) is superior to the spatial resolution obtained through techniques like PET or EEG, it is too coarse to differentiate between smaller populations of more specialised neurons. This might be particularly important in regions like the insula and the ACC, whose integrative role means that several types of neurons might exist in close proximity to each other. Nocireceptive neurons have been detected in both regions by using techniques with higher spatial resolution (Hutchison et al., 1999; Frot et al., 2008; Frot, Faillenot and Mauguiere, 2014), which suggests that fMRI might simply not be able to distinguish between activation in these regions driven by nociceptive responses and activation in regions driven by other types of input.

Another possibility is that the analytical techniques being used are not optimised for the detection of differences. Analyses typically looking to localise function to a particular region (or collection of regions) commonly determine whether a sufficient number of voxels within that region reach a threshold level of activation under a particular condition. Regions meeting these criteria after data are smoothed and spatially averaged are considered to be activated by that condition. Such an approach largely ignores (and, in the case of smoothing and spatial averaging, obscures) the spatial pattern that might give rise to overall activation within a given cluster. Thus two activation maps might identify a common cluster, but the fine-grained spatial pattern that gives rise to this cluster might be different. This possibility is the basis for a newer technique called multivoxel pattern analysis (MVPA), which seeks patterns of activation that distinguish between conditions.

MVPA is the basis for a new 'neurosignature', proposed by Wager et al. (2013). In a comprehensive set of experiments, Wager and colleagues first establish a neurosignature that differentiates between four levels of perceived pain. They then demonstrate that this neurosignature can distinguish between painful and non-painful stimuli in an independent data set. In a third experiment they use the neurosignature to distinguish between social and physical pain. Finally, they demonstrate the sensitivity of this neurosignature to an analgesic agent (reminfentanil).

This study represents an important step towards elucidating neural responses specifically associated with pain. The paper represents a substantial technical step forward, and its importance in directing pain neuroimaging towards improved specificity should not be overlooked. Nevertheless, a number of limitations of this initial step need to be made clear, particularly where they highlight further challenges for the field of pain neuroimaging:

1 Moving towards clinical utility: despite publication in an important clinical journal, the clinical utility of this neurosignature remains to be seen. Some immediate uses – such as providing an alternative dependent measure for use in drug discovery studies – are possible, but many of the clinical benefits of such a neurosignature would seem to derive from their application to clinical pain states. FMRI designs generally require evoked stimuli with specific timings (such that the evoked state can be compared to another condition, or to baseline). Thus the study describes responses to acute thermal pain and, as stated by the authors, 'has not been validated for clinical pain and cannot currently be used in clinical tests' (Wager et al., 2013: 1396). The challenges of imaging chronic pain are endemic to the field rather than a specific flaw of this work. Combining this analytical approach with percept-related MRI or incorporating techniques like resting state fMRI, ASL or PET, which are less reliant on discrete evoked stimuli, might be helpful in this regard.
2 Ability to distinguish current pain status: the paper by Wager and colleagues establishes the robustness of the neurosignature in distinguishing between coarse categories. In their first study they collapse data across four levels of perceived pain and establish the model on its ability to distinguish these combined maps (rather than categorising individual trials for the presence or absence of pain). In subsequent studies, the model is tested for its ability to distinguish between high (painful) and low (non-painful) temperatures, or between discrete categories (social vs physical pain). While in their

second study the researchers examine the model's ability to distinguish painful temperatures on a trial-by-trial basis, future work should focus on improving the power to detect pain on single trials (i.e., to detect whether an individual is in pain at any given point in time).

3 Distinguishing between equally salient states: while the pattern of activation traditionally referred to as the 'pain matrix' is more accurately characterised as a 'salience matrix', this term has little utility from the perspective of cognitive neuroscience. It tells us very little about what individual regions are contributing without explaining why broad swaths of cortex evolved only to solve the most rudimentary adaptive discrimination (does this stimulus require attention?) – a function that remains intact in lower species without cortical development. Nevertheless, no analysis of pain-specific responses can be complete without acknowledging the confound between pain and salience. What is more painful is always more salient. The converse, however (that what is more salient is always more painful), is clearly not the case. Thus the same caution needs to be applied to spatial-based algorithms as to more traditional methods. Wager and colleagues' model differentiates social from physical pain, but it is not clear whether these discriminations are made possible by differences in the degree to which the respective stimuli draw attention to, or require, immediate responses. Matching for salience is difficult, as even designs that have explicitly attempted to do so rely on relatively crude measures. Nevertheless, providing such a measure, even if incomplete, should be fundamental to specificity studies.

4 Are differences detected at the level of the brain critical to perceptual distinctions? A further step in determining the brain changes that give rise to perceptual changes is establishing their necessity or their sufficiency for those perceptual differences. It is entirely possible that the spatial patterns that best differentiate between perceptual states are entirely epiphenomenal and play no important role in instantiating those states (just as the observation of puddles might indicate a rainy day, though puddles result from rain rather than vice versa).

This final issue is related to an obstacle that lingers along the path of obtaining greater specificity: the types of design commonly employed in fMRI studies. Traditionally, functional imaging studies have employed single-session designs in which a particular physical or cognitive state is evoked and the resultant activations are attributed to that state. These designs, while useful, are strictly correlational and do not allow for inferences about causal mechanisms or about the neural operations that are necessary or sufficient for a particular state. Advancing our understanding of the neural operations that underlie specific states requires the development of better designs for inferring causality. These include longitudinal designs where one scan might be before a particular intervention and another afterwards. Such designs are challenging, given the high signal-to-noise ratio in fMRI (which results in reduced power to detect differences between time points), but recent studies have suggested good test–retest reliability in fMRI designs that use thermal pain (Letzen et al., 2014; Quiton et al., forthcoming), supporting the feasibility of longitudinal designs in the study of pain with fMRI. Similarly, techniques like transcranial magnetic stimulation (TMS), which can disrupt or enhance neural processes, can be used with fMRI to provide stronger causal inferences.

Concluding remarks

There have been many advances in our understanding of nociception and pain modulation since the advent of neuroimaging. Neuroimaging research, however, is costly and has temporal and spatial limitations that restrict its ability to examine some aspects of pain, including the identification of activation patterns specific to pain. Despite these challenges, however, neuroimaging remains our only method of collecting non-invasive, *in vivo* information about brain function in humans. This compels technical innovation to move towards stronger inferences and improved specificity. Longitudinal, interventional designs and multimodal approaches can help move the field towards stronger causal inferences, while new analytical techniques have begun to improve our ability to identify neural responses specific to pain. Nevertheless, it will remain best practice to supplement neuroimaging data with findings from lesion and animal studies and other neuroscientific techniques that allow for more direct inferences.

References

Allison, T., McCarthy, G., Wood, C. C., Darcey, T. M., Spencer, D. D. and Williamson, P. D. 1989. Human cortical potentials evoked by stimulation of the median nerve. I: Cytoarchitectonic areas generating short-latency activity. *Journal of Neurophysiology* 62: 694–710.

Andersson, J. L. R., Lilja, A., Hartvig, P., Lüngstrîm, B., Gordh, T., Handwerker, H. and Torebjîrk, E. 1997. Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography. *Experimental Brain Research* 117: 192–9.

Apkarian, A. V., Bushnell, M. C., Treede, R. D. and Zubieta, J. 2005. Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain* 9: 463–84.

Apkarian, A. V., Darbar, A., Krauss, B. R., Gelnar, P. A. and Szeverenyi, N. M. 1999. Differentiating cortical areas related to pain perception from stimulus identification: Temporal analysis of fMRI activity. *Journal of Neurophysiology* 81: 2956–63.

Apkarian, A. V., Stea, R. A., Manglos, S. H., Szeverenyi, N. M., King, R. B. and Thomas, F. D. 1992. Persistent pain inhibits contralateral somatosensory cortical activity in humans. *Neuroscience Letters* 140: 141–7.

Arendt-Nielsen, L. and Yarnitsky, D. 2009. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *Journal of Pain* 10: 556–72.

Baliki, M. N., Geha, P. Y. and Apkarian, A. V. 2009. Parsing pain perception between nociceptive representation and magnitude estimation. *Journal of Neurophysiology* 101: 875–87.

Baumgartner, U., Iannetti, G. D., Zambreanu, L., Stoeter, P., Treede, R. D. and Tracey, I. 2010. Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: A high-resolution fMRI study. *Journal of Neurophysiology* 104: 2863–72.

Becerra, L., Harris, W., Grant, M., George, E., Boas, D., Borsook, D. 2009. Diffuse optical tomography activation in the somatosensory cortex: Specific activation by painful vs. non-painful thermal stimuli. *PLoS One* 4: e8016.

Beecher, H. K. 1946. Pain in men wounded in battle. *Annals of Surgery* 123: 96–105.

Bessou, P. and Perl, E. R. 1969. Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *Journal of Neurophysiology* 32: 1025–43.

Bingel, U. and Tracey, I. 2008. Imaging CNS modulation of pain in humans. *Physiology* 23: 371–80.

Bingel, U., Lorenz, J., Glauche, V., Knab, R., Glascher, J., Weiller, C. and Buchel, C. 2004. Somatotopic organization of human somatosensory cortices for pain: A single trial fMRI study. *Neuroimage* 23: 224–32.

Borsook, D., Upadhyay, J., Chudler, E. H. and Becerra, L. 2010. A key role of the basal ganglia in pain and analgesia: Insights gained through human functional imaging. *Molecular Pain* 6 (27). doi:10.1186/1744-8069-6-27.

Boyd, D., Butler, M., Carr, D. B., Cohen, M. J., Devor, M., Dworkin, R., Greenspan, J. D., Jensen, T. S., King, S., Koltzenburg, M., Loeser, J. D., Merskey, H., Okifuji, A., Paice, J., Serra, J., Treede, R. D. and Woda, A. 2011. IASP pain terminology: An update on the IASP taskforce on taxonomy. Part III: Pain terms, a current list with definitions and notes on usage. In *IASP Taxonomy*, 3rd edn, ed. by J. D. Loeser. Seattle, WA: IASP Press, pp. 209–14.

Brooks, J. C. and Tracey, I. 2007. The insula: A multidimensional integration site for pain. *Pain* 128: 1–2.

Brooks, J. C., Zambreanu, L., Godinez, A., Craig, A. D. and Tracey, I. 2005. Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage* 27: 201–9.

Burgess, P. R., Perl, E. R. 1967. Myelinated afferent fibres responding specifically to noxious stimulation of the skin. *Journal of Physiology* 190: 541–62.

Bush, G., Luu, P. and Posner, M. I. 2000. Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences* 4: 215–22.

Bushnell, M. C., Ceko, M. and Low, L. A. 2013. Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience* 14: 502–11.

Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J. I. and Carrier, B. 1999. Pain perception: Is there a role for primary somatosensory cortex *Proceedings of the National Academy of Sciences of the United States of America* 96: 7705–9.

Campbell, C. M. and Edwards, R. R. 2009. Mind–body interactions in pain: The neurophysiology of anxious and catastrophic pain-related thoughts. *Translational Research: The Journal of Laboratory and Clinical Medicine* 153: 97–101.

Casey, K. L. 2000. Concepts of pain mechanisms: The contribution of functional imaging of the human brain. *Progress in Brain Research* 129: 277–87.

Chen, J. I., Ha, B., Bushnell, M. C., Pike, B. and Duncan, G. H. 2002. Differentiating noxious- and innocuous-related activation of human somatosensory cortices using temporal analysis of fMRI. *Journal of Neurophysiology* 88: 464–74.

Chudler, E. H., Anton, F., Dubner, R. and Kenshalo, D. R., Jr. 1990. Responses of nociceptive S1 neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: Effect of interstimulus interval. *Journal of Neurophysiology* 63: 559–69.

Coghill, R. C., Sang, C. N., Maisog, J. M. and Iadarola, M. J. 1999. Pain intensity processing within the human brain: A bilateral, distributed mechanism. *Journal of Neurophysiology* 82: 1934–43.

Colloca, L., Klinger, R., Flor, H. and Bingel, U. 2013. Placebo analgesia: Psychological and neurobiological mechanisms. *Pain* 154: 511–14.

Craig, A. D. 2002. How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience* 3: 655–66.

Craig, A. D. 2010. Once an island, now the focus of attention. *Brain Structure and Function* 124: 395–6.

Craig, A. D. B. 2003a. A new view of pain as a homeostatic emotion. *Trends in Neurosciences* 26: 303–7.

Craig, A. D. B. 2003b. Pain mechanisms: Labeled lines versus convergence in central processing. *Annual Reviews in Neuroscience* 26: 1–30.

Craig, A. D. B. 2009. How do you feel – now? The anterior insula and human awareness. *Nature Reviews Neuroscience* 10: 59–70.

Critchley, H. D. 2004. The human cortex responds to an interoceptive challenge. *Proceedings of the National Academy of Sciences of the United States of America* 101: 6333–4.

Critchley, H. D., Wiens, S., Rotshtein, P., Ohman A. and Dolan, R. J. 2004. Neural systems supporting interoceptive awareness. *Nature Neuroscience* 7: 189–95.

Davis, K. D. 2000. Studies of pain using fMRI. In *Pain Imaging*, ed. by M. C. Bushnell and K. L. Casey. Seattle, WA: IASP Press, pp. 195–210.

Davis, K. D. and Pope, G. E. 2002. Noxious cold evokes multiple sensations with distinct time courses. *Pain* 98: 179–85.

Davis, K. D., Hutchison, W. D., Lozano, A. M. and Dostrovsky, J. O. 1994. Altered pain and temperature perception following cingulotomy and capsulotomy in a patient with schizoaffective disorder. *Pain* 59: 189–99.

Davis, K. D., Pope, G. E., Crawley, A. P. and Mikulis, D. J. 2002. Neural correlates of prickle sensation: A percept-related fMRI study. *Nature Neuroscience* 5: 1121–2.

Davis, K. D., Pope, G. E., Crawley, A. P. and Mikulis, D. J. 2004. Perceptual illusion of 'paradoxical heat' engages the insular cortex. *Journal of Neurophysiology* 92: 1248–51.

Davis, K. D., Wood, M. L., Crawley, A. P. and Mikulis, D. J. 1995. fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation. *Neuroreport* 7 (1): 321–5.

De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M. and Smith, S. M. 2006. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage* 29: 1359–67.

Derbyshire, S. W. G., Jones, A. K. P., Gyulai, F., Clark, S., Townsend, D. and Firestone, L. L. 1997. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain* 73: 431–45.

Descartes, R. 1664. L'homme *de René Descartes et un traitté* De la formation du foetus *du mesme autheur, avec les remarques de Louis de La Forge, docteur en medecine … sur le* Traité de l'homme *de René Descartes & sur les figures par luy inventées*, ed. by C. Clerselier, with a Preface by F. Schuyl. Paris: Charles Angot.

Devinsky, O., Morrell, M. J. and Vogt, B. A. 1995. Contributions of anterior cingulate cortex to behavior. *Brain* 118: 279–306.

Downar, J., Crawley, A. P., Mikulis, D. J. and Davis, K. D. 2000. A multimodal cortical network for the detection of changes in the sensory environment. *Nature Neuroscience* 3: 277–83.

Downar, J., Mikulis, D. J. and Davis, K. D. 2003. Neural correlates of the prolonged salience of painful stimulation. *Neuroimage* 20: 1540–51.

Downar, J., Crawley, A. P., Mikulis, D. J. and Davis, K. D. 2001. A cortical network for the detection of novel events across multiple sensory modalities. *Neuroimage* 13: S310.

Downar, J., Crawley, A. P., Mikulis, D. J. and Davis, K. D. 2002. A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. *Journal of Neurophysiology* 87: 615–20.

Duerden, E. G. and Albanese, M. C. 2011. Localization of pain-related brain activation: A meta-analysis of neuroimaging data. *Human Brain Mapping* 34: 109–49.

Dum, R. and Strick, P. 1992. Medial wall motor areas and skeletomotor control. *Current Opinion in Neurobiology* 2: 836–39.

Dum, R., Levinthal, D. and Strick, P. 2009. The spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. *Journal of Neuroscience* 29: 14223–35.

Edwards, R. R. 2005. Individual differences in endogenous pain modulation as a risk factor for chronic pain. *Neurology* 65: 437–43.

Eisenberger, N. I., Lieberman, M. D. and Williams, K. D. 2003. Does rejection hurt? An FMRI study of social exclusion. *Science* 302: 290–2.

Farmer, M. A., Baliki, M. N. and Apkarian, A. V. 2012. A dynamic network perspective of chronic pain. *Neuroscience Letters* 520: 197–203.

Farrell, M. J., Laird, A. R. and Egan, G. F. 2005. Brain activity associated with painfully hot stimuli applied to the upper limb: A meta-analysis. *Human Brain Mapping* 25: 129–39.

Feinstein, J. S., Khalsa, S. S., Salomons, T. V., Prkachin, K. M., Frey-Law, L. A., Lee, J. E., Tranel and D., Rudrauf, D. 2015. Preserved emotional awareness of pain in a patient with extensive bilateral damage to the insula, anterior cingulate, and amygdala. *Brain Structure & Function*. doi: 10.1007/s00429-014-0986-3.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van, E. D. C. and Raichle, M. E. 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America* 102: 9673–8.

Friston, K. J. 1994. Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping* 2: 56–78.

Friston, K. 2002. Beyond phrenology: What can neuroimaging tell us about distributed circuitry? *Annual Review of Neuroscience* 25: 221–50.

Friston, K. J. 2011. Functional and effective connectivity: A review. *Brain Connectivity* 1: 13–36.

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E. and Dolan, R. J. 1997. Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 6: 218–29.

Frot, M., Faillenot, I. and Mauguiere, F. 2014. Processing of nociceptive input from posterior to anterior insula in humans. *Human Brain Mapping* 35 (11): 5486–99.

Frot, M., Magnin, M., Mauguiere, F. and Garcia-Larrea, L. 2007. Human SII and posterior insula differently encode thermal laser stimuli. *Cerebral Cortex* 17: 610–20.

Frot, M., Mauguiere, F., Magnin, M. and Garcia-Larrea, L. 2008. Parallel processing of nociceptive, A-delta inputs in SII and midcingulate cortex in humans. *Journal of Neuroscience* 28: 944–52.

Fuchs, P. N., Peng, Y. B., Boyette-Davis, J. A. and Uhelski, M. L. 2014. The anterior cingulate cortex and pain processing. *Frontiers in Integrative Neuroscience* 8 (35). doi: 10.3389/fnint.2014.00035.

Garcia-Larrea, L. 2012. The posterior insular–opercular region and the search of a primary cortex for pain. *Neurophysiologie Clinique* 42: 299–313.

Gelnar, P. A., Krauss, B. R., Sheehe, P. R., Szeverenyi, N. M. and Apkarian, A. V. 1999. A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks. *Neuroimage* 10: 460–82.

Greenspan, J. D., Lee, R. R. and Lenz, F. A. 1999. Pain sensitivity alterations as a function of lesion location in the parasylvian cortex. *Pain* 81: 273–82.

Gusnard, D. A. and Raichle, M. E. 2001. Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience* 2: 685–94.

Haber, S. N. and Knutson, B. 2009. The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology* 35: 4–26.

Halkjaer, L., Melsen, B., McMillan, A. S. and Svensson, P. 2006. Influence of sensory deprivation and perturbation of trigeminal afferent fibers on corticomotor control of human tongue musculature. *Experimental Brain Research* 170: 199–205.

Hari, R., Karhu, J., Hamalainen, M., Knuutila, J., Salonen, O., Sams, M. and Vilkman, V. 1993. Functional organization of the human first and second somatosensory cortices: A neuromagnetic study. *European Journal of Neuroscience* 5: 724–34.

Hashmi, J. A. and Davis, K. D. 2008. Effect of static and dynamic heat pain stimulus profiles on the temporal dynamics and interdependence of pain qualities, intensity, and affect. *Journal of Neurophysiology* 100: 1706–15.

Henderson, L. A., Gandevia, S. C. and Macefield, V. G. 2007. Somatotopic organization of the processing of muscle and cutaneous pain in the left and right insula cortex: A single-trial fMRI study. *Pain* 128: 20–30.

Hu, L., Valentini, E., Zhang, Z. G., Liang, M. and Iannetti, G. D. 2014. The primary somatosensory cortex contributes to the latest part of the cortical response elicited by nociceptive somatosensory stimuli in humans. *Neuroimage* 84: 383–93.

Hua, l. H., Strigo, I. A., Baxter, L. C., Johnson, S. C. and Craig, A. D. 2005. Anteroposterior somatotopy of innocuous cooling activation focus in human dorsal posterior insular cortex. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* 289: R319–R325.

Hutchison, W. D., Davis, K. D., Lozano, A. M., Tasker, R. R. and Dostrovsky, J. O. 1999. Pain-related neurons in the human cingulate cortex. *Nature Neuroscience* 2: 403–5.

Iannetti, G. D. and Mouraux, A. 2010. From the neuromatrix to the pain matrix (and back). *Experimental Brain Research* 205: 1–12.

Iannetti, G. D., Salomons, T. V., Moayedi, M., Mouraux, A. and Davis, K. D. 2013. Beyond metaphor: Contrasting mechanisms of social and physical pain. *Trends in Cognitive Sciences* 17: 371–8.

Iwata, K., Kamo, H., Ogawa, A., Tsuboi, Y., Noma, N., Mitsuhashi, Y., Taira, M., Koshikawa, N. and Kitagawa, J. 2005. Anterior cingulate cortical neuronal activity during perception of noxious thermal stimuli in monkeys. *Journal of Neurophysiology* 94: 1980–91.

Jones, A. K. P., Brown, W. D., Friston, K. J., Qi, L. Y. and Frackowiak, R. S. J. 1991. Cortical and subcortical localization of response to pain in man using positron emission tomography. *Proceedings of the Royal Society of London, Series B: Biological Sciences* 244: 39–44.

Kenshalo, D. R., Iwata, K., Sholas, M. and Thomas, D. A. 2000. Response properties and organization of nociceptive neurons in area 1 of monkey primary somatosensory cortex. *Journal of Neurophysiology* 84: 719–29.

Kenshalo, D. R., Jr. and Isensee, O. 1983. Responses of primate, SI cortical neurons to noxious stimuli. *Journal of Neurophysiology* 50: 1479–96.

Kenshalo, D. R., Jr., Chudler, E. H., Anton, F. and Dubner, R. 1988. SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. *Brain Research* 454: 378–82.

Koyama, T., Kato, K., Tanaka, Y. Z. and Mikami, A. 2001. Anterior cingulate activity during pain-avoidance and reward tasks in monkeys. *Neuroscience Research* 39: 421–30.

Kucyi, A. and Davis, K. D. 2014. The dynamic pain connectome. Trends Neurosci.

Kurth, F., Zilles, K., Fox, P. T., Laird, A. R. and Eickhoff, S. 2010. A link between the systems: Functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Structure and Function* 214: 519–34.

Lamour, Y., Willer, J. C. and Guilbaud, G. 1983. Rat somatosensory (SmI) cortex. I: Characteristics of neuronal responses to noxious stimulation and comparison with responses to non-noxious stimulation. *Experimental Brain Research* 49: 35–45.

Lee, M. C., Mouraux, A. and Iannetti, G. D. 2009. Characterizing the cortical activity through which pain emerges from nociception. *Journal of Neuroscience* 29: 7909–16.

Legrain, V., Iannetti, G. D., Plaghki, L. and Mouraux, A. 2011. The pain matrix reloaded: A salience detection system for the body. *Progress in Neurobiology* 93: 111–24.

Letzen, J. E., Sevel, L. S., Gay, C. W., O'Shea, A. M., Craggs, J. G., Price, D. D. and Robinson, M. E. 2014. Test–retest reliability of pain-related brain activity in healthy controls undergoing experimental thermal pain. *Journal of Pain* 15: 1008–14.

Liang, M., Mouraux, A. and Iannetti, G. D. 2011. Parallel processing of nociceptive and non-nociceptive somatosensory information in the human primary and secondary somatosensory cortices: Evidence from dynamic causal modeling of functional magnetic resonance imaging data. *Journal of Neuroscience* 31: 8976–85.

Lyons, I. M. and Beilock, S. L. 2012. When math hurts: Math anxiety predicts pain network activation in anticipation of doing math. *PLoS One* 7: e48076.

Macdonald, G. and Leary, M. R. 2005. Why does social exclusion hurt? The relationship between social and physical pain. *Psychological Bulletin* 131: 202–23.

Mancini, F., Haggard, P., Iannetti, G. D., Longo, M. R. and Sereno, M. I. 2012. Fine-grained nociceptive maps in primary somatosensory cortex. *Journal of Neuroscience* 32: 17155–62.

Mancini, F., Sambo, C. F., Ramirez, J. D., Bennett, D. L., Haggard, P. and Iannetti, G. D. 2013. A fovea for pain at the fingertips. *Current Biology* 23: 496–500.

Mancini, F., Bauleo, A., Cole, J., Lui, F., Porro, C. A., Haggard, P. and Iannetti, G. D. 2014. Whole-body mapping of spatial acuity for pain and touch. *Annals of Neurology* 75: 917–24.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houde, O., Crivello, F., Joliot, M., Petit, L. and Tzourio-Mazoyer, N. 2001. Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Research Bulletin* 54: 287–98.

Melzack, R. and Wall, P. D. 2004. *The Challenge of Pain*. London: Penguin Books.

Merskey, H. and Bogduk, N., eds. 1994. Pain terms: A current list with definitions and notes on usage. In *Classification of Chronic Pain*, 2nd edn. Seattle, WA: IASP Task Force on Taxonomy, IASP Press, pp. 209–13.

Moayedi, M. and Davis, K. D. 2013. Theories of pain: From specificity to gate control. *Journal of Neurophysiology* 109: 5–12.

Morrison, I., Perini, I. and Dunham, J. 2013. Facets and mechanisms of adaptive pain behavior: Predictive regulation and action. *Frontiers in Human Neuroscience* 7 (755). doi: 10.3389/fnhum.2013.00755.

Moulton, E. A., Keaser, M. L., Gullapalli, R. P. and Greenspan, J. D. 2005. Regional intensive and temporal patterns of functional MRI activation distinguishing noxious and innocuous contact heat. *Journal of Neurophysiology* 93: 2183–93.

Mouraux, A. and Iannetti, G. D. 2009. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. *Journal of Neurophysiology* 101: 3258–69.

Mouraux, A., Diukova, A., Lee, M. C., Wise, R. G. and Iannetti, G. D. 2011. A multisensory investigation of the functional significance of the 'pain matrix'. *Neuroimage* 54: 2237–49.

Nash, P. G., Macefield, V. G., Klineberg, I. J., Gustin, S. M., Murray, G. M. and Henderson, L. A. 2010. Changes in human primary motor cortex activity during acute cutaneous and muscle orofacial pain. *Journal of Oral & Facial Pain* 24: 379–90.

Nieuwenhuys, R., Voogd, J. and van Huijzen, C. 2008. *The Human Central Nervous System*, 4th edn. Berlin: Springer.

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M. and Mauguiere, F. 2002. Representation of pain and somatic sensation in the human insula: A study of responses to direct electrical cortical stimulation. *Cerebral Cortex* 12: 376–85.

Paul, P. 2011. Rejection may hurt more than feelings. *New York Times*, 14 May. At http://www.nytimes.com/2011/05/15/fashion/is-rejection-painful-actually-it-is-studied.html?_r=1 (accessed 27 September 2015).

Penfield, W., Boldrey, E. 1937. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 60: 389–443.

Peyron, R., Laurent, B. and Garcia-Larrea, L. 2000. Functional imaging of brain responses to pain: A review and meta-analysis. *Neurophysiologie Clinique/Clinical Neurophysiology* 30: 263–88.

Picard, N. and Strick, P. L. 2001. Imaging the premotor areas. *Current Opinion in Neurobiology* 11: 663–72.

Ploner, M., Gross, J., Timmermann, L. and Schnitzler, A. 2006. Pain processing is faster than tactile processing in the human brain. *Journal of Neuroscience* 26: 10879–82.

Poldrack, R. A. 2006. Can cognitive processes be inferred from neuroimaging data? *Trends in Cognitive Sciences* 10: 59–63.

Pollatos, O., Gramann, K. and Schandry, R. 2007. Neural systems connecting interoceptive awareness and feelings. *Human Brain Mapping* 28: 9–18.

Pollatos, O., Kirsch, W. and Schandry, R. 2005. Brain structures involved in interoceptive awareness and cardioafferent signal processing: A dipole source localization study. *Human Brain Mapping* 26: 54–64.

Pons, T. P., Garraghty, P. E. and Mishkin, M. 1992. Serial and parallel processing of tactual information in somatosensory cortex of rhesus monkeys. *Journal of Neurophysiology* 68: 518–27.

Porro, C. A., Cettolo, V., Francescato, M. P. and Baraldi, P. 1998. Temporal and intensity coding of pain in human cortex. *Journal of Neurophysiology* 80: 3312–20.

Price, D. D. 2000. Psychological and neural mechanisms of the affective dimension of pain. *Science* 288: 1769–72.

Quiton, R. L., Keaser, M. L., Zhuo, J., Gullapalli, R. P. and Greenspan, J. D. forthcoming. Intersession reliability of fMRI activation for heat pain and motor tasks. *Neuroimage Clinical*.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A. and Shulman, G. L. 2001. A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America* 98: 676–82.

Rainville, P. 2002. Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology* 12: 195–204.

Rainville, P., Carrier, B., Hofbauer, R. K., Bushnell, M. C. and Duncan, G. H. 1999. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. *Pain* 82: 159–71.

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B. and Bushnell, M. C. 1997. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 277: 968–71.

Romaniello, A., Cruccu, G., McMillan, A. S., Arendt-Nielsen, L. and Svensson, P. 2000. Effect of experimental pain from trigeminal muscle and skin on motor cortex excitability in humans. *Brain Research* 882: 120–7.

Seminowicz, D. A. and Davis, K. D. 2007. A re-examination of pain–cognition interactions: Implications for neuroimaging. *Pain* 130: 8–13.

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J. and Davidson, R. J. 2011. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Reviews Neuroscience* 12: 154–67.

Sherrington, C. S. 1903. Science and medicine in the modern university. *Science* 18: 675–84.

Smith, S. M. 2012. The future of FMRI connectivity. *Neuroimage* 62: 1257–66.

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A. R. and Beckmann, C. F. 2009. Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America* 106: 13040–5.

Starr, C., Sawaki, L., Wittenberg, G., Burdette, J., Oshiro, Y., Quevedo, A. and Coghill, R. 2009. Roles of the insular cortex in the modulation of pain: Insights from brain lesions. *Journal of Neuroscience* 29: 2684–94.

Talbot, J. D., Marrett, S., Evans, A. C., Meyer, E., Bushnell, M. C. and Duncan, G. H. 1991. Multiple representation of pain in human cerebral cortex. *Science* 251: 1355–8.

Timmermann, L., Ploner, M., Haucke, K., Schmitz, F., Baltissen, R. and Schnitzler, A. 2001. Differential coding of pain intensity in the human primary and secondary somatosensory cortex. *Journal of Neurophysiology* 86: 1499–503.

Treede, R. D., Kenshalo, D. R., Gracely, R. H. and Jones, A. K. P. 1999. The cortical representation of pain. *Pain* 79: 105–11.

Uddin, L. Q. 2015. Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience* 16: 55–61.

Valentini, E., Hu, L., Chakrabarti, B., Hu, Y., Aglioti, S. M. and Iannetti, G. D. 2012. The primary somatosensory cortex largely contributes to the early part of the cortical response elicited by nociceptive stimuli. *Neuroimage* 59: 1571–81.

Vogel, H., Port, J. D., Lenz, F. A., Solaiyappan, M., Krauss, G. and Treede, R. D. 2003. Dipole source analysis of laser-evoked subdural potentials recorded from parasylvian cortex in humans. *Journal of Neurophysiology* 89: 3051–60.

Vogt, B. A. and Sikes, R. W. 2000. The medial pain system, cingulate cortex, and parallel processing of nociceptive information. *Progress in Brain Research* 122: 223–35.

Vogt, B. A. and Sikes, R. W. 2009. Cingulate nociceptive circuitry and roles in pain processing: The cingulate premotor pain model. In *Cingulate Neurobiology and Disease*, ed. by B. A. Vogt. New York: Oxford University Press, pp. 312–38.

Vogt, B. A., Sikes, R. W. and Vogt, L. T. 1993. Anterior cingulate cortex and the medial pain system. In *Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook*, ed. by B. A. Vogt and M. Gabriel. Boston: Birkhauser, pp. 313–44.

Vogt, B. A., Vogt, L., Farber, N. B. and Bush, G. 2005. Architecture and neurocytology of monkey cingulate gyrus. *Journal of Comparative Neurology* 485: 218–39.

Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C. W. and Kross, E. 2013. An fMRI-based neurologic signature of physical pain. *New England Journal of Medicine* 368: 1388–97.

Weinstein, S. 1968. Intensive and extensive aspects of tactile sensitivity as a function of body part, sex, and laterality. In *The Skin Senses*, ed. by D. R. Kenshalo. Springfield, IL: Thomas, pp. 195–222.

Weissman-Fogel, I., Moayedi, M., Taylor, K. S., Pope, G. and Davis, K. D. 2010. Cognitive and default-mode resting state networks: Do male and female brains 'rest' differently? *Human Brain Mapping* 31: 1713–26.

Zhang, Z. G., Hu, L., Hung, Y. S., Mouraux, A. and Iannetti, G. D. 2012. Gamma-band oscillations in the primary somatosensory cortex: A direct and obligatory correlate of subjective pain intensity. *Journal of Neuroscience* 32: 7429–38.

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C. and Wager, T. D. 2011. Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods* 8: 665–70.