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Distinguishing pain from nociception, salience, and arousal: How autonomic nervous system activity can improve neuroimaging tests of specificity

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Abstract

Pain is a subjective, multidimensional experience that is distinct from nociception. A large body of work has focused on whether pain processing is supported by specific, dedicated brain circuits. Despite advances in human neuroscience and neuroimaging analysis, dissociating acute pain from other sensations has been challenging since both pain and non-pain stimuli evoke salience and arousal responses throughout the body and in overlapping brain circuits. In this review, we discuss these challenges and propose that brain-body interactions in pain can be leveraged in order to improve tests for pain specificity. We review brain and bodily responses to pain and nociception and extant efforts toward identifying pain-specific brain networks. We propose that autonomic nervous system activity should be used as a surrogate measure of salience and arousal to improve these efforts and enable researchers to parse out pain-specific responses in the brain, and demonstrate the feasibility of this approach using example fMRI data from a thermal pain paradigm. This new approach will improve the accuracy and specificity of functional neuroimaging analyses and help to overcome current difficulties in assessing pain specific responses in the human brain.

Keywords

brain-body; pain specificity; salience; arousal; functional neuroimaging; autonomic nervous system

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Introduction

Pain is fundamental to survival. It motivates us to escape danger, seek care, and learn to avoid harm in the future. Successful identification of pain-specific brain patterns could enhance diagnosis and prognosis of pain in the clinic, as well as reveal fundamental truths about the nature of pain as a percept and how it is instantiated in the brain. Yet despite decades of efforts, it is still unclear whether pain is dissociable from other sensations at the level of the central nervous system, i.e., whether pain is a special type of percept mediated by unique, dedicated neural circuits (Craig, 2003; Perl, 2007), or if it is a sensation experienced in response to any extremely salient sensory stimulus (Legrain et al., 2011). *Pain* is a complex, subjective phenomenon defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (IASP, 1994). These sensory and emotional components of pain distinguish it from *nociception,* which is defined as the neural process of encoding stimuli that damage or threaten to damage tissue (Merskey, 1994), yet they also highlight the link between pain and salience. *Salience* is defined as a characteristic of a stimulus that makes it perceived as distinct from its surroundings (Itti and Koch, 2001; Menon and Uddin, 2010; Uddin, 2015). Regardless of stimulus modality, salient stimuli capture our attention, cause autonomic and emotional responses, and modify our behavior, similar to acute pain (Bernstein, 1969; Bradley, 2009; Lang, 2014; Liberati et al., 2016; Menon and Uddin, 2010; Mouraux et al., 2011; Parr and Friston, 2018). Acute pain also automatically captures our attention (Iannetti and Mouraux, 2010; Legrain et al., 2009; Legrain et al., 2011) to generate a wide range of adaptive behaviors including withdrawal from the stimulus, seeking relief, and collecting information to predict future damage (Eccleston and Crombez, 1999; Fields, 2018). Thus, determining if and how pain can be distinguished from nociception and salience is an area of active research, and the question of whether there may be pain-specific brain responses is still a controversial issue in need of additional empirical data (Berkley and Hubscher, 1995; Moayedi and Davis, 2013; Mouraux and Iannetti, 2018).

We propose that that there may be unique pain-related processes that do not overlap with other sensory processes in the brain. Yet because pain shares characteristics with other salient somatosensory and non-somatosensory stimuli across modalities, perhaps difficulty in controlling for the non-specific features of pain (i.e., features of pain that are shared with non-pain stimuli) has restricted our ability to acquire the necessary empirical data to resolve this debate. New approaches are necessary to distinguish pain from other sensations. We propose that measuring and accounting for brain responses associated with autonomic nervous system (ANS) arousal in the periphery will help identify and rule out acute pain-related brain processes that are related to salience and arousal and thereby isolate pain-specific brain processes. Though machine learning classifiers and multivariate analyses have achieved recent success in identifying pain-specific patterns of brain activity (Marquand et al., 2010; Schulz et al., 2012; Wager et al., 2013), accounting for salience and arousal has the potential to enhance the accuracy of such classifiers and further our understanding of the brain response specific to pain. In line with the approach and theory we outline, two recent empirical studies demonstrate promise for accounting for salience using either subjective or peripheral ANS measures to evaluate pain-specific brain responses (Horing et al., 2019;

Liang et al., 2019). Here, we review why accounting for ANS activity holds such promise for the important test of whether pain-specific processes exist in the human brain.

As illustrated in Figure 1A, we assume that the brain response to pain is comprised of: 1) nonspecific processes that are shared between pain and other sensations (e.g., salience and arousal); 2) features shared by somatosensory sensations (e.g. intensity estimation and location processing); 3) responses that differentiate between innocuous and noxious stimuli, irrespective of subjective experience (i.e., nociception); and 4) pain-specific processes. Thus, we define pain-specific processes as brain responses that are *uniquely associated* with subjective pain and are not involved in the processing of stimuli of other modalities. To be pain-specific, associations with pain must remain after accounting for non-specific and domain-general responses, somatosensory responses, and the effects of nociceptive inputs (Figure 1B). By studying bodily responses alongside brain responses to pain and non-pain control stimuli, we can account for the non-specific factors of salience and arousal. We believe that this approach may also have utility in the future for accounting for other non-specific factors, though they will not be discussed further here.

This review is comprised of two parts; first, we evaluate the current knowledge on pain and its specificity and work demonstrating that pain shares general features with other non-painful stimuli that influence the brain's response to pain, confounding our current ability to detect pain-specific brain responses. We then describe a new approach to link arousal patterns in the brain and periphery in service of parsing out similarities between pain, salience, and arousal to determine a pain-specific brain response. Finally, we demonstrate the feasibility of this approach using example data from an fMRI study of acute pain. We focus here on stimulus-evoked pain (e.g., pain elicited by noxious heat, pressure, visceral, electrical stimulation), though this approach has the promise to inform the investigation of the specificity of other types of pain in the future.

Distinguishing pain and nociception using responses in the brain and body

As mentioned earlier, pain is distinct from nociception, the neural process of encoding and processing noxious stimuli (IASP, 1994). Functional neuroimaging and electrophysiological studies in humans and animals have revealed a wide range of brain regions consistently modulated by noxious mechanical, thermal, and chemical stimuli including the primary and secondary somatosensory cortex, anterior cingulate cortex (ACC), insula, thalamus, prefrontal cortex (PFC), inferior/posterior parietal cortex, and periaqueductal gray (PAG) (Apkarian et al., 2005; Davis and Moayedi, 2013; Derbyshire et al., 1997; Duerden and Albanese, 2013; Iadarola et al., 1998; Melzack, 1999; Talbot et al., 1991) (see Figure 2A). The term 'pain matrix' has been used widely to describe this set of brain regions involved in human nociceptive processing (Garcia-Larrea and Peyron, 2013; Iannetti and Mouraux, 2010). However, there is mixed processing of pain and nociception in the pain matrix, and many of these regions may not be specific to pain. Pain and nociception are distinct processes that can, and should, be distinguished (Garland, 2012). Pain can exist in the absence of nociceptive input (e.g., the experience of pain from amputated limb (Melzack, 1990)) and nociceptive input does not always produce pain (e.g., battlefield analgesia (Beecher, 1946, 1956); attentional modulation of pain (Torta et al., 2017)). Thus, one

continued thread of research on pain-specific processing focuses on distinguishing pain from nociception.

Indeed, much research has been devoted to identifying brain regions that uniquely process nociceptive information or pain and how nociceptive information is translated into the experience of pain (Apkarian et al., 1999; Atlas et al., 2014; Baliki et al., 2009; Buchel et al., 2002; Craig et al., 2000). For instance, in one of the first functional magnetic resonance imaging (fMRI) investigations of acute thermal pain, Apkarian et al. (1999) differentiated between brain activity related to stimulus intensity (variations in temperature over time) and pain (variations in perception over time) (Apkarian et al., 1999). A functional gradient separated nociception and pain: anterior regions (e.g., insula) were more related to the time course of the stimulus, while posterior regions (e.g., BA 5/7, i.e., the somatosensory association cortex) were more related to the time course of perceived pain. Buchel et al. (2002) reported similarly that anterior portions of the dorsal posterior ACC (dpACC) were linked to stimulus intensity regardless of subjective pain (Buchel et al., 2002) and discriminated noxious and innocuous stimulation, while posterior portions of the dpACC tracked subjective pain. A more recent fMRI study (Atlas et al., 2014) also observed similar gradients of sensitivity to temperature and pain using voxel-wise multilevel mediation analysis. The left insula and the cingulate cortex both exhibited gradients such that anterior portions were related to temperature (and not pain), posterior portions were related to pain (and not temperature), and middle portions formally mediated temperature effects on subjective pain (Atlas et al., 2014). These results suggest that pain is subserved by not only pain-specific and temperature-specific processes, but also key brain networks that link or convert nociceptive inputs (e.g., stimulus intensity) into pain.

Machine learning and multi-voxel pattern analyses (MVPA) have also been used to determine whether patterns of activity can discriminate painful and non-painful stimuli above and beyond the effects of temperature (Woo et al., 2017b). The stimulus intensity independent pain signature-1 (SIIPS1) is a brain-based pattern that is sensitive to pain, but independent of the stimulus intensity that elicits the pain (Woo et al., 2017b). The SIIPS1 pattern of predictive weights includes portions of regions within the so-called “pain matrix” (e.g., insula, ACC, and thalamus) that were activated by noxious stimulation but also predicted pain above and beyond the effect of temperature, as well as regions in the PFC and striatum, which are not classic targets of ascending nociceptive pathways, that predicted variations in pain but were not influenced by differences in temperature (Woo et al., 2017b). This classification approach demonstrates considerable success in distinguishing pain from non-pain, suggesting that some brain responses may be sensitive and specific to pain, rather than nociception.

Painful and noxious stimuli also reliably modulate responses in the ANS (for a review, see Kyle and McNeil (2014) (Kyle and McNeil, 2014)), consistent with pain’s relevance for survival. The ANS is comprised of both a sympathetic and a parasympathetic branch, which together innervate end organs in the periphery in accordance with changing physiological and psychological demands. Noxious stimuli elicit robust ANS responses across multiple end organs (for a brief synopsis of peripheral ANS measures and pain, see Figure 2B). Specifically, noxious stimuli can enhance sympathetic activity, resulting in enhanced SCR

(Geuter et al., 2014; Hampf, 1990; Loggia et al., 2011; Mischkowski et al., 2019; Nickel et al., 2017; Paine et al., 2009; Schestatsky et al., 2007), and elicit parasympathetic withdrawal, as indexed by reductions of vagally-mediated heart rate variability (HRV) during pain (Bendixen et al., 2012; Pollatos et al., 2012; Sclocco et al., 2016a; Treister et al., 2012b). Some measures (e.g. increases in heart rate (HR) (Hampf, 1990; Loggia et al., 2011; Moltner et al., 1990; Paine et al., 2009; Treister et al., 2012a; Victor et al., 1987), blood pressure (Chalaye et al., 2013; Kregel et al., 1992; Reyes del Paso et al., 2011; Reyes Del Paso et al., 2014; Victor et al., 1987), pupil diameter (Eisenach et al., 2017; Geuter et al., 2014; Höfle et al., 2008; Mischkowski et al., 2019), and some measures of heart rate variability (Aslaksen et al., 2007; Chouchou et al., 2011; Terkelsen et al., 2005) are likely to reflect activity in both branches of the ANS, which can operate reciprocally, in parallel, or independently (Berntson et al., 1991; Berntson et al., 1994).

Recently, pain researchers have begun assessing whether peripheral ANS responses may be specific to pain or nociception. In one study, ten minutes of tonic heat pain were administered to 39 healthy volunteers while they rated their subjective pain continuously. Researchers found that SCR was more related to changes in stimulus intensity than subjective pain (Nickel et al., 2017). However, opposing conclusions were found in a series of acute pain studies that included a larger range of temperatures across both innocuous and noxious ranges (Mischkowski et al., 2019). In those studies, temperature effects on SCR and pupil dilation were mediated by subjective pain, and simply labeling a noxious stimulus as painful increased the stimulus-evoked SCR response, even in response to the same objective temperature. Since combining multiple metrics of the ANS response across different end organs best explains variance in pain intensity in both regression (Geuter et al., 2014) and multivariate classifier models (Donaldson et al., 2003), understanding the sensitivity of different ANS measures to pain and nociception will be an important direction for future work.

Together, this work indicates that it is possible to distinguish pain from nociception at the level of the central and peripheral nervous system and that portions of both the “pain matrix” and the ANS process both nociceptive and nociceptive-independent pain information. However, in the interest of evaluating pain specificity, an important limitation of this body of work is that studies that focus entirely on dissociating pain from nociception rarely compare pain and nociception with other stimulus modalities. Though pain intensity may scale with nociceptive input, it may also be related to non-specific features of the stimulus, such as salience (Wiech et al., 2010), aversiveness/unpleasantness (Bushnell et al., 2013), and/or endogenous fluctuations in arousal and attention (Ploner et al., 2010). This begs the question of whether pain-related processes identified in these studies are specific to the subjective sensation of pain elicited by noxious stimulation, or whether they might be associated more broadly with non-specific processes that are shared between pain and other sensory modalities. In the next section, we discuss two primary domain-general processes that may account for a large portion of the non-specific brain response to pain: salience processing and arousal.

What are salience and arousal, and how are they represented in the brain and body?

Salience is a perceived characteristic of a stimulus that makes it is more likely to be distinct from other stimuli (Itti and Koch, 2001; Uddin, 2015; Yantis and Hillstrom, 1994). Salience is one of the most universal and non-specific factors in a large variety of exteroceptive sensations, including acute pain (Craig, 2009). The perceived *salience* of a stimulus is different from the sensory *intensity* of a stimulus, similar to the distinction between pain and nociception, as salience is affected by interoceptive and environmental factors (Borsook et al., 2013). For example, a fire might have a certain stimulus intensity (e.g., temperature, luminance), but the perceived salience of the fire may vary depending on psychological factors (e.g., attention) and environmental factors (e.g., context). A fire in one's kitchen cabinet is likely more salient than a fire on the stovetop or in a fireplace (Figure 3).

The salience network is comprised of brain regions that process salient environmental changes regardless of stimulus modality. It has been postulated that the anterior insula and the dorsal ACC – two key regions of the pain matrix discussed above - are hubs of the salience network (Downar et al., 2003; Seeley et al., 2007; Taylor et al., 2009), which also includes the amygdala, ventral tegmental area, thalamus, hypothalamus, and PAG (Menon and Uddin, 2010; Seeley et al., 2007) (purple regions in Figure 2A). A wide range of functions has been ascribed to these regions: They are involved in interoceptive processing (Seeley et al., 2007), respond to emotion (Critchley, 2009), reward (Menon and Levitin, 2005), and threats to homeostatic regulation (Peyron et al., 2000), are activated by a variety of exteroceptive sensations (Craig, 2009; Critchley, 2009), show intrinsic connectivity during resting state (Seeley et al., 2007), and facilitate network switching (Goulden et al., 2014; Sridharan et al., 2008). For extensive discussions on salience and the salience network, please see Menon and Uddin (Menon and Uddin, 2010) and Uddin (Uddin, 2015).

One factor that can render stimuli salient is arousal (Mather and Sutherland, 2011; Sutherland and Mather, 2018). Arousal is a state of heightened awareness of and sensitivity to the environment (Critchley et al., 2013), and can influence which stimuli in an environment are most salient (e.g., Figure 3). A state of arousal enables an organism to act upon its environment by engaging motoric, emotional, and motivational systems and enhancing sensitivity to sensory input (Calderon et al., 2016; Pfaff et al., 2012). Arousal is a heterogenous construct, and the term has been used variously to describe multiple concepts, including physiological (autonomic) arousal, affective (i.e., subjective) arousal, and wakefulness (Satpute et al., 2018). Here we focus on autonomic arousal to index the state of being aware of and sensitive to one's environment. Arousal is usually associated with both sympathetic nervous system outflow (e.g., increased HR or SCR) and parasympathetic nervous system withdrawal (e.g., decreased vagally mediated HRV; Figure 2). Though it is tempting to use a single measure of autonomic arousal as a proxy for the psychological state of being aroused, activity at different end organs does not always correspond in a one-to-one fashion (Berntson and Cacioppo, 2007; Cacioppo and Tassinary, 1990; Norman, 2016), as autonomic output results not only from brain processes but also mechanisms in the periphery (e.g., the sinoatrial node of the heart) and spinal reflexes. Thus, combining autonomic metrics across many endorgans permits a more precise characterization of physiological arousal.

Physiological arousal is thought to be driven by activity in a network of regions that is referred to as the central autonomic network (CAN in Figure 2A (Benarroch, 1993; Berntson et al., 1993; Cacioppo et al., 2007)). A great deal of animal work (Jhamandas and Renaud, 1987; Jordan and Spyer, 1986; Sawchenko and Swanson, 1981; Smith et al., 1991; Strack et al., 1989), as well as post-mortem human work (Arango et al., 1988) and work with direct stimulation of cortical tissue in humans (Chouchou et al., 2019; Oppenheimer et al., 1992), has linked ANS responses in the periphery with a network of regions in the brain, including cortical structures such as the anterior and posterior insular cortex and ACC, midbrain structures such as the thalamus and amygdala, and brainstem structures such as the PAG, the nucleus tractus solitarius of the medulla (NTS), the paraventricular nucleus of the hypothalamus (PVN), and the parabrachial nuclei (PBN) (red and purple regions in Figure 2A). In fMRI studies, it is also widely established that activity in regions of the CAN corresponds with ANS activity (Critchley et al., 2000; Eisenbarth et al., 2016; Napadow et al., 2008; Sclocco et al., 2016b; Thayer et al., 2012) (for a meta-analysis, see (Beissner et al., 2013)). However, widespread cortical activation has been found to correlate with autonomic parameters in fMRI (e.g., Valenza et al., 2019); thus, we focus only on regions that are corroborated by both fMRI studies as well as studies using animals, electrical stimulation, lesions, or post-mortem tissues. The regions that have the strongest convergent evidence are the ACC, insula, PAG, amygdala, and thalamus (see Figure 2A). The CAN is responsible for coordinating organized ANS responses across multiple end-organs that together enable the body to effectively minimize or escape potential bodily threat, and activity in the CAN reflects both efferent and afferent control of autonomic functions, as well as both sympathetic and parasympathetic peripheral activity. For instance, activity in the posterior insula, which is the target of many ascending projections from the periphery via the lamina I spinothalamocortical tract (Craig, 2002; Craig, 2009; Damasio and Carvalho, 2013; Dum et al., 2009), tends to be involved in *afferent* control of cardiac function, whereas activity in the anterior insula tends to be involved in *efferent* control of cardiac function (Cechetto, 2014; Macey et al., 2012; Palma and Benarroch, 2014). Further, electrical stimulation has suggested functional dissociations between the middle and posterior human insular cortex in the control of the two branches of the ANS (at least with respect to the heart). Posterior stimulation is associated with tachycardia, corresponding to sympathetic control, while more anterior stimulation is associated with bradycardia, corresponding to parasympathetic control (Chouchou et al., 2019), consistent with animal work (Marins et al., 2016; Oppenheimer & Cechetto, 1990).

Emerging evidence suggests that physiological arousal may also be related to activity and connectivity within the salience network (Schneider et al., 2016; Xia et al., 2017; Young et al., 2017). Indeed, interoceptive ascending inputs are delivered to the thalamus by autonomic afferent nuclei in the CAN network (e.g., NTS and PBN) and integrated in the posterior insula and ACC, and the salience network projects the information to autonomic efferent nuclei and the dorsal motor nucleus to activate a viscero-motor response (Uddin, 2015). Further, stimuli that exhibit characteristics that could make them perceived as more salient, such as those that are more intense (e.g., louder sounds, brighter lights, and images with greater emotional valence) or more distinct from their surroundings, elicit greater physiological arousal responses (Barry and Furedy, 1993; Beissner et al., 2013; Bull and

Lang, 1972; Gatchel and Lang, 1973; Napadow et al., 2008; Simons and Lang, 1976; Smith and Strawbridge, 1969; Turpin and Siddle, 1979; Uno and Grings, 1965). We therefore assume that more salient stimuli evoke greater physiological responses.

Given the strong relationship between pain, salience, and arousal, we propose that researchers in search of pain-specific brain processes should isolate and account for variations in salience by statistically controlling for physiological arousal. Doing so will enhance identification of pain-specific processes. In the following sections, we evaluate evidence of functional and anatomical overlap between salience, arousal, and pain, and propose an approach by which to use this overlap to isolate and evaluate pain-specific brain processes.

Relationships between pain, salience, and physiological arousal

As mentioned earlier, few studies that distinguish pain from nociception in the interest of isolating pain-specific processes have accounted for non-specific processes such as salience and arousal. An active debate over whether there are pain-specific brain responses (Berkley and Hubscher, 1995; Hu and Iannetti, 2016a; Moayedi and Davis, 2013; Mouraux and Iannetti, 2018; Zunhammer et al., 2016) persists in large part because painful stimuli 1) are salient and automatically capture our attention; 2) elicit physiological arousal across multiple end organs (Chalaye et al., 2013; Eisenach et al., 2017; Geuter et al., 2014; Hampf, 1990; Höfle et al., 2008; Kregel et al., 1992; Loggia et al., 2011; Mischkowski et al., 2019; Moltner et al., 1990; Nickel et al., 2017; Paine et al., 2009; Reyes del Paso et al., 2011; Reyes Del Paso et al., 2014; Schestatsky et al., 2007; Treister et al., 2012a; Victor et al., 1987); and 3) recruit much of the same neural circuitry as salience and arousal. Further, many of the brain regions within the pain matrix are associated with processing stimulus-general effects across sensory modalities. The insula, for instance, is the key integration region in many theories of cortical pain perception (reviewed in Moayedi, 2014), and electrical stimulation and lesion of the posterior insula produces pain in patient populations (Garcia-Larrea et al., 2010; Mazzola et al., 2009; Montavont et al., 2015). Yet the insula has also been variously associated with disgust (Wicker et al., 2003), pleasantness (Koelsch et al., 2006), and awareness (Craig, 2009), and is activated by noxious stimulation even in patients with congenital insensitivity to pain (Salomons et al., 2016). Moreover, insula lesions do not abolish pain processing (Baier et al., 2014; Feinstein et al., 2016; Starr et al., 2009). Similarly, the dorsal ACC (dACC) contains nociceptive neurons (Hutchison et al., 1999) and was one of the earliest loci of pain modulation (Rainville et al., 1997), yet pain can persist after cingulotomies (Yen et al., 2005), and heated debate concerns the dACC's role in conflict (Kerns et al., 2004), foraging (Kolling et al., 2012), and response inhibition (Braver et al., 2001; Garavan et al., 2002) – non-specific functions that may be linked with pain, but certainly are not specific to pain. These two regions are widely considered to act as hubs of the salience network (Downar et al., 2003; Seeley et al., 2007; Taylor et al., 2009), as mentioned above, and have been proposed to make up a "task-set network" (Dosenbach et al., 2006) based on the fact that they are co-activated by nearly all cognitive and affective tasks (Dosenbach et al., 2006; Yarkoni et al., 2011). Most importantly, in direct comparisons, these regions and others in the so-called pain matrix all show considerable activity in response to not only painful stimulation, but also olfactory stimuli (Lotsch et al.,

2012), non-painful pressure (Wey et al., 2014), and auditory, visual, and non-nociceptive somatosensory stimuli (Lui et al., 2008; Mouraux et al., 2011).

Similarly, while individual studies may measure whether stimulus-evoked ANS responses are more related to nociception or pain (Mischkowski et al., 2019; Nickel et al., 2017), none of these studies have compared ANS responses to pain with other arousing modalities. ANS responses are linked to subjective experience across many different domains (e.g., auditory, visual, and emotional stimuli elicit ANS responses (Beissner et al., 2013; Bradley et al., 2001; Napadow et al., 2008; Smith and Strawbridge, 1969; Turpin and Siddle, 1979; Uno and Grings, 1965)). The CAN also overlaps to a large extent with pain matrix (including the insula, ACC, and PAG; Figure 2A). Activation in brain regions typically active during pain, including the dACC, thalamus, anterior insula, and amygdala, is associated with greater skin conductance responses (i.e., greater sympathetic arousal) to painful versus innocuous stimuli (Dubé et al., 2009; Piché et al., 2010). Furthermore, much (though not all) of the brain's response to noxious, relative to innocuous, stimuli overlaps with a network that may be involved in central regulation of peripheral blood flow via sympathetic afferents (Maihöfner et al., 2011)., suggesting that this network may be involved in modulation of arousal-related processes in the periphery during pain. Thus, activation of what is sometimes called the pain matrix may be explained in large part by CAN activity corresponding with evoked autonomic arousal, a process that is not specific to pain.

The above evidence is consistent with the argument that no brain regions or responses are specific to pain (Carmon et al., 1976; Iannetti et al., 2008; Iannetti and Mouraux, 2010; Legrain et al., 2011). However, there is an alternative interpretation of this work: pain-specific brain responses may exist, but these responses may be obfuscated by domain-general brain responses that are sensitive to features of sensory stimuli across all modalities. These domain-general processes must be appropriately accounted for in order to identify pain-specific brain responses.

State of the field: Evidence of pain specificity—To evaluate the role of non-specific processes such as salience, Mouraux et al. (2011) tested various sensory stimuli, including painful heat, non-nociceptive electrical stimuli, and visual and auditory stimuli. Across participants, average salience ratings were correlated with the magnitude of stimulus-evoked blood oxygenation level dependent (BOLD) response in most regions of the pain matrix, even within non-painful sensory modalities. That is, even highly salient auditory and visual stimuli caused brain responses in insula, ACC, and S2 similar to pain (Mouraux et al., 2011). Yet these results do not conclusively suggest a lack of pain-specific responses in the brain since analyses did not account for within-subjects variations in salience. A follow-up analysis by Liang and colleagues (2019) (Liang et al., 2019) used the same data (as well as a second similar dataset) but matched painful and non-painful sensory stimuli within subjects using trial-by-trial salience ratings. Pain-specific brain responses (i.e. those that differed from equally salient innocuous touch, visual stimuli, and auditory stimuli) were indeed present when stimuli were matched based on perceived salience, specifically within the insula and secondary somatosensory cortex (SII), as well as when the authors used MVPA. Successful pain classification was observed when MVPA was restricted to either pain matrix regions or non-pain matrix regions. These results indicate that painspecific patterns of

activation indeed exist, but it is critical to account for dynamic variations in salience specificity to pain. This work, however, did not measure relationships with subjective pain, but instead treated pain as a categorical percept, which was not distinguished from nociception. A remaining question is whether brain responses can specifically predict the subjective experience of pain, above and beyond both salience and nociception, which is critical to the search for brain-based biomarkers of subjective pain (Mouraux and Iannetti, 2018; Poldrack, 2011; Robinson et al., 2013; Woo et al., 2017a).

Two promising candidate regions for pain-specificity are the dorsal posterior insula (dpIns) and SII. Electrical stimulation of the dpIns can produce pain (Mazzola et al., 2009; Montavont et al., 2015) and one ASL study (Segerdahl et al., 2015) found that the dpIns uniquely correlated with pain reports during tonic capsaicin-induced pain, but was insensitive to vibratory stimulation. However, dpIns stimulation also increases physiological arousal (Chouchou et al., 2019) and the ASL study could not conclusively rule out the possibility that the dpIns also plays a role in non-specific processes (Davis et al., 2015), in part because non-somatosensory stimuli were not presented. A recent study by Horing & colleagues took a definitive step towards identifying pain-specific brain processes. They accounted for *both* salience and modality-specificity by comparing painful heat with auditory stimuli and matching stimuli on the basis of stimulus-evoked physiological arousal (i.e., SCR). SII and dpIns both showed greater activation to heat (both painful and non-painful) compared to sound, and the activity in the SII and dorsal anterior insula were significantly related to perceived intensity rating (Horing et al., 2019). However, only SII showed both specificity to nociception (heat vs. sound, noxious vs innocuous heat) *and* pain (correlation with subjective ratings). This is an important advance toward evidence of specificity, although a complete demonstration will require additional control modalities.

Pain-specific patterns of activity may also be distributed, rather than isolated within specific regions, since individual brain regions are often insufficient for the production of pain (Penfield and Boldrey, 1937; Feinstein et al., 2016; Foltz and White, 1962; Geschwind, 2010; though see Mazzola et al., 2009 & Montavont et al., 2015). As alluded to earlier, an increasing number of neuroimaging studies have applied multivariate analyses such as MVPA and machine learning classifiers to extract latent information from neuroimaging data across brain regions (Kragel et al., 2018). Multivariate patterns of brain activation have shown considerable sensitivity and specificity to acute pain in healthy individuals (Cecchi et al., 2012; Marquand et al., 2010; Schulz et al., 2012; Wager et al., 2013) and have revealed significant pain-related patterns in patients with chronic pain (Callan et al., 2014; Lopez-Sola et al., 2017). The Neurologic Pain Signature, for example, is a physical pain-specific pattern in the brain that predicts subjective pain and is driven by activation in the PAG, thalamus, secondary somatosensory cortex, posterior and anterior insula, and ACC (Wager et al., 2013). It discriminates heat/mechanical/electrical/visceral pain from warmth and the anticipation of pain, social, and vicarious pain (Krishnan et al., 2016; Wager et al., 2013; Woo et al., 2017a; Woo et al., 2014). In addition, MVPA applied to electroencephalography signals in response to repeated pain stimuli predicted individuals' pain sensitivity (with an accuracy of 83%) (Schulz et al., 2012) and a machine learning algorithm on patterns of whole-brain fMRI BOLD signals distinguished between painful and non-painful thermal stimuli (with an accuracy of 81–84%) (Brown et al., 2011).

While extremely promising and productive, to our knowledge most of these patterns have not yet fully accounted for salience, although the recent work by Liang et al. (Liang et al., 2019) is a promising step in this direction. When studies do not formally account for salience using subjective or physiological measures, differences attributed to pain may simply reflect the fact that pain is more salient and arousing than most non-painful stimuli. Thus, what has been observed to be a pain-specific pattern could still be partially related to pain-related salience and arousal, leaving open the question of whether purported pain-specific brain processes described above are indeed specific to pain (Hu and Iannetti, 2016b; Salomons et al., 2016). In the next section, we outline an approach that builds on the work of Horing et al. (Horing et al., 2019) and uses peripheral signals of autonomic arousal to account for salience and arousal processing in the brain, rather than experimentally matching the salience of stimuli based on subjective ratings. This approach circumvents assumptions that painful and non-painful stimuli must be matched on these attributes, as arousal and salience responses might be different in each individual (e.g., phobia-related visual cues could produce an attentional bias and increase arousal in a person with phobia more than in non-fearful participants (Aue et al., 2013; Ohman and Soares, 1994)) and are also affected by experimental context and stimulus novelty (Foley et al., 2014; Kalat, 1974).

How can we use brain-body connections to determine pain specificity in the brain?

A proposal to use autonomic activity to isolate non-specific salience and arousal in responses to pain—We propose that we must consider the role of nonspecific processes and related responses in the brain and body to isolate and understand pain-specific responses. We suggest that researchers investigating pain-specific brain responses measure and statistically control for the brain signals associated with salience and arousal by including continuous physiological measures of arousal (down-sampled to the timing of the BOLD signal) in their FMRI analyses as nuisance regressors of no interest. One or more measures of physiological arousal should be used (such as SCR, HR, HRV, BP, or pupil dilation), although integrating across physiological measures is likely to be best, as discussed below. To the extent that the brain response to pain is non-specific, brain activity may correspond temporally with physiological arousal not only during pain but also during endogenous fluctuations in arousal between stimuli. If a non-painful control condition is also assessed (e.g. warm temperature), this brain activity should correspond temporally to non-painful stimulus evoked arousal as well. The residualized BOLD signal associated with painful stimuli, compared to non-pain control stimuli, that remains after removing variance associated with ANS-related arousal should be less confounded by non-specific features of pain, and thus arguably more specific to pain. Though this approach would primarily account for stimulus-related salience and fluctuations in endogenous arousal, it is also possible that it accounts at least partially for other non-specific factors, such as fear, anxiety, or threat-processing, since salience and arousal are also related to emotion and motivation. It should be noted that raw physiological signals measured during the scan should be preprocessed and converted into informative variables, if necessary, prior to downsampling to the timing of the BOLD signal. For example, in our initial feasibility application described below, we computed a continuous timeseries of respiration flow rate, the integral of respiratory excursion per each cycle period (Bach et al. 2016), from the raw respiration signal, and included it as a regressor, rather than using the raw respiration trace. On the other

hand, since electrodermal activity is directly linked to physiological arousal, the SCR signal can be used as a regressor for our approach after appropriate preprocessing (e.g. filtering, smoothing, down-sampling).

To test the feasibility of our approach, we turned to empirical data from a subset of participants from a previously published study (for more details, please see Atlas et al., 2014. In brief, participants received 4 different intensities of thermal stimuli (non-painful warm, low pain, medium pain, and high pain) and provided pain ratings on every trial. SCR, photoplethysmography (PPG), and respiration were measured continuously during scanning and preprocessed using the PsPM toolbox, then downsampled to the resolution of the TR (2s; 0.5Hz). For SCR, we applied low-pass filter of 1Hz, and smoothed using a moving average of each second. We converted PPG signal (obtained by peripheral pulse oximeter) into heart beat using the pspm_ppu2hb function and calculated heart rate per each TR. Respiration flow rate (integral of respiratory excursion per each respiration cycle period) was computed from raw respiration signal in PsPM using pspm_resp_pp function. To evaluate our approach, we extracted data from SII and insula and used single trial analysis (Atlas et al., 2014; Mumford et al., 2014; Rissman et al., 2010) to fit heat-evoked area under the curve (AUC) estimates for each trial in three models (see Figure 4). Model 1 estimated AUC after regressing out standard nuisance regressors (head motion and spikes), identical to our original processing pipeline (Atlas et al., 2014). Model 2 included standard nuisance regressors (motion, spikes) as well as regressors for physiological arousal (SCR, HR) and noise (respiration). Note that though respiration could contain some arousal-related signal (e.g., if a participant holds their breath in anticipation of or during pain), respiratory fluctuations also introduce noise into both the BOLD timeseries and the timeseries of other peripheral autonomic measures. Model 3 included the same physiological regressors as Model 2, but measured relationships between AUC and pain while controlling for stimulus intensity (i.e. nociception). We tested each model using the general linear model, in which subjective pain was the independent variable and AUC for each ROI was the dependent variable. Preliminary results are illustrated in Figure 4. The residual brain activity in the right insula, but not in the SII, is significantly predicted by pain ratings after regressing out nuisance variables (Model 1), while the residual brain activity in both regions is significantly predicted by pain ratings after regressing out the effect of arousal as well as nuisance (Model 2). However, after regressing out the effect of nociception from the brain activity in Model 3, pain ratings do not predict brain activity in either region, suggesting responses in these five subjects were driven by nociception, rather than subjective pain. Of course, given the small sample size and the fact that this study was not designed to evaluate pain specificity (i.e. other stimulus modalities were not presented), conclusions from these findings pertain to the utility of this recommended analytical approach, rather than speaking empirically to presence of pain-specific brain responses. However, we believe this preliminary example provides promising support for the argument that regressing out the effect of arousal using ANS activity will improve tests of pain specificity.

Caveats—Our approach is not without limitations. For one, our approach advises measuring the construct of ‘arousal’, but to do so most precisely, it may be necessary to combine autonomic measurements (e.g., SCR, pupil diameter, HR, HRV, BP) across

different end-organs (e.g., dermis, pupil, heart, and vasculature, respectively; (Norman, 2016)). Indeed, identifying brain responses commonly associated with physiological arousal across many different end-organs may elucidate brain processes that are involved in the central regulation of peripheral arousal more broadly, rather than processes that are specific to one autonomic system or end-organ. Given that ANS metrics are influenced by factors outside the brain, including spinal reflexes (Pickering and Paton, 2006) and cells in the periphery (such as the sinoatrial node, which serves as a pacemaker to modulate intrinsic heart rate in the absence of central autonomic influence; Jose and Collison, 1970; Opthof, 2000; Mangoni and Nargeot, 2008), brain correlates that are common to multiple ANS responses might better correspond to central regulation of peripheral arousal than regions that exhibit different patterns of activation for ANS metrics from different end-organs. Furthermore, combinations of ANS measurements across many end-organs better predicts graded differences in pain intensity (Donaldson et al., 2003; Geuter et al., 2014; Jiang et al., 2018; Matthewson et al., 2019; Treister et al., 2012a), demonstrating the utility of studying the arousal response as a whole for capturing the pain percept. However, this can be a constraint of our method, as multimodal measurement of the ANS response can be costly and can demand intensive processing resources. Techniques such as principal component analysis will help reduce the dimensionality of autonomic time series from multiple end-organs and identify shared variance across peripheral signals. Another potential caveat to our approach is that it makes no strong assumptions on the direction of brain-body interactions (e.g., whether pain-evoked ascending ANS activity elicits a brain response, or the brain sends descending signals to regulate the ANS response to pain, or both), but rather argues that central activity related to arousal (either efferent or afferent) is a process that is not unique to pain and therefore should be accounted for to better identify pain-specific brain responses. Whether correlations between BOLD activity and autonomic metrics reflect efferent, versus afferent, brain activity is not well established (see Napadow (2008) (Napadow et al., 2008) and Maihöfner et al. (2011) (Maihöfner et al., 2011) for a similar concern). Further, best practices for accounting for differences in the time course of the autonomic signal, relative to the BOLD signal, have yet to be determined (though see Iacovella & Hasson, 2011 (Iacovella and Hasson, 2011) for a thoughtful discussion on decisions regarding removing ANS correlates from fMRI data). Further, though the vast majority of studies that have examined brain correlates of autonomic measures have directly correlated the autonomic time series with voxel time series (Beissner et al., 2013), it is likely that the temporal correspondence between autonomic measures and BOLD activity is heterogenous throughout the brain (Chang and Glover, 2009; Chang et al., 2008; Chen et al., 2019). In longer block designs, timing may not matter as much, since signals are sustained over time allowing researchers to decouple autonomic activity regardless of slight shifts in timing. For example, one study suggested that autonomic signals can be shifted up to 30 seconds relative to the BOLD signal with minimal impact on observed BOLD-autonomic correlations (Eisenbarth et al., 2016). However, in event-related designs where precise timing is more important, conclusions may be affected if the temporal correspondence between the BOLD and autonomic time series is incorrectly specified. Thus, this approach might be best suited for tonic pain stimuli, or for stimuli that last several seconds rather than brief transient stimuli such as shocks, although researchers can explore approaches such as shifting the ANS regressors in time to capture potential delays when longer stimuli are not

possible. With these design caveats in mind, concerns regarding the direction and timing of brain-body interactions are unlikely to limit the promise of our approach for identifying pain specificity, as whether brain activity is afferent versus efferent should not affect how specific it is to pain.

Future Application of this Approach—As pain is a complex phenomenon, it is interesting and also complicated to postulate which components of pain would be left after regressing out the non-specific effects. The ability to shift our attention to painful stimuli and process pain-related information (i.e., the source of the pain, where the body is affected, how likely the stimulus is to damage tissue) is crucial for survival of an organism. Acute pain strongly motivates prediction, decision, and actions (e.g., one takes one's hand away from boiling water to prevent future tissue damage; (Van Damme et al., 2010)) and some have argued that pain has a higher priority to be processed than other non-painful but salient and arousing sensations (Wiech and Tracey, 2013). Thus, pain may be distinguished from other percepts based on its function to motivate defensive behaviors and enable survival. Work on the neural circuitry of survival and threat processing may indicate potential circuitry that could persist accounting for the non-specific effects of pain (for a review on threat and neural survival circuits, please see LeDoux and Daw (2018) (LeDoux and Daw, 2018)). In addition, subjective pain experience related signals in the OFC, ventro-medial PFC, ACC, and insula (Atlas et al., 2014) and distinguishable patterns of sensory modality in the primary sensory cortices (e.g., pain versus touch, pain versus auditory stimuli) (Liang et al., 2013) could survive as a pain-specific brain response even after regressing out non-specific components. It is important here to note that the presence of pain-specific brain responses does not necessarily suggest that overall processing of pain is *entirely* different from the processing of other sensations in the brain, but rather that some components may be pain-specific, even if they co-exist with other brain processes that are related to pain but also shared with other sensations. For example, though expectations can modulate pain through domain-specific modulatory mechanisms (for instance, within the insular cortex (Fazeli and Büchel, 2018; Sharvit et al., 2015)), expectancy effects on pain are also related to activity in the ventrolateral prefrontal cortex (vlPFC) in a domain-general fashion (Petrovic et al., 2010). Indeed, most modulatory mechanisms are likely to involve both domain-general and domain-specific processes (Atlas and Wager, 2013).

Of course, it is also possible that statistically controlling for non-specific effects of pain does not leave any brain response that is specific to pain. Indeed, in our preliminary application of this approach, two regions that have been implicated as pain-related, the insula and SII, no longer exhibited correlations with pain when we accounted for both physiological arousal and nociception (Figure 4). Does this suggest that pain is not a unique percept? On the contrary, it is possible that pain may be distinct from other sensations not in the brain *processes* involved but in the *relative contribution* of each of those constituent processes. Throughout this review, we have argued that it is important to account for brain processes that pain may share with other sensations, namely salience processing and arousal. But we remark here that if accounting for these non-specific processes leaves no 'pain-specific' pattern of brain activation, that does not necessarily imply that the brain response to pain *cannot* be distinguished from the brain's responses to other stimuli. Rather, the *relative*

contribution of each of these constituent non-specific processes - that is how salience and arousal processing work in tandem during pain perception, as well as how they work with nociception and other processes non-specific to pain that were not discussed here (e.g., motivation to survive, fear or threat processing) – may be what distinguishes the brain's response to the pain from its response to other percepts. In other words, the relative balance and interacting contributions between arousal, salience, nociception, and other non-specific factors in explaining the brain's response to pain may be unique from the relative weights or contributions in any other percept. For example, pain may differ from other salient and threatening stimuli in terms of the relative contribution of the amygdalar evaluation of threat, hippocampal processing of contextual information, prefrontal switching of amgydalar threat signals into behavioral response, and motor cortex preparation and execution of behavior, all processes involved in survival and threat processing (LeDoux and Daw, 2018). Empirical questions remain open, and application of our approach is a promising direction for answering these questions and identifying what remains of the brain response to pain after accounting for non-specific processes.

We have focused presently primarily on experimental research using neuroimaging to measure the brain response to acute pain. To advance the scientific endeavor of identifying pain specificity in the brain, it will be necessary to accumulate converging evidence from various approaches, spanning not only neuroimaging data but also direct brain stimulation/inhibition and lesion studies in animals. Our approach has the potential to fill a much-needed role in the pursuit of techniques that can help inform clinical assessment and treatment of pain. In patients with chronic pain, complementing brain data with ANS measures has already enhanced differentiation of clinical pain states. One recent study combined brain data (cerebral blood flow and functional connectivity) with pulse rate variability in patients with chronic low back pain to distinguish between high and low clinical pain states with over 90% accuracy (Lee et al., 2018). This study demonstrates that meaningful variance in chronic pain states can be explained by ANS arousal. To the extent that we can account for brain activity associated with those physiological responses, we can rule out non-specific variance in the brain's response to pain and begin to identify more pain-specific responses.

If we successfully identify pain-specific brain patterns that cannot be explained by salience and arousal, this work could have great potential for use in clinics as a diagnostic and prognostic biomarker for pain. Despite decades of efforts of clinicians and researchers, we still rely on subjective reporting to characterize pain, which has a risk of being biased by self-presentation concerns and has limitations in the clinic, especially when trying to understand the pain of infants and patients with cognitive impairments or without an ability to make conscious reports (i.e., patients in a coma). The need to evaluate pain in these patient populations has hastened the search for biomarkers of pain. Yet it has also increased the potential for ethical dilemmas (Davis, 2016; Robinson et al., 2013), as these patients can neither confirm nor deny if the pain biomarker maps onto their subjective pain. Thus, it is critical that scientists use caution when searching for neuroimaging pain biomarkers, using the approach recommended here or others. Salience circuits have been implicated in chronic pain (Borsook et al., 2013), but our goal in the present review was to suggest an approach that can determine whether there are circuits that are specific to acute pain, above and beyond the effects of salience. Further testing will be necessary to validate whether our

recommended approach generalizes to identification of pain-specific brain processes in patients populations, especially because there may be potential differences in arousal-related autonomic processing in patient populations, particularly comatose patients. For an in-depth discussion on ethical issues of neuroimaging pain biomarker, please see Davis (2016) (Davis, 2016).

Conclusion

In this review, we suggest that pain is a complex phenomenon composed of non-specific factors and a potentially pain-specific response that distinguishes pain from other sensations. Though current work identifying a truly pain-specific brain response remains elusive, we have argued that parsing out non-specific responses to pain by studying brain-body interactions can improve the specificity of analyses and may uncover pain-specific neural patterns and brain responses in the future. To achieve this goal, it is necessary to measure brain processes associated with nociception as well as stimulus salience and arousal. We recommend multimodal data acquisition through the brain (CNS) and body (ANS) and that this approach be applied to multivariate data analysis that has achieved recent success in beginning to identify pain-specific neural signatures. The brain responses that are uniquely specific to pain, and not to stimulus intensity, salience, or arousal, will guide us to better measurements and improve our ability to characterize pain in research and in the clinic.

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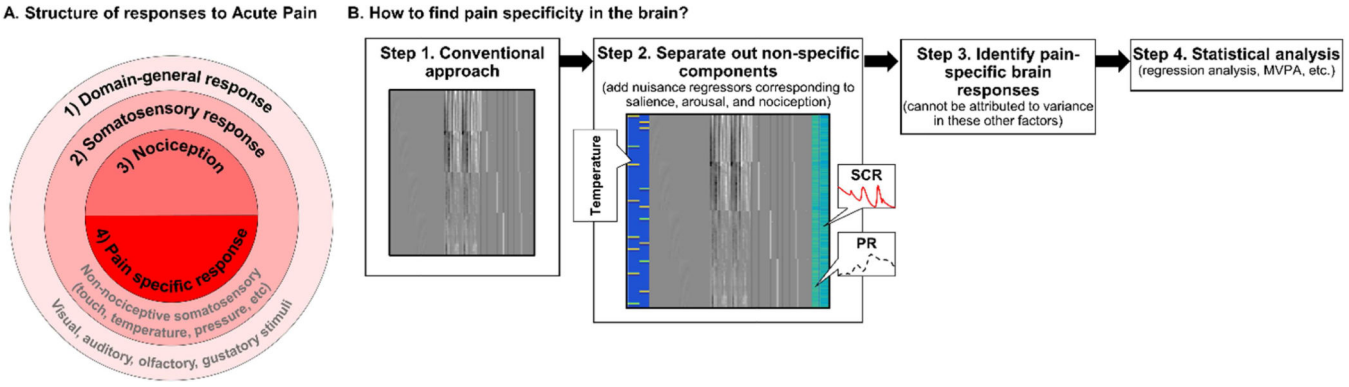
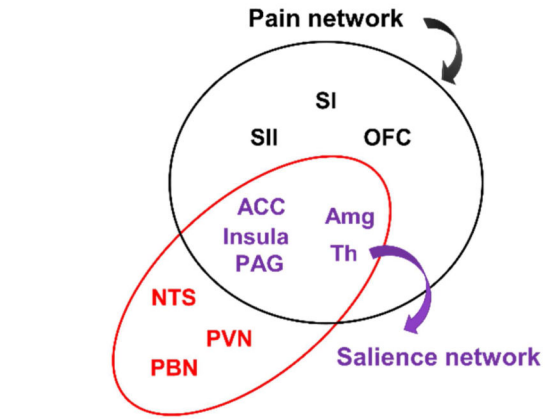


Figure 1. Hierarchy of specific and non-specific components of the brain response to acute pain and approach for identifying pain-specific responses

A. Brain responses to pain are composed of four hierarchical components of processing, illustrated in concentric rings from most general (outer pink circle) to most specific (inner red semi-circle): 1) domain-general responses to any sensations regardless of the sensory modality of the stimulus (e.g. arousal, attention, salience, valence), 2) processing of somatosensory information regardless of nociception (e.g. intensity, location, and modality), 3) processing of nociceptive information, regardless of pain perception; and 4) pain-specific responses (i.e. those that track the subjective pain experience).

B. Here we illustrate a potential fMRI analysis pipeline that leverages autonomic nervous system (ANS) isolate pain-specific BOLD responses. Step 1 depicts a conventional fMRI analysis that models only standard nuisance regressors (e.g., motion, global signal, spikes, intercepts). If correlations between BOLD responses and subjective pain are evaluated, results are unlikely to be specific to pain. Step 2 depicts a design matrix that incorporates additional regressors (in color) corresponding to temperature effects (left, blue) and the timeseries of recorded autonomic measures (right, green), such as skin conductance (SCR) or pupillary response (PR), alongside nuisance regressors. This design matrix thereby accounts for differences in arousal (non-specific response) and nociception. Residual associations between brain activity and subjective pain can therefore be evaluated (Steps 3 and 4), which are more likely to be specific to pain.

A. Pain, salience, and autonomic networks in CNS



B. Multimodal measurements of ANS

Measure	End Organ	Innervation	Effect of Acute Pain
Skin Conductance Response (SCR)	Dermis	Sympathetic	Increase [48-54]
Heart Rate (HR; derived from ECG or PPG)	Heart	Sympathetic and Parasympathetic	Increase [49, 50, 53, 58, 56, 60]
Heart Rate Variability (HRV; derived from ECG or PPG)	Heart	Parasympathetic*	Decrease [55-57, 110]
Pupil Dilation (PR)	Eye	Sympathetic and Parasympathetic	Increase [48, 52, 65, 66]
Blood Pressure (BP)	Vasculature	Primarily sympathetic+	Increase [58, 61-64]

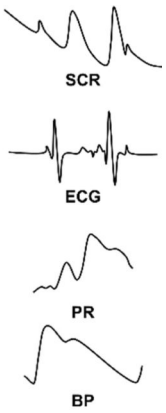


Figure 2. Measurements of brain and bodily responses to pain

A. Anatomical overlap between pain (black and purple regions), salience (purple regions), and autonomic networks (red and purple regions) in central nervous system. Amg: amygdala; ACC: anterior cingulate cortex; NTS: nucleus tractus solitarius of the medulla; OFC: orbitofrontal cortex; PAG: periacqueductal gray; PBN: parabrachial nuclei; PVN: paraventricular nucleus of the hypothalamus; SI: primary somatosensory cortex; SII: secondary somatosensory cortex; Th: thalamus.

B. Various ANS measurements (e.g., skin conductance response, heart rate, heart rate variability, pupil dilation, blood pressure) across different end-organs are related to pain. Because these end-organs are innervated by different branches of the autonomic nervous system and influenced by different mechanisms in the periphery, they provide non-overlapping information about arousal, and are best used in combination. *Many measures of HRV are parasympathetically mediated, but some measures are jointly influenced by both the sympathetic and parasympathetic nervous system. +Blood pressure in the vasculature is primarily controlled by the sympathetic nervous system, but parasympathetic control of the heart also influences blood pressure.

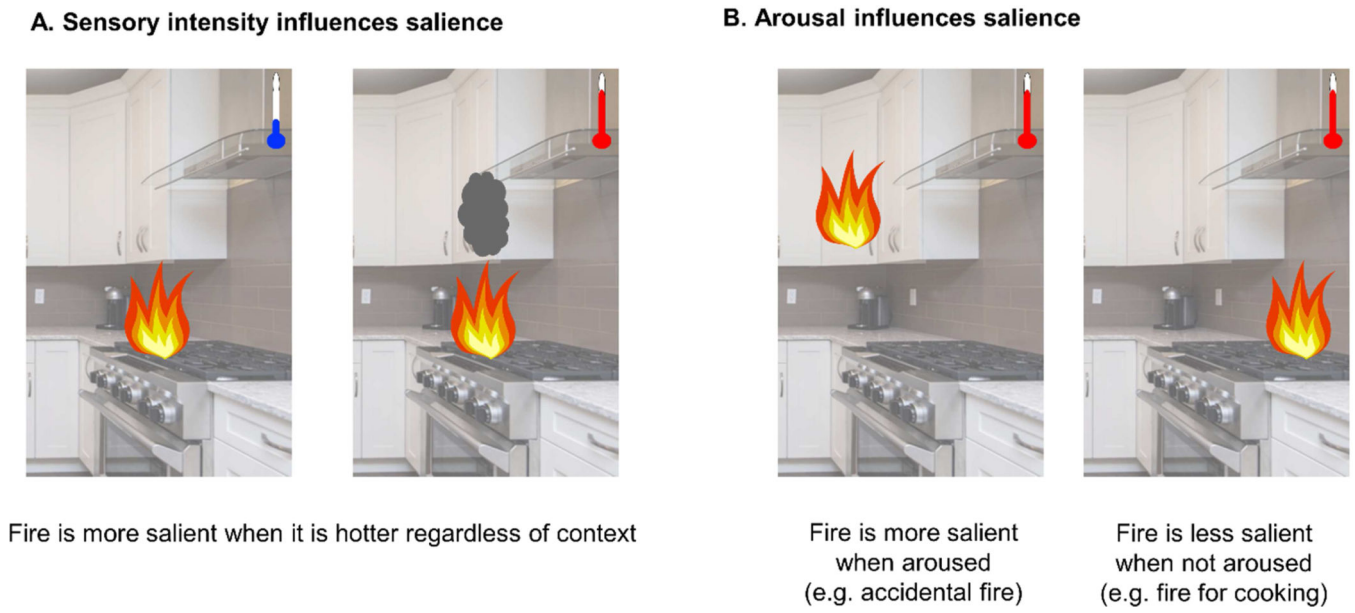


Figure 3. How sensory intensity and arousal influence perception in the environment

Salience, or the perception that a stimulus is distinct from its surroundings, is influenced by a number of factors including (A) objective properties of the stimulus (e.g., its intensity) and (B) properties of the perceiver that influence the perceiver's perception of the stimulus (e.g., whether the perceiver is aroused). The temperature of a fire is an objective feature of the stimulus (e.g., its intensity) that will affect how salient it is. If a perceiver is more aroused (e.g., because they reached toward a cabinet and learned it was on fire), the fire would be perceived as more salient than if a perceiver were less aroused (e.g., because they intentionally start a fire on their gas stovetop to prepare a meal).

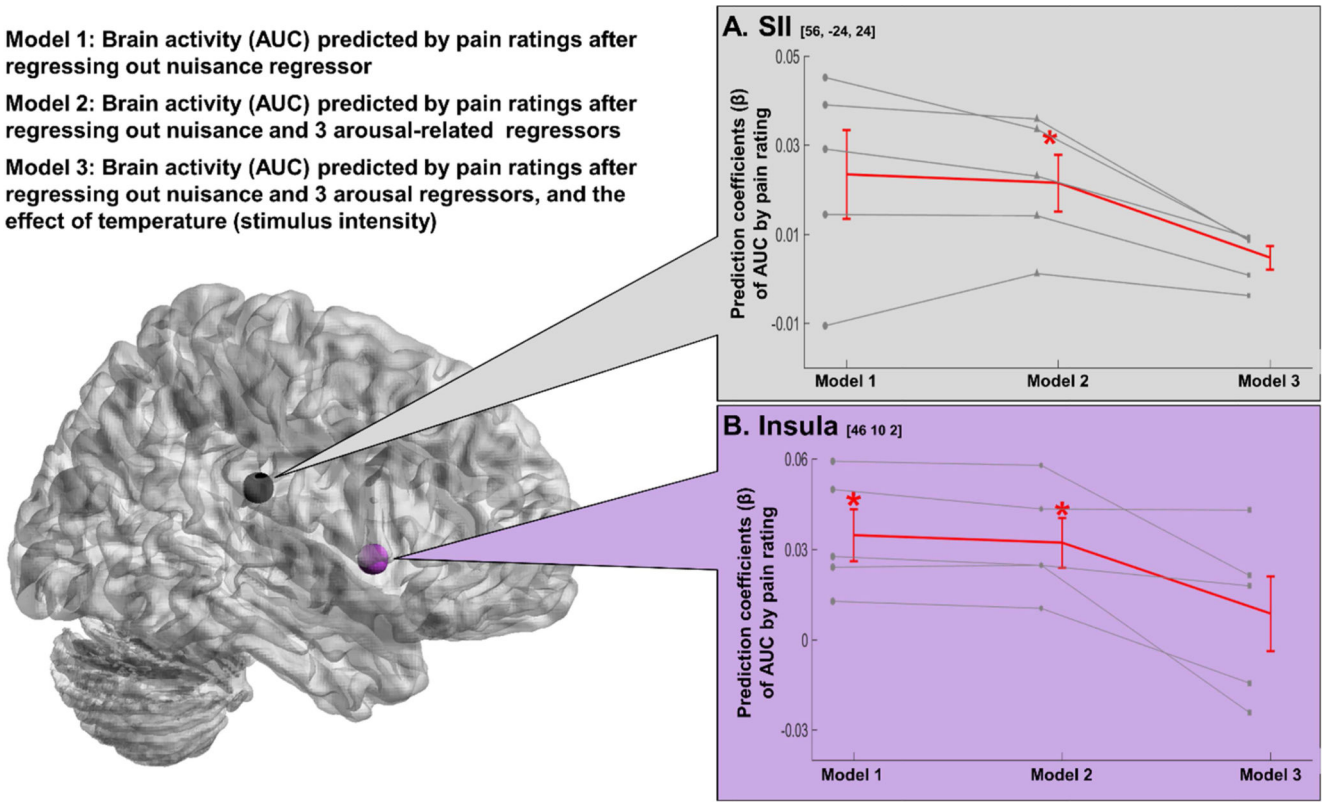


Figure 4. Preliminary result of our approach to using autonomic activity to isolate non-specific salience and arousal in the brain response to pain.

Here we illustrate our approach by applying it to a subset of fMRI data (n = 5) acquired during an acute thermal pain task (Atlas et al., 2014). To test the effect of regressing out physiological arousal using autonomic nervous system (ANS) activity, we evaluated three regression models that measured subjective pain as a function of brain activity. We extracted data from right secondary somatosensory cortex (SII) and right middle insula, two ROIs previously associated with subjective pain (Atlas et al., 2014), and used single trial analysis (Atlas et al., 2014; Mumford et al., 2014; Rissman et al., 2010) to generate heat-evoked area under the curve (AUC) estimates for each trial based on three models. Model 1 included only traditional nuisance regressors (motion, spikes, and intercepts). Model 2 included nuisance regressors and regressors for physiological responses (skin conductance response, respiration, and heart rate). Model 3 included nuisance regressors, regressors for physiological responses, and the effect of stimulus intensities (4 levels; warm, low, medium, and high pain) to account for nociceptive processing. We used linear regression to evaluate the link between subjective pain and AUC estimates generated by each model and tested effects across participants.