Common and distinct neural representations of aversive somatic and visceral stimulation in healthy individuals

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Abstract

Pain is a primary driver of motivated behavior and learning. Different varieties of pain may be encoded in different brain circuits, but the neural similarities and differences across different types of pain are not well understood. Here, we examine the similarites and differences in brain processing of visceral and somatic pain, one of the most fundamental distinctions in the pain field. We analyze data from 7 fMRI studies (N = 165) and 5 types of pain and discomfort—esophageal, gastric, and rectal distension, cutaneous thermal stimulation, and vulvar pressure—to establish and validate generalizable pain representations. We first evaluate an established multivariate brain measure, the Neurologic Pain Signature (NPS), as a potential common nociceptive pain system across all pain types. Then, we develop a multivariate classifier for visceral vs. somatic pain. The NPS (1) responded robustly in 98% of participants across all types, (2) correlated with perceived intensity of visceral pain/discomfort, and (3) showed specificity to pain when compared with non-painful cognitive and affective conditions drawn from 12 additional studies (total N = 180, AUROC 0.93). Pre-defined signatures for other types of negative affect did not respond to visceral pain. The novel visceral vs. somatic classifier reliably distinguished somatic (thermal) from visceral (rectal) stimulation in both cross-validation and independent cohorts (AUROC 0.84). Other types reflected mixtures of somatic and visceral patterns. These results validate the NPS as measuring a common core nociceptive pain system across pain types, and lay a foundation for new brain-based biomarkers for particular types of pain.

Introduction

Pain is a primary force motivating human behavior, learning, and neuroplasticity. It is defined primarily as an aversive experience [1] that arises from its signal value as an indicator of current or future bodily harm [2]. But a century of research on conditioning and reinforcement learning demonstrates that pain is more than a momentary experience. The danger signals underlying pain drive neuroplastic changes in the central nervous system that mediate escape, avoidance, and other defensive behaviors [3, 4]. However, despite important progress, our mechanistic understanding of pain and its brain bases remain incomplete [5].

One crucial gap relates to the brain representations underlying different types of pain. Neurological and functional differences may track differences in etiology, qualities, or the types of tissues affected, which have different implications for the organization of motivated behavior. However, most mechanistic pain studies in humans, including functional neuroimaging studies, have been limited to cutaneous somatic stimulation, mainly on the hand or foot, as a way of evoking pain [6]. Visceral pain—pain arising from soft tissues and internal organs—is particularly understudied, despite it being one of the most common disease-related forms of pain (e.g., in irritable bowel syndrome (IBS)) and one of the primary causes for seeking medical attention [7].

Several important differences between somatic (cutaneous or musculoskeletal) and visceral pain have e fundamentally different types of pain. *First*, visceral pain

has different *sensory* characteristics: it is less clearly localized, less well correlated with objective stimulation intensity, and very often referred to other body parts [8]. *Second*, visceral pain is thought to have a stronger *affective* dimension (reflected in higher unpleasantness relative to intensity ratings), though evidence supporting this hypothesis is limited [9, 10]. Differences in afferent input[8] and/or central brain representations may account for these differences in sensory and affective perceptual features. One common assumption is that somatic and visceral pain are processed in different systems – the "lateral pain system" (lateral thalamus, somatosensory cortex, posterior insula) and "medial pain system" (medial thalamus, anterior cingulate/medial prefrontal cortex), respectively. However, definitive evidence for this distinction has been elusive. Despite the relevance of this knowledge gap, only a few studies in small samples of healthy controls have compared visceral and somatic pain directly using functional brain imaging. These studies have yielded mixed findings, including similarities as well as differential responses in somatosensory, cingulate, insular, and prefrontal cortices [10, 11, 12, 13, 14] and in subcortical regions including hippocampus and dorsal pons [10].

Recently, building on advances in multivariate brain models to predict pain and other perceptual outcomes [15, 16, 17, 18], Wager et al. used functional magnetic resonance imaging (fMRI) to identify a spatially distributed pattern of brain responses that predicts the perceived intensity of experimentally induced thermal somatic pain in healthy individuals. This model is referred to as the "neurologic pain signature" (NPS) [19], to provide a label for testing in new samples and studies. The NPS includes positive predictive weights (i.e. increased response predicts increased pain) in the thalamus, anterior insula and frontal operculum, posterior insula and secondary somatosensory cortex, anterior midcingulate cortex (aMCC), and lateral parietal cortex. It also includes negative predictive weights (i.e. increased activity is associated with reduced pain) in ventromedial prefrontal cortex (vmPFC), lateral temporal cortex, occipital cortex, and medial parietal cortex including posterior cingulate cortex (PCC) and precuneus. The NPS has now been evaluated in over 40 published study cohorts (for reviews, see [20, 21]. Several studies of conceptually similar yet non-painful affective processes have indicated that the NPS is specific to somatic pain when compared with social rejection, negative emotion, and vicarious pain ("pain" felt when viewing images of others in pain). Each of these conditions has a distinct, reliable neural measure that can be used to predict affective intensity, and the predictive brain patterns for these types of affect are uncorrelated with the NPS [22, 23, 24]. Further, these studies showed limited evidence for generalizability of the NPS to other types of somatic pain (mechanical, electrical, and laser) [24, 25]. However, whether the NPS generalizes to capturing visceral pain has not been systematically tested. This is crucial to determine (a) whether the NPS captures common core responses across diverse types of evoked pain, particularly visceral and somatic pain, and (b) whether there are systematic differences between visceral and somatic pain that cannot be captured by the NPS. Jointly, these goals can inform us on whether pain is a multi-component or multidimensional process at the neural level, and what the essential neural 'ingredients' might be for different types of pain.

To address these knowledge gaps, we pursued two complementary aims. *First*, we aimed to investigate if ystem" responding to different types of somatic and visceral

aversive stimulation. To address this aim, we tested whether different types of putative visceral pain activate the NPS and/or signatures for other affective processes (negative emotion, social rejection, and vicarious pain). This approach allowed us to test the generalizability of the NPS to visceral stimulation, and to evaluate whether visceral pain activates more “emotional” brain patterns compared to somatic pain, as commonly assumed, respectively. *Second*, we aimed to investigate whether aversive somatic and visceral stimulation evoke reliably different patterns of activity across the brain. Specifically, we aimed to test the historical assumption that somatic and visceral pain are primarily represented in the “lateral” and “medial” pain systems, respectively, especially as a recently published study based on voxel-wise univariate comparisons suggests a more nuanced picture [10]. For this purpose, in addition to voxel-wise comparisons, we trained a classifier that differentiates these two types of stimulation in individual participants based on patterns of stimulus-evoked activity in pre-defined cortical networks. Robust, person-level classification with large effect sizes would demonstrate differences in the neural basis of visceral and somatic pain, thereby providing a basis for future brain-based biomarkers for visceral pain perception [26].

Results

AIM 1: Identifying a common core pain system responding to aversive somatic and visceral stimulation

Expression of the Neurologic Pain Signature during visceral and somatic stimulation (NPS generalizability)

We tested whether the NPS responded similarly to both aversive/painful visceral and somatic stimulation. To this end, we computed the expression of the NPS for contrasts of aversive stimulation versus non-painful stimulation or aversive stimulation versus baseline (depending on the study; see Materials and Methods for details). NPS expression in the four visceral pain/discomfort studies is shown in Fig. 1A.a, with the highest response in the esophageal pain study (Study 5). NPS response was 0.043 ± 0.009 [t(14) = 4.66, p = 0.0004, d_a = 1.20 [0.423 1.977], accuracy = 86.67%] for Study 1 (gastric pain); 0.045 ± 0.010 [t(14) = 4.69, p = 0.0003, d_a = 1.21 [0.432 1.988], accuracy = 93.33%] for Study 2 (rectal discomfort); 0.053 ± 0.007 [t(28) = 8.08, p < 0.0001, d_a = 1.50 [0.917 2.083], accuracy = 96.6%] for Study 3 (rectal discomfort), and 0.122 ± 0.006 t(29) = 20.49, p < 0.0001, d_a = 3.74 [2.901 4.579], accuracy = 100%] for Study 5 (esophageal pain). These effect sizes (d_a) are 1.5 to 5 times larger than typical “large effects” [27]. The accuracy statistics reported above indicate that the NPS can accurately detect which of the two conditions is noxious for an individual participant in a forced-choice test.

Robust regression analysis demonstrated that the NPS response significantly predicted pain/discomfort intensity VAS ratings, even though the stimulus intensity was individually calibrated ($r_{weighted}$ = 0.40, β_{robust} = 12.44 ± 04.45, p = 0.0064; Fig. 1A.b). Individual samples for visceral studies were correlated r = [illegible] two rectal studies, respectively. We note that sample sizes

varied from N = 15–29, and therefore individual-study correlations are likely to be highly unstable [28]. A full treatment of individual differences in pain responses remains for future larger-sample studies.

The NPS response in the 3 somatic pain studies is shown in Fig. 1B. NPS response was 0.093 ± 0.011 [$t(14) = 8.61$, $p < 0.0001$, $d_a = 2.22$ [1.310 3.130], accuracy = 100%] for Study 4 (vulvar pain); 0.132 ± 0.009 [$t(27) = 15.22$, $p < 0.0001$, $d_a = 2.88$ [2.132 3.628], accuracy = 100%] for Study 6 (thermal pain) and 0.089 ± 0.007 [$t(32) = 12.11$, $p < 0.0001$, $d_a = 2.11$ [1.508 2.712], accuracy = 100%] for Study 7 (thermal pain).

Overall, these results indicate that the NPS responded robustly to both somatic and visceral pain, and correlated with the subjective visceral pain experience. Comparing effect sizes, effects are larger in thermal, vulvar, and esophageal pain than rectal and gastric pain, suggesting that while the NPS generalizes, systems beyond the NPS may also be important for gastric and rectal pain.

Expression of other affective signatures during visceral and somatic stimulation (NPS sensitivity)

Because visceral pain is often thought to have a greater affective nature than somatic pain, we additionally tested whether brain responses to visceral and somatic stimulation were more similar to the NPS than other brain-based markers that track self-reported differences in social rejection [23], picture-induced negative emotion [22], and vicarious pain [24].

As illustrated in Fig. 2A, over all studies together, data acquired during pain correlated significantly and positively with the NPS (average within-person Pearson spatial correlation r = 0.074 ± .0030 (SE), $t(164) = 24.41$, $d_a = 1.92$ [1.662 2.177], $p < 0.0001$, $q_{FDR} < .05$). This association was significant for each individual study, across both somatic and visceral types (Fig. 2B). Turning to signatures for other affective processes in healthy individuals, data acquired during pain also correlated significantly and positively with the neural signatures for social rejection (r = 0.017 ± 0.0019, $t(164) = 8.77$, $d_a = .697$ [0.526 0.866], $p < 0.0001$, $q_{FDR} < .05$) and negative emotion (PINES) (r = 0.006 ± 0.0019, $t(164) = 3.45$, $d_a = .246$ [0.091 0.4004], $p = .0007$, $q_{FDR} < .05$), demonstrating some match to these other patterns, but with associations 4 and 12 times weaker, respectively, than associations with the NPS (for full details, see Table S1). In addition, the positive associations with these patterns were not consistent across pain types; associations with the rejection pattern were driven by one rectal and the thermal studies, and associations with the PINES were driven by esophageal and vulvar studies (Fig. 2B). A significant negative correlation was found with the signature for vicarious pain (r = -0.012 ± 0.0021, $t(164) = -5.78$, $d_a = -0.445$ [-0.604 -0.284], $p < 0.0001$, $q_{FDR} < .05$), indicating lack of a positive match to this pattern. The correlation with the NPS was significantly stronger than the correlations with the three other neural signatures [ANOVA $F(3,492) = 286.23$, $p < 0.0001$; $p < 0.0001$ for all three pairwise comparisons versus NPS after Bonferroni correction for multiple testing].

Expression of the Neurologic Pain Signature during pain, negative emotion, and cognitive control (NPS specificity)

Because the studies used to examine commonalities between somatic and visceral pain in the analyses reported above differ in terms of scanning hardware, pulse sequences, participant demographics, and experimental designs, we conducted a separate validation to evaluate whether the NPS can reliably discriminate individual brain responses to painful stimuli from non-painful control manipulations across a sample of independent studies (i.e. specificity of the NPS), with 6 studies manipulating pain (by thermal, mechanical, or rectal stimulation) and 12 control studies involving either manipulations of cognitive control or negative emotion (see [31] for details). This analysis revealed that the NPS could effectively discriminate brain responses to different kinds of pain from conceptually related experimental manipulations (AUROC = .93, sensitivity = 73%, specificity = 92%, accuracy = 86 ± 2.1%, d_a = 2.13 [1.804 2.449]).

Voxel-wise analysis of responses common to aversive somatic and visceral stimulation

To identify brain regions that exhibited similar changes in fMRI activation during somatic and visceral stimulation, we performed a voxel-based conjunction analysis of visceral and somatic stimulation modalities (each thresholded at $q < .05$ False Discovery Rate [FDR]-corrected [32]). For each of the visceral ($N = 89$) and somatic subsets ($N = 76$), we controlled for the effect of study using covariates for differences across studies (4 visceral studies and 3 somatic studies, total $N = 165$, see Materials and Methods for details).

The conjunction analysis revealed that regions *activated* by somatic (Fig. 4A, Table S2) and visceral stimulation (Fig. 4B, Table S4) overlapped in a distributed set of brain regions (Fig. 4C, Table S6) including midbrain, cerebellum, lentiform nucleus (putamen and pallidum), hypothalamus, thalamus (ventral lateral and ventral posterior lateral nucleus), parahippocampal gyrus/entorhinal cortex, insula (posterior, middle, and anterior parts), postcentral gyrus (including a medial cluster in primary somatosensory cortex (SI) and a ventral lateral cluster including parietal/Rolandic operculum/secondary somatosensory cortex (SII)), adjacent inferior parietal lobule, superior temporal gyrus, and inferior frontal gyrus (ventrolateral prefrontal cortex (vlPFC)), lateral precentral gyrus including primary motor cortex (MI) and premotor cortex, anterior and posterior midcingulate cortex (aMCC, pMCC) and adjacent medial frontal gyrus, and superior/middle frontal gyrus (dorsolateral prefrontal cortex (dlPFC)).

The conjunction analysis also revealed that regions *deactivated* by somatic (Fig. 4A, Table S3) and visceral stimulation (Fig. 4B, Table S5) overlapped in multiple brain regions (Fig. 4D, Table S7) including thalamus (pulvinar), hippocampus, parahippocampal gyrus/perirhinal cortex, temporal pole, rostral middle/inferior temporal gyrus, occipital cortex and adjacent caudal middle and superior temporal gyrus, perigenual and subgenual anterior cingulate cortex (pACC, sACC) and adjacent medial, middle and superior frontal gyrus (vmPFC and dorsomedial prefrontal cortex (dmPFC)), lateral middle and superior frontal gyrus (dlPFC), PCC and adjacent precuneus, superior parietal lobule, left dorsal precentral gyrus (MI, premotor cortex), and left dorsal postcentral gyrus (SI).

AIM 2: Identifying brain systems that differentiate visceral and somatic aversive stimulation

Development and validation of a network-based classifier that differentiates visceral and somatic stimulation

To further test if representations of the different types of somatic and visceral aversive stimulations differ at a broader spatial scale, we next assessed whether brain responses to different types of visceral and somatic stimulation were differentially correlated with 7 canonical resting-state cortical networks [33]. This approach provides inferences about whether each of these networks is activated on average during each pain type. Detailed results of this analysis (based on point-biserial correlations) are provided as Supplementary Material (Supplementary Results, Table S8). Broadly, they revealed some commonalities across all pain types, including activation of the 'ventral attention' network and deactivation of the 'default network' (Fig. 5A). (The network names are based on Yeo et al., and by using them, we do not imply that their function is limited to or primarily related to the label). They also revealed differences: the 'somatomotor' network was activated in some pain types (thermal, vulvar, and esophageal) but deactivated in others (rectal). The 'fronto-parietal' network was similarly activated by some (rectal, esophageal) but deactivated in others (thermal). Beyond these variations in which networks were activated and deactivated, there were also variations in the *degree* to which each network was activated or deactivated.

The variations noted above could serve as the basis for a brain-based classifier for somatic versus visceral pain capable of making accurate predictions about new individual participants. Many pain types (e.g., esophageal, gastric, vulvar) may potentially include both somatic and visceral elements and cannot be defined as purely somatic or visceral a priori. Therefore, we first trained a logistic regression-based pattern classifier to discriminate between the clearest examples of somatic and visceral aversive stimulation available: cutaneous thermal stimulation (Study 7) and rectal distension with an inflatable balloon (Study 2). The data used for classification were the spatial correlations of each individual participant's stimulus-induced activity map with each of the 7 resting-state networks. We tested classification accuracy on out-of-sample participants in Studies 2 and 7 using 10-fold cross-validation. Then, we tested the classifier's performance on data of all pain types in independent studies, including thermal (Study 6) and rectal (Study 3) studies, and gastric (Study 1), vulvar (Study 4), and esophageal (Study 5) studies.

The classifier exhibited high levels of discriminability for thermal versus rectal when applied to out-of-sample participants in cross-validation (AUROC = .92, sensitivity = 94%, specificity = 80%, balanced accuracy = 87 ± 4.4%, d_a = 2.22 [1.46 2.98]). As illustrated in Fig. 5B-C and Table S8, *somatic stimulation* was indicated by a combination of (a) more positive correlations with the somatomotor network (? = = 19.89 ± 5.94, p = 0.0008), driven by a positive correlation in thermal versus negative in rectal; (b) positive k (? = = 14.21 ± 5.72, p = 0.013) driven by zero correlation in

thermal versus a negative correlation in rectal; and (c) more positive correlations with the ventral attention network (? = = 12.54 ± 5.50, p = 0.023), driven by a more strongly positive correlation in thermal. On the other hand, *visceral stimulation* was indicated by (a) more positive correlations with the fronto-parietal network (? = = -12.35 ± 4.09, p = 0.0025), driven by a significant positive correlation in rectal versus a near-zero negative correlation in thermal; and (b) more positive correlations with the default network (? = = -11.89 ± 4.02, p = 0.0031), driven by a near-zero negative correlation in rectal versus a strong negative correlation in thermal. More positive correlations with the limbic network exhibited a nonsignificant trend towards predicting visceral stimulation (? = = -8.66, p = 0.063, driven by a zero correlation in rectal versus a non-significant negative correlation in thermal).

Testing the pattern classification model on the remaining studies, which include gastric (Study 1), rectal (Study 3), vulvar (Study 4), esophageal (Study 5), and thermal (Study 6) stimulation, revealed a continuum of somato-visceral expression. The classifier demonstrated successful prospective generalization to new studies when tested on the rectal (Study 3) and thermal (Study 6) test sets (AUROC = .84, sensitivity = 82%, specificity = 69%, balanced accuracy = 76 ± 5.7%, d_a = 1.34 [0.765 1.915]). The esophageal ($P_{somatic}$ = 96.67 ± 3.28%, p < .0001) and vulvar ($P_{somatic}$ = 86.67 ± 8.78%, p = 0.083) studies were largely classified as somatic (although the latter only exhibited a non-significant trend), whereas the gastric ($P_{somatic}$= 66.67 ± 12.17%, p = .97) study exhibited an intermediate classification rate (Fig. 5D).

Voxel-wise analysis of differential responses to aversive somatic and visceral stimulation

To identify brain regions that exhibited differential levels of fMRI activity for visceral and somatic stimulation, we conducted a standard voxel-wise general linear model (GLM) analysis comparing stimulation modalities while controlling for the effect of individual studies (4 visceral studies and 3 somatic studies, total *N* = 165, see Materials and Methods for details).

Of the regions that showed significant *activation* (i.e., increased activity to somatic or visceral stimulation compared to baseline), regions demonstrating significantly stronger activation during somatic compared to visceral stimulation included midbrain, cerebellum, basal ganglia (caudate, lentiform nucleus, claustrum), thalamus (midline/medial dorsal/anterior nuclei), insula (posterior, middle, and anterior), inferior parietal lobule, postcentral gyrus/SI, parietal operculum/SII, temporoparietal junction, aMCC/pMCC, (pre)motor cortex, and middle frontal gyrus (dlPFC) (Table S9, Fig. 3A-B & 3E.a). Regions more strongly activated by visceral stimulation included thalamus (pulvinar), lentiform nucleus, amygdala, (caudal) parahippocampal gyrus, fusiform gyrus, occipital cortex (lingual gyrus, cuneus), precuneus/PCC, middle temporal gyrus, inferior & superior parietal lobule, and precentral/middle frontal gyrus (details in Table S10, Fig. 4A-B & 4E.a).

Of the regions that showed significant deactivation (i.e., decreased activity to somatic or visceral stimulation compared to baseline), regions demonstrating significantly stronger deactivation during

 cluded rostral hippocampus/parahippocampal

gyrus/entorhinal cortex, fusiform gyrus, temporal pole, middle and inferior temporal gyrus, occipital cortex (inferior & middle occipital gyrus, lingual gyrus, cuneus), pACC, sACC, vmPFC, orbitofrontal cortex (OFC) and dmPFC, PCC, precuneus, superior and inferior parietal lobule, vlPFC, and right dlPFC (Table S11, Fig. 4A-B & 4E.b). A more limited number of regions showed significantly stronger deactivation during visceral compared to somatic stimulation, including caudal hippocampus/parahippocampal gyrus and adjacent fusiform gyrus, caudate, right precentral/medial frontal gyrus, and right superior parietal lobule (Table S12, Fig. 4A-B & 4E.b).

Discussion

Understanding the common and distinct brain representations underlying visceral and somatic pain is critical for assessing the neurophysiological mechanisms underlying different forms of pain. While previous studies have pointed to both commonalities and differences [10], this study is, to the best of our knowledge, the first to identify brain-wide commonalities that generalize across studies and types of painful stimulation, and the first to identify brain network-level changes that are robust enough to permit brain-based classification of visceral versus somatic pain in independent participants. These findings can be integrated in a two-stage classifier that can be applied to future studies *(*Fig. 6*).* In the first step, the NPS is applied to accurately discriminate pain from non-painful cognitive and affective processes. If a brain representation is identified as pain-related by the NPS, our newly developed somato-visceral pain classifier can be applied to accurately discriminate visceral from somatic pain. This demonstration and model involved several key findings, which we review below.

First, the NPS responded to all types of visceral stimulation and predicted individual visceral pain/discomfort ratings, confirming involvement of the NPS as a common ‘core pain-related network’ that generalizes across modalities. Our NPS results are corroborated by the results of our voxel-based GLM conjunction analysis in that the vast majority of key NPS regions were shown to be commonly responsive to somatic and visceral stimulation. Further, the NPS captured visceral and somatic pain/discomfort better than neural signatures for other (i.e. non-pain) affective processes (rejection, vicarious pain, and negative emotion), indicating that the neural basis of visceral discomfort/pain has more in common with somatic pain than with other affective processes. In addition to these results demonstrating the generalizability and sensitivity of the NPS, we also demonstrated its specificity to pain in that the NPS could accurately discriminate brain responses to different kinds of pain from non-painful affective and cognitive experimental manipulations. However, not all types of pain activated the NPS equally strongly; for example, thermal and esophageal pain produced stronger NPS responses than gastric and rectal visceral stimulation. While it was impossible here to equate the stimulus timing and subjective pain intensity across these pain types (see below), these findings suggest variation in brain responses across pain types, even within the visceral modality.

The notion of variation in brain representation across pain types, even within each modality, was supported by findings from network-level analyses. We observed qualitative differences in the pattern of ...atic pain. Increased engagement of the somatomotor network

for somatic (i.e. cutaneous thermal) pain versus the fronto-parietal network for visceral (i.e. rectal) aversive stimulation provided a double dissociation between the brain patterns elicited by each pain modality/type. Such findings generally preclude arguments that brain differences result from one pain type being less intense or less reliable than others, and instead point to genuine processing differences. In addition, these findings were robust enough to allow brain-based classification of whether, in a particular test condition, an individual experienced somatic or visceral pain with 94% sensitivity and 80% specificity (and 82% sensitivity, 69% specificity when applied to novel studies/cohorts). More positive correlations with somatomotor, dorsal attention, and ventral attention networks were predictive of the cutaneous stimulation, whereas higher correlations with fronto-parietal (more positive) and default (less negative) networks were predictive of the rectal stimulation.

This network-based classification model permitted a novel examination of pain types that, although heuristically classified as visceral or somatic, may contain elements of both. Esophageal stimulation—even though we stimulated the distal (i.e. smooth muscle, viscerally innervated) part of the esophagus—was classified as somatic (i.e. similar to cutaneous thermal pain). By contrast, painful vulvar stimulation is sometimes considered somatic, but both gastric and vulvar stimulation fell part-way between somatic and visceral (i.e. rectal) outcomes in their brain patterns. These types of pain may involve a mixture of different pain-related brain representations, with variation in the mixture across individuals.

Though they have not tested a priori multivariate measures like the NPS or brain-based classifiers, previous univariate voxel-based GLM analyses revealed both convergence with and divergence from our findings. Strigo *et al.* compared brain responses to visceral and cutaneous pain stimuli (esophageal balloon distension and heat on the midline chest, respectively, matched for perceived intensity) in 7 healthy subjects. They found similar regions activated by both modalities, with a stronger anterior insula response to cutaneous pain (which is in line with our findings), and a stronger motor cortex and MCC response to visceral pain (which is at variance with the stronger motor cortex and MCC response to somatic pain in our study). Dunckley *et al.* used visceral (rectal balloon distension) and cutaneous (heat on left foot/midline lower back) stimuli (matched for perceived unpleasantness) in 10 healthy volunteers. They found stronger deactivations in response to visceral pain in the pACC, vmPFC, and PCC, which is at variance with our findings. Further, they found stronger anterior insula activation per intensity rating unit in visceral compared to cutaneous pain [13], which is at variance with the abovementioned results of Strigo et al. as well as our results, although we did not calculate activation per intensity rating unit, which may account for this discrepancy. In another study (N = 10), Dunckley *et al.* compared brainstem responses to visceral (electrical stimulation of the rectum) and cutaneous (electrical stimulation of the lower abdomen) stimuli (matched for perceived intensity), and found increased activation in the midbrain (nucleus cuneiformis) in visceral versus somatic pain, which again differs from our present findings (higher midbrain response to somatic pain). More recently, Koenen *et al.* compared brain responses to intensity-matched painful rectal distension and cutaneous thermal stimulation in 22 healthy women[10]. During the ascending phase of the stimulus, visceral pain induced greater activation in SI, dorsal and ventral anterior insula, a/pMCC, and midbrain when compared with somatic pain, which differs from our

findings, as we found stronger responses to somatic pain in all these regions. Further, somatic pain induced stronger dlPFC activation, which is in line with our results. During the plateau phase of the stimulus, stronger responses to somatic pain were found in posterior insula (in line with our results), and hippocampus (at variance with our results). Further, they found common activation responses in inferior parietal lobule (as we found), but also in dlPFC and vlPFC (which were differentially (de)activated by both modalities in our study), and vmPFC (which was deactivated for both somatic and visceral pain in the present study).

This variability reinforces known issues with small studies and suggests that larger sample sizes – which are approximately an order of magnitude larger in our study (N = 165) than most previous studies (N = 7–22) – are needed to identify reproducible patterns. Differences across studies could be related to stimulation procedure (fixed intensity versus individually titrated, level of intensity, stimulation type), fMRI task design, and differences in sex distribution, among other factors. However, our study suggests that it is possible to identify a common generalizable brain basis for somatic and visceral pain/discomfort, as well as reproducible pain type-specific brain processes, in spite of inter-study variation. Therefore, we believe that the differences in stimulation type, duration, etc., between the studies included in the present paper in one sense represent a largely inevitable limitation (see below), but also constitute a strength from a generalizability perspective, as we demonstrate common activation patterns across variations in these parameters. This is especially important because generalizability is seldom assessed and is one of the core aims of this paper.

In addition, our results partially confirm the historical assumption that somatic and visceral aversive stimulation are represented in “lateral” and “medial” pain systems, respectively, but also offer a more nuanced view. We found stronger responses to somatic stimulation in some parts of the “lateral” system (SI/SII and posterior insula, somatomotor network), but we also found stronger responses to somatic stimulation in parts of the medial system (aMCC and anterior insula). Visceral stimulation was characterized by stronger responses in other medial regions not typically associated with nociception, including vmPFC and other ‘default mode’ and ‘limbic’ regions. ‘Default mode’ regions have recently been identified as contributing to aspects of evoked and clinical [23, 34, 35] pain, and the modulation of pain in animal models[36, 37] via fronto-striatal pathways[36]. Likewise, visceral stimulation was characterized by stronger responses in some lateral regions not typically associated with nociception (the ‘fronto-parietal’ network). These findings suggest that both an expansion and a refinement of the cortical circuits that contribute to different types of pain, and pain in different individuals, is needed—and that the field may be ready to move beyond the traditional medial/lateral pain system distinction.

Further, in our study, more positive activation of the somatomotor network was the strongest predictor in the classifier distinguishing cutaneous from rectal stimulation, and it likely contributed importantly to the fact that the esophageal pain test dataset was classified as somatic by the classifier. These results are in line with previous findings in that sensorimotor region activation in response to cutaneous (mostly thermal) pain has been consistently reported in meta-analyses of pain functional brain imaging studies [6, 39]. In a meta-analysis of rectal

distension studies, on the contrary, no such activation was found in healthy subjects [40]. Evidence regarding sensorimotor cortex activation in response to painful gastric distension are sparse but have been mixed, with some studies showing activation and others not [41]. Esophageal stimulation studies, on the contrary, have consistently reported responses in sensorimotor cortex [42, 43]. Further, the fact that stronger activation in the dorsal and ventral attention networks were predictive of cutaneous thermal stimulation versus rectal distension may be related to observations that these networks are involved in maintaining internally cued focus on and reorienting attention towards salient external stimuli, respectively [44]. Hence, stronger responses may be triggered by the exteroceptive somatic pain stimuli. Again, brain responses to esophageal pain (delivered by stimulating the distal, viscerally innervated part) showed an atypical pattern compared to other visceral stimulation types (with even activation in the ventral attention network compared to the somatic stimulation types), which may additionally explain the classification of the esophageal pain test data as somatic.

On the other hand, greater activation in the fronto-parietal network was the strongest network-level predictor in the classifier distinguishing rectal from cutaneous stimulation. This network includes anterior PFC, dlPFC, dmPFC, anterior insula, and inferior parietal lobule [45]. All the regions of this network have been shown to be responsive to aversive rectal distension in healthy volunteers in the abovementioned meta-analysis on task-based rectal distension studies [40], but also appear in meta-analyses on brain responses to somatic pain [6, 38]. This resting-state network, which is anatomically positioned to integrate information from the dorsal attention network (regulating externally oriented attention in a top-down fashion) and the default network (involved in internally oriented modes of cognition including memory retrieval and assessment of self-relevance) has been involved in executive functioning, including cognitive control, decision making and response selection [45]. Therefore, we may speculate that the interoceptive nature of visceral pain/discomfort versus the more exteroceptive nature of somatic pain, which require different cognitive and behavioral responses, may account for this finding. This interpretation may also account for the finding that less deactivation in the default network was predictive of rectal versus cutaneous stimulation. Further, as the fronto-parietal network has specifically been involved in discrimination of ambiguous, non-familiar stimuli [45], the vaguer perceptual characteristics of the visceral stimuli may also account for our findings.

This paper has several limitations that should be addressed. The stimulation procedures and fMRI task designs of the different visceral and somatic stimulation studies were similar, but not identical. More specifically, the duration of stimuli was different between modalities and types of stimulation, ranging from 1 second stimulations analyzed as events in Study 4 (esophageal pain) to 30 second stimulations analyzed as blocks in Study 1 (gastric pain). However, this is to a certain extent unavoidable as long mechanical esophageal stimulation is not feasible due to the induction of peristaltic effects, and shorter gastric distension stimuli are impossible due to the time needed to inflate large volume gastric balloons. Further, the intensity level at which stimulations were performed differs between studies, with individually titrated stimuli used in some studies and fixed intensity stimuli in others. Moreover, severe discomfort rate stimulation in the rectal studies, as pain threshold can

often not be reached during rectal distension in healthy subjects due to intolerable levels of urgency to defecate. These differences could account for some of the differences in brain responses found between different stimulation types in the present study, and this should ideally be addressed in future studies where the similarity of stimuli is maximized. Further, studies with different stimulation intensities for each type of visceral stimulation should be performed to develop a visceral NPS (ideally, one per visceral stimulation type, based on our current results) and compare them directly with the somatic NPS. Including manipulations and/or ratings of non-pain affective processes in the same paradigm to allow within-subject comparison of responses of the different affective signature to these different types of stimuli as well as their relationship with subjective ratings constitutes another interesting future direction to replicate, validate, and extend our present results. Finally, we do not analyze sex differences here, which would require a larger sample of male and female participants and a different set of analyses. Future work is required to properly evaluate sex differences in brain responses to visceral and somatic pain. However, these limitations are outweighed by a number of strengths, including the large total sample size and direct comparison of visceral and somatic stimulation modalities, as well as different stimulation types within each of these two modalities, with the latter increasing generalizability.

In conclusion, neural representations of visceral and somatic pain/discomfort showed an important degree of overlap, confirming involvement of a 'core pain-related network' common to different modalities of pain/discomfort and types of stimulation within these modalities. This network is well characterized by the NPS, as it was responsive to different visceral (as well as somatic) stimulation types, and as it accurately discriminates pain from non-painful cognitive and affective processes. However, visceral and somatic pain/discomfort also showed some distinct neural features, as our newly developed classifier accurately discriminated visceral from somatic pain. These findings can be summarized as a two-stage classification process *(*Fig. 6*)*, with the NPS serving as a first-stage "pain/no-pain" classifier, and images classified as pain sorted into somatic and visceral types based on the new, second brain pattern. Further, brain responses to visceral discomfort/pain did not correlate appreciably with the neural signatures of non-pain affective processes, which challenges the often assumed "stronger affective nature" of visceral pain at the neural level. Finally, important differences were found within the visceral modality, with responses to aversive esophageal distension being more similar to painful thermal cutaneous stimulation than to aversive rectal distension.

Methods

fMRI data from 7 studies were retrospectively aggregated to identify common and distinct brain representations for visceral and somatic pain. Standard preprocessing and mass-univariate general linear models were applied to fMRI data before they were combined for multi-study analyses. Details regarding participants, stimulation procedures, task design, MRI data acquisition, and first-level data analysis are described in the Supplementary Methods (for a summary see Table 1).

Table 1
Summary of studies

Study	Stimulation	*N* (Female)	Age (Mean ± SD)	Field Strength	Contrast	Voxel Size
1	Gastric	15 (10)	31.9 ± 8.8	3 T	$certain_{pain}$ – $safe_{nopain}$	2.50 × 2.50 × 2.50 mm^3
2	Rectal 1	15 (9)	29.5 ± 10.5	3 T	$certain_{pain}$ – $safe_{nopain}$	2.75 × 2.75 × 3 mm^3
3	Rectal 2	29 (15)	22.5 ± 2.8	3 T	$certain_{pain}$ – $safe_{nopain}$	2.5 × 2.5 × 2.5 mm^3
4	Vulvar	15 (15)	23.2 ± 1.6	3 T	$certain_{pain}$ – $safe_{nopain}$	2.50 × 2.50 × 2.50 mm^3
5	Esophageal	30 (14)	30.4 ± 8.7	3 T	stimulation – rest	3.75 × 3.75 × 3.3 mm^3
6	Thermal 1	28 (10)	25.2 ± 7.4	3 T	high heat – rest	3.4 × 3.4 × 3.4 mm^3
7	Thermal 2	33 (22)	27.9 ± 9.0	3 T	high heat – low heat	3.0 × 3.0 × 3.0 mm^3

As an additional validation, we applied the NPS to brain responses from 18 studies that manipulated processes that are conceptually related to pain (total $N = 270$, $N = 15$ per study, archival data from https://neurovault.org/collections/3324/, see [31] for details). These studies include manipulations intended to evoke brain activity related to pain, cognitive control, and negative emotion. Hence, we use brain responses to pain manipulations to test the sensitivity of the NPS, and responses to "control" studies of cognitive control and negative emotion to evaluate the specificity of the NPS. To perform these tests, we computed the cosine similarity between the NPS and brain maps for each subject. This cosine similarity measure served as the basis for single-interval classification (pain vs. no pain) with a cutoff selected to maximize overall accuracy.

Statistical Analysis. Second-level statistical models were conducted using CANlab neuroimaging analysis tools, which is an open source toolbox written for MATLAB (see https://canlab.github.io/).

Brain responses to visceral and somatic pain were analyzed by performing a second (group) level univariate GLM analysis, i.e. a multiple regression including the pain versus baseline/rest contrast for each of the 4 visceral and 3 somatic pain studies [$certain_{pain}$ – $safe_{nopain}$ for Study 1 (gastric pain), Study 2 and 3 (rectal discomfort), and Study 4 (vulvar pain); pain – rest for Study 5 (esophageal pain); pain – rest for Study 6 (cutaneous thermal pain); and pain – nonpainful warmth for Study 7 (cutaneous thermal

pain)]. Contrasts of interest for the regression included: somatic pain and visceral pain - implicit baseline, somatic pain - implicit baseline, visceral pain – implicit baseline, somatic – visceral stimulation, and visceral – somatic stimulation, thresholded at a voxel-level threshold of $q_{FDR} < 0.05$, controlling for study (via nuisance regressors).

To identify brain regions that exhibited overlapping activation and deactivation, a conjunction analysis using the minimum test statistic was performed[46]. In this approach, regions that showed either increased or decreased activation for both the somatic and visceral contrasts ($q_{FDR} < 0.05$) exhibited a significant effect. To identify brain regions that showed significant differences in activation, the somatic – visceral and the visceral – somatic contrasts were inclusively masked with the contrast of somatic and visceral > baseline. Differences in deactivation were identified using the same procedure, with an inclusive mask of somatic and visceral < baseline.

To quantify the NPS response in each of the studies, the signature response was estimated for each test subject by taking the dot product of vectorized activation images with the signature pattern, yielding a continuous scalar value, as previously described[19]. This value was scaled using the l2 norms of activation images and signature patterns, to reduce differences in scaling across studies. Effect sizes (d_a) are reported as a continuous measure of the NPS' ability to separate pain from no pain (i.e. the difference between the average NPS response in the pain and baseline conditions, divided by the pooled standard deviation). T-statistics were computed using a one-sample t-test of these differences. Confidence intervals (with 95% coverage) for effect size estimates were computed using the method proposed by Hedges and Olkin[47]. Classification accuracy was estimated as the proportion of individuals who had larger NPS response to stimulation compared to baseline conditions.

To test whether NPS responses in visceral pain studies 1–3 and 5 predicted pain ratings, we used robust regression analysis (to downweight the influence of potential outliers), controlling for study. For this purpose, we calculated the average of the online VAS ratings of pain intensity during the $certain_{pain}$ and $safe_{nopain}$ conditions over all trials, and subtracted the ratings obtained during the $safe_{nopain}$ condition from the ratings obtained during the $certain_{pain}$ condition in each subject ($\Delta certain_{pain}$-$safe_{nopain}$) for study 1–3. For the esophageal pain study (Study 5), we used the average of the pain ratings, and ratings during rest were assumed to be zero because online ratings were not collected during rest. Inference was made on the regression coefficients using a one-sample t-test, and a weighted correlation between NPS responses and VAS ratings was estimated using IRLS weights.

To compare the brain responses to the different pain modalities in the different studies with the NPS and other recently developed neural signatures for negative affect, social rejection, and vicarious pain as well as seven resting-state networks[33], we used whole-brain spatial correlations (based on Pearson correlation coefficients ranging from − 1 to 1, with their significance tested by a one-sample t-test on Fisher r-to-z transformed values). A repeated measures ANOVA was performed to confirm that these pain manipulations produced brain responses that were more similar to the NPS than to other brain

signatures. In the case of the resting-state networks, which are binary masks, we more prefer to these correlation coefficients as point-biserial correlations for clarity. FDR correction was used for inference, correcting across 4 comparisons when evaluating similarity to brain signatures and across 7 comparisons for the resting-state networks.

Finally, we trained a between-subject classifier to differentiate visceral discomfort (Study 2, rectal stimulation) from somatic pain (Study 7, cutaneous heat) by entering Fisher transformed point-biserial correlation coefficients with the 7 resting-state networks for each subject into a logistic regression analysis with somatic versus visceral stimulation as the binary dependent variable. To estimate the generalizability of the classifier, 10-fold cross validation was performed on the training data. To verify the stability of cross-validated models, we iterated the entire 10-fold procedure 1,000 times and examined the standard deviation of classification error and mean Pearson correlation of parameter estimates across all iterations. This model assessment revealed that the model was quite stable. Classification error had a standard deviation of only 1.06%, and model parameters exhibited a correlation of $r = 0.9998$. For out-of-sample tests, the average model coefficients from all cross-validation folds were applied to the remaining testing data (studies 1, 3, 4, 5, and 6). Binomial tests were used to compare the proportion of subjects being classified as either somatic or visceral in the test data (studies 1, 3, 4, 5, and 6), relative to the threshold determined from the training sample (62.49% somatic).

Declarations

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Figures

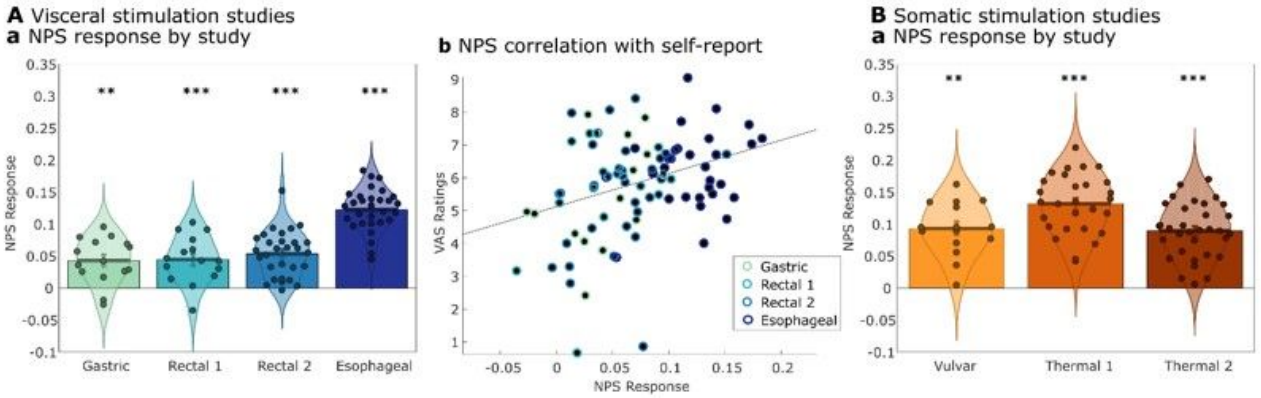


Figure 1

Response of the neurologic pain signature (NPS) to different types of aversive/painful stimulation.

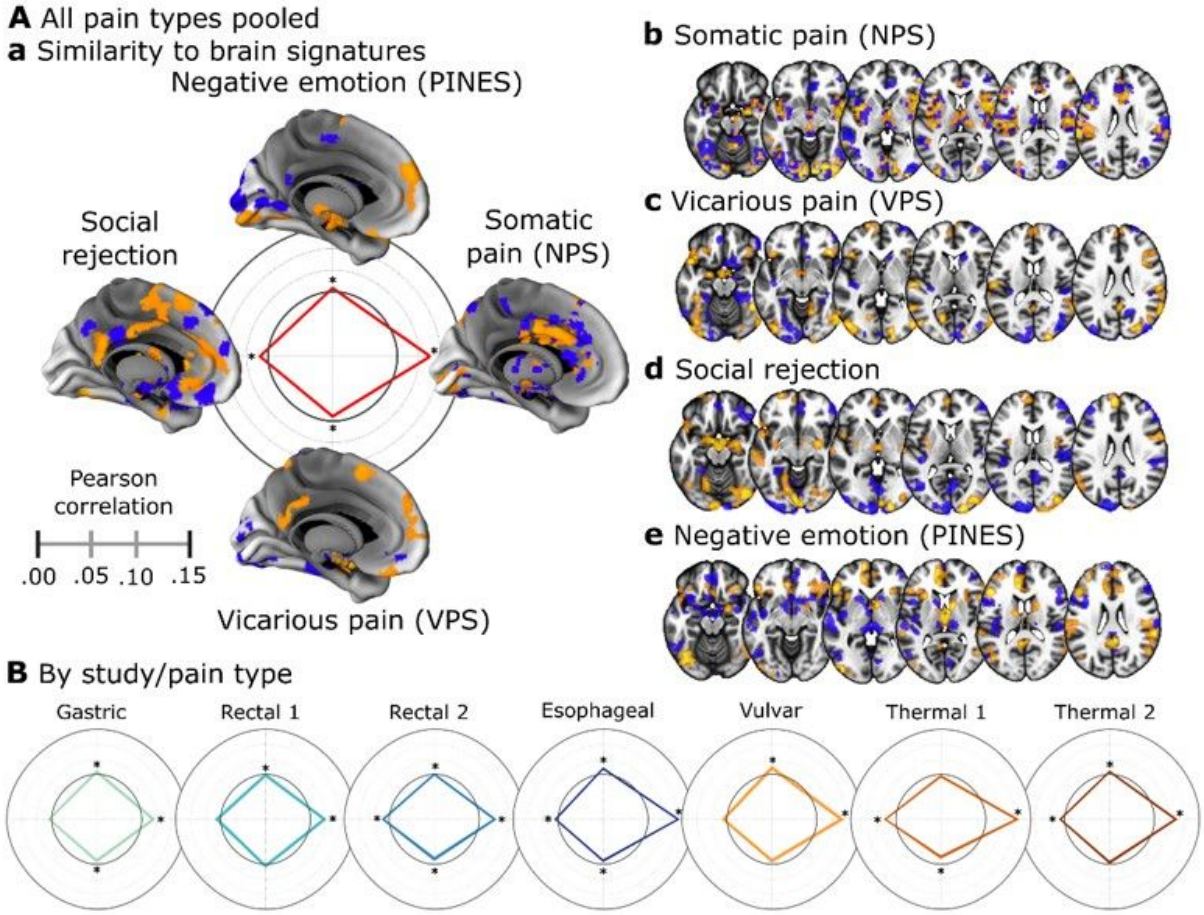
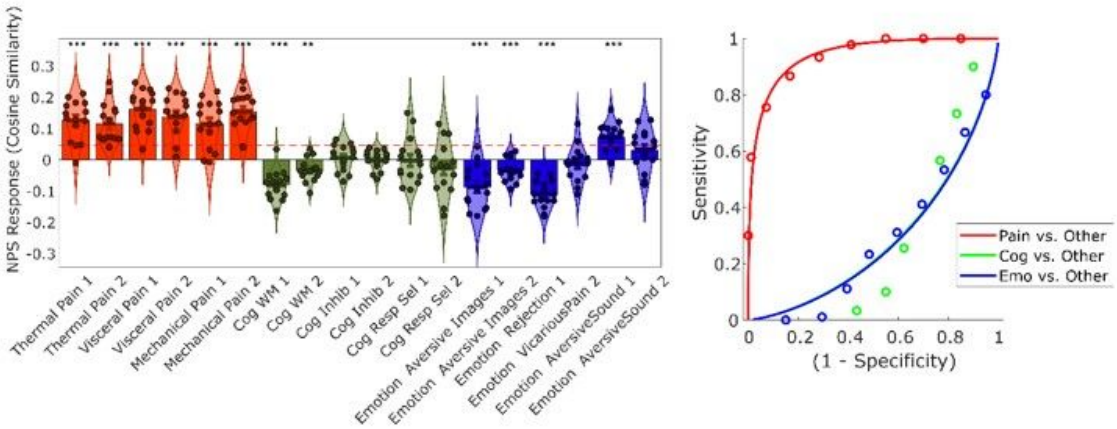


Figure 2

Spatial similarity between responses to different pain types and neurologic signatures.



Neurologic pain signature (NPS) expression discriminates brain responses to painful and non-painful experimental manipulations.

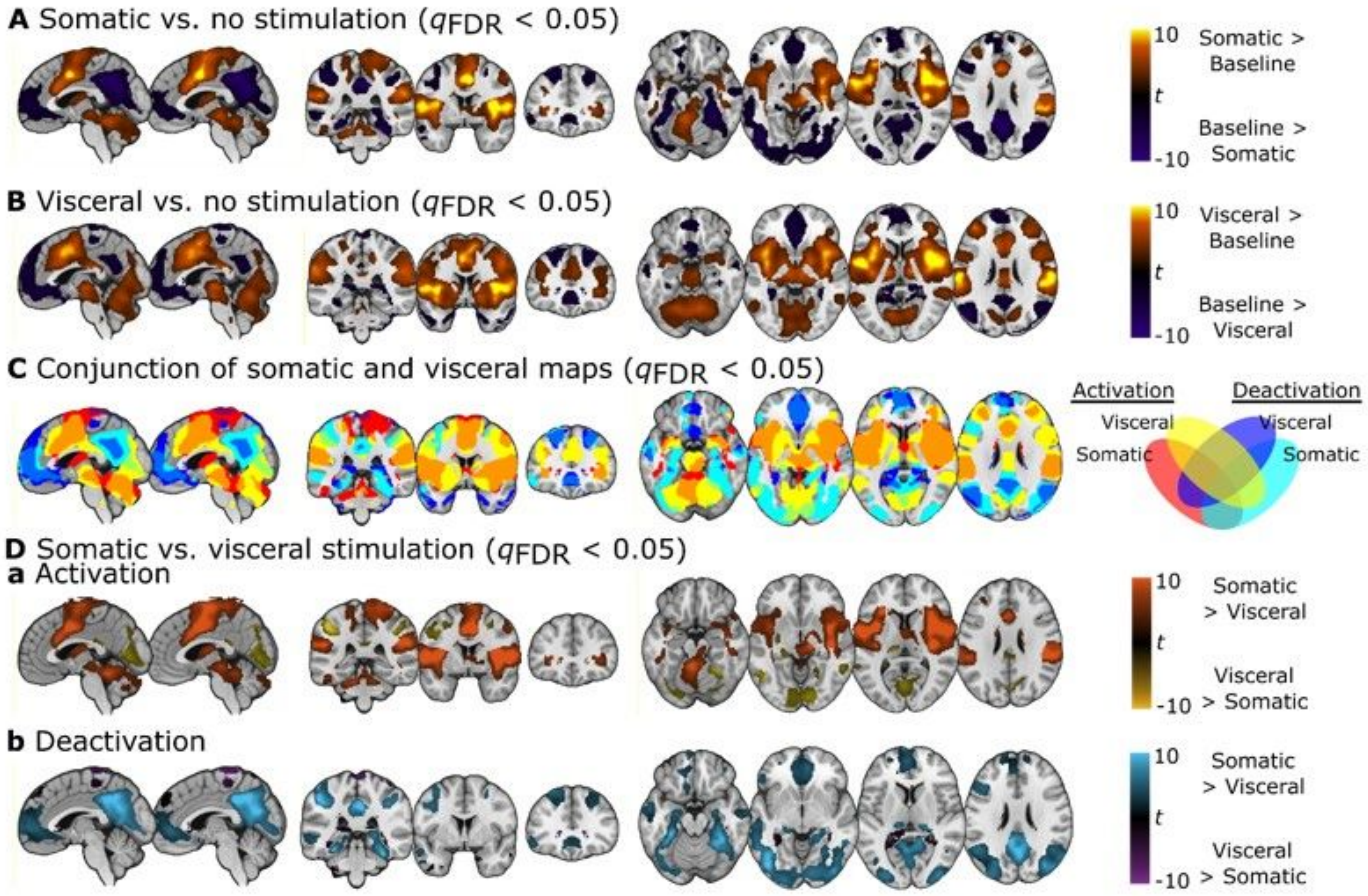


Figure 4

Common and distinct fMRI activation for somatic and visceral pain, assessed using univariate voxel-based GLMs.

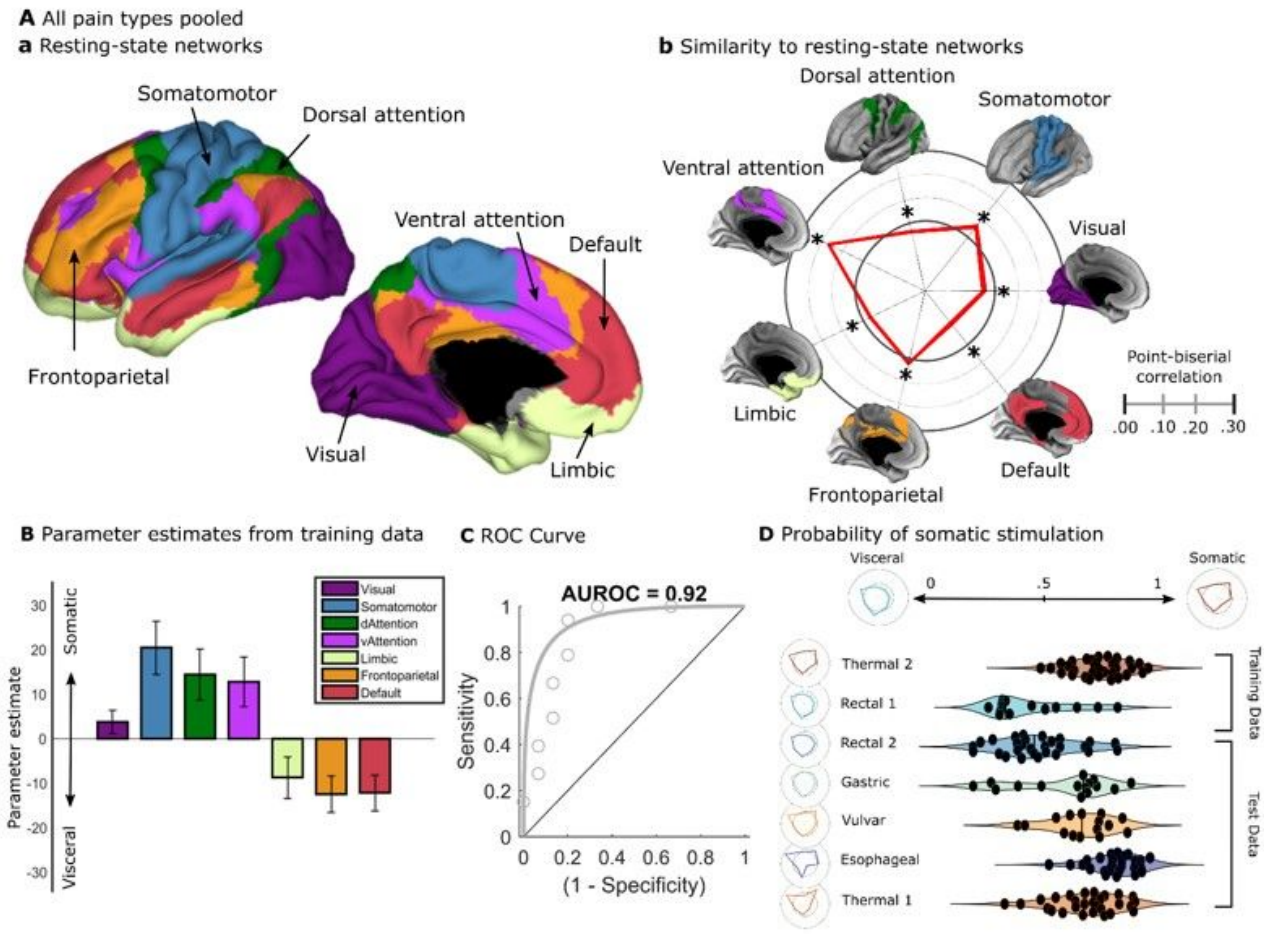


Figure 5

Classification of brain responses based on point-biserial correlations with resting-state networks.

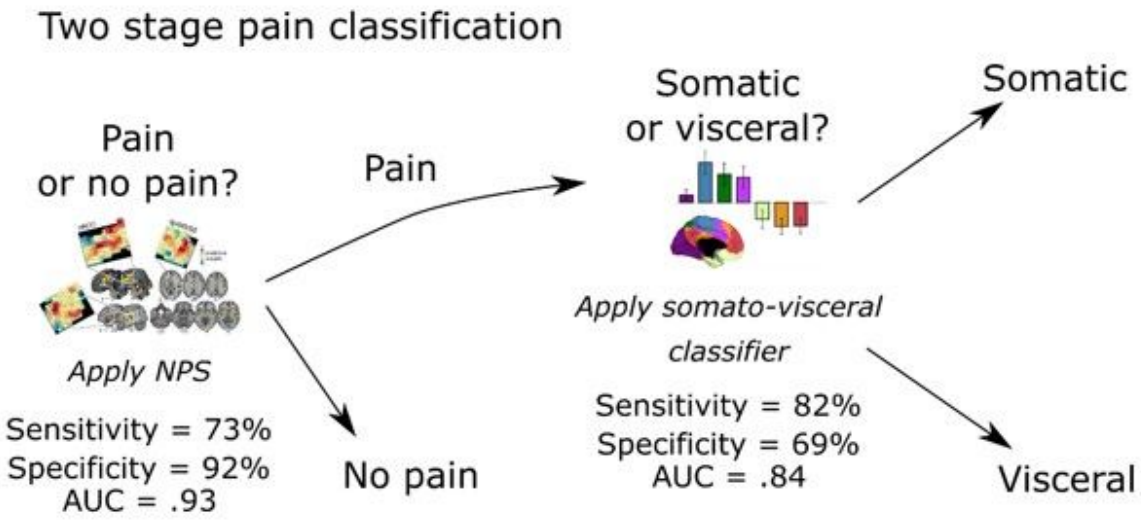


Figure 6

Overview of the proposed two-stage pain classification process based on the biomarkers validated and developed in this paper.

Supplementary Files

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- NPSVisceralPainNatCommSupplementaryMaterialsfinal.docx