Generalizable representations of pain, cognitive control, and negative emotion in medial frontal cortex

Philip A. Kragel1*, Michiko Kano2,3, Lukas Van Oudenhove4, Huynh Giao Ly4, Patrick Dupont5, Amandine Rubio6,7,8, Chantal Delon-Martin6,7, Bruno L. Bonaz6,7,8, Stephen B. Manuck9, Peter J. Gianaros9, Marta Ceko1, Elizabeth A. Reynolds Losin10, Choong-Wan Woo11,12, Thomas E. Nichols11,13 and Tor D. Wager1*

The medial frontal cortex, including anterior midcingulate cortex, has been linked to multiple psychological domains, including cognitive control, pain, and emotion. However, it is unclear whether this region encodes representations of these domains that are generalizable across studies and subdomains. Additionally, if there are generalizable representations, do they reflect a single underlying process shared across domains or multiple domain-specific processes? We decomposed multivariate patterns of functional MRI activity from 270 participants across 18 studies into study-specific, subdomain-specific, and domain-specific components and identified latent multivariate representations that generalized across subdomains but were specific to each domain. Pain representations were localized to anterior midcingulate cortex, negative emotion representations to ventromedial prefrontal cortex, and cognitive control representations to portions of the dorsal midcingulate. These findings provide evidence for medial frontal cortex representations that generalize across studies and subdomains but are specific to distinct psychological domains rather than reducible to a single underlying process.

A central aim of cognitive neuroscience is to identify how different mental processes are represented in brain activity. The medial frontal cortex (MFC), which includes multiple functionally distinct cortical areas in the superior frontal and cingulate gyri, is one brain region that has been linked to diverse psychological domains, i.e., sets of related psychological states with different adaptive functions. Clearly, different areas within MFC encode different functions, but there is a striking convergence of overlapping functions across domains in several ‘hub’ areas, particularly the anterior midcingulate cortex (aMCC). Research across species has linked activity in aMCC with multiple functions, including cognitive control, reward-based learning and decision making, somatic pain, and processing of emotional and social information. In fact, this area responds to such a variety of tasks, and so many underlying functions have been proposed to explain its responses, that it has been described as a “Rorschach test” and understanding it a “holy grail for many cognitive neuroscientists.”

Theories of aMCC function often explain the numerous signals in this area as components of an underlying process that operates across domains. Candidate processes have included conflict monitoring, adaptive control (i.e., control processes broadly engaged by negative affect and nociception), cognitive effort, valuation of actions and control, and detecting threats to survival, among others. These models have value because they offer integrative explanations for aMCC engagement across multiple domains. However, measuring brain activity across domains with functional MRI (fMRI) glosses over a potential multiplicity of different local neural circuits with distinct functions. Electrophysiological and optogenetic studies of likely homologs of human aMCC provide evidence for distinct subpopulations of neurons with different functional properties. Recent evidence suggests that multivariate patterns of fMRI activity can, in some cases, identify representations distributed across subpopulations of cells, including identifying functionally dissociable patterns within aMCC associated with different tasks.

Thus, unified accounts of aMCC function make predictions about the similarity of multivariate brain representations across domains that have not been adequately tested. If a set of domains activate representations of a single underlying process, then engaging these representations by tasks from these domain sets should produce similar patterns of brain activity in aMCC and other MFC areas. Conversely, if different domains engage an underlying pattern that is specific to each domain and not shared by other domains, this would provide evidence against a common underlying process.

Here we test these predictions using a construct-validation approach grounded in psychometric theory. We investigated three constructs that engage MFC: pain, cognitive control, and negative emotion (see Methods). We sampled human fMRI data from 18...
studies (15 subjects per study, total \( n = 270 \)) in a balanced, hierarchical structure, with three different experimental pain manipulations in each domain (for example, evoked cutaneous pain, visceral nociceptive pain, and acute mechanical stimulation pain) and two independent studies for each of these experimental manipulations (i.e., subdomain; Fig. 1a). Although it is commonplace in neuroimaging studies to equate a pattern of activity from a single study with a ‘representation’, measurement theory and first principles dictate that representations of latent constructs must be generalizable. For instance, a representation of ‘pain’ must generalize across different types of painful stimuli. Our approach allowed us to develop multivariate models that localize brain representations that correspond to a single domain, rather than being driven by the particulars of a subdomain or idiosyncrasies of an individual study (Fig. 1b). In this way, these models assess the generalizability of brain representations and test the validity of the theoretical constructs of pain, cognitive control, and negative emotion.

### Results

#### Anatomical delineation of psychological domains

Given evidence for regional specialization of cingulate function on the basis of cytoarchitecture\(^2\), we first applied representational similarity analysis\(^3\) within six anatomically defined cortical regions of interest: posterior midcingulate (pMCC), aMCC, perigenual anterior cingulate, subgenual anterior cingulate, ventromedial prefrontal (vmPFC), and dorsal MFC (dMFC; Fig. 2). By assessing how similar patterns of brain activity are across studies, subdomains, and domains in a single model, representational similarity analysis can provide evidence for generalizable brain representations.

This analysis revealed generalizable representations of pain-stimulated activity in aMCC, pMCC, and dMFC that were not shared by other domains. Parameter estimates for the pain domain—across heat, mechanical, and visceral pain subdomains and controlling for study-level and subdomain-level effects—were positive within aMCC (\( \hat{\beta} = 0.990 \pm 0.266 \) (s.e.m.), \( z = 3.72, P = 0.0002 \)), pMCC (\( \hat{\beta} = 0.470 \pm 0.186 \) (s.e.m.), \( z = 2.55, P = 0.0107 \)), and dMFC (\( \hat{\beta} = 0.294 \pm 0.116 \) (s.e.m.), \( z = 2.59, P = 0.0097 \)). See Supplementary Table 1 for more information. These results indicate that patterns of pain-evoked activity in these areas are qualitatively distinct from activity patterns elicited during manipulations of cognitive control or negative emotion, independent of subdomain and study. Accordingly, in terms of aMCC activity patterns, participants in pain studies across different subdomains were more similar to each other (\( r = 0.1289 \pm 0.0039 \) (s.e.m.)) than to those in studies of cognitive control (\( r = 0.0083 \pm 0.0026 \) (s.e.m.); 95% confidence interval (CI) of difference \([0.1089, 0.1325]\)) or negative emotion (\( r = 0.0111 \pm 0.0032 \) (s.e.m.), 95% CI of difference \([0.1051, 0.1297]\); Fig. 2). Because these correlations are computed across subdomains, they are unlikely to be driven by similarity in any particular subdomain or study. Qualitatively similar results held for patterns of activity in pMCC and dMFC, although they were smaller in magnitude (Supplementary Tables 1 and 2). These findings are concordant with...
theoretical models that implicate the aMCC in pain\textsuperscript{39,40} and with studies identifying nociceptive circuits in dorsal anterior cingulate cortex\textsuperscript{41}. Observations of aMCC activity during noxious stimulation have often been attributed to more general mechanisms, such as directing attention, response selection, or responding to salient events. However, we identified representations of evoked pain distinct from those related to cognitive and emotional domains, which are also attention-demanding, salient, and involve motor preparation, ruling out such general explanations as the primary drivers of aMCC responses during painful stimulation.

The regional analysis also revealed generalizable representations of negative emotion—across social emotion, emotional pictures, and emotional sounds—in vmPFC (\(\bar{\beta} = 0.514 \pm 0.140\) (s.e.m.), \(z = 3.65, P = 0.0003\)) and dMFC (\(\bar{\beta} = 0.404 \pm 0.133\) (s.e.m.), \(z = 3.03, P = 0.0024\); Supplementary Table 2). Within vmPFC, patterns of activation from different subdomains of negative emotion were more similar to each other (\(r = 0.0474 \pm 0.0027\) (s.e.m.)) than they were to evoked pain (\(r = 0.0117 \pm 0.0023\) (s.e.m.), 95% CI of difference = [0.0270, 0.0440]) or cognitive control (\(r = 0.0072 \pm 0.0020\) (s.e.m.), 95% CI of difference = [0.0316, 0.0484]) studies (Supplementary Table 4). These observations agree with those of recent neuroimaging studies identifying representations of cross-modal subjective value\textsuperscript{42} and perceived emotion\textsuperscript{15} in vmPFC. By revealing representations of negative emotion that generalize across stimulus modality and social contexts, these results further substantiate the notion that vmPFC integrates emotional value across diverse stimuli\textsuperscript{14,17}. Further, these data suggest that, although pain-
confirmatory analyses using different model parameterizations produced qualitatively similar results (Supplementary Fig. 3).

To quantify the weight of evidence favoring generalizable representations specific to each of the three domains, we additionally conducted model comparisons using the Bayesian information criterion in each region of interest (see Methods for details). Results of this analysis corroborate inferences drawn on individual parameter estimates (Table 1). aMCC representations were best explained by a model including the domain of pain (in addition to terms for study and subdomain), but not cognitive control or negative emotion. vmPFC representations, on the other hand, were best explained by modeling the domain of negative emotion but not pain or cognitive control. The best fitting models of dMFC and full MFC representations included all three domains, indicative of diverse coding in these regions. Additional model comparisons using the Brainnetome atlas, a parcellation based on functional and anatomical connectivity\(^6\), provide evidence for generalizable representations in other brain regions outside the MFC as well (Supplementary Table 6 and Supplementary Fig. 4).

Searchlight mapping of psychological domains. As there is well-established variability in the anatomy of the cingulate sulcus\(^7\), we additionally conducted searchlight mapping\(^40\) to localize domain-specific representations without strongly relying on the boundaries between regions and to lessen the impact of anatomical variability. In this approach, we modeled the similarity structure of spherical volumes (radius = 8 mm) centered at each voxel in MFC, identifying areas wherein local patterns of brain activity contain generalizations representations of pain, cognitive control, and negative emotion. By examining patterns of activation in small spherical volumes, these searchlights provide a smooth estimate of pattern information\(^40\) that is not constrained by fixed boundaries that may not match the anatomy of every subject (of importance here, as ~40% of the population has a paracingulate gyrus\(^7\), which extends the spatial extent of MCC).

The results of the searchlight analysis were largely concordant with those based on anatomical parcellation (Fig. 4a,d). Generalizable representations of painful stimulation were found in aMCC within the cingulate sulcus (\(z_{\text{peak}} = 4.88\), Montreal Neurological Institute coordinates (MNI)\(_{\text{xyz}} = [2, 14, 24]\), \(P = 1.06 \times 10^{-4}\), \(q < 0.05\) false discovery rate (FDR)-corrected) and extending into dMFC (\(z_{\text{peak}} = 5.58\), MNI\(_{\text{xyz}} = [2, 8, 46]\), \(P = 2.41 \times 10^{-4}\), \(q < 0.05\) FDR-corrected). Also consistent with the regional analysis, representations of negative emotion were found in dMFC, above the dorsal bank of the cingulate sulcus in pre-supplementary motor area (SMA; \(z_{\text{peak}} = 3.00\), MNI\(_{\text{xyz}} = [-10, 10, 52]\), \(P = 0.0027\)) and vmPFC (\(z_{\text{peak}} = 3.78\), MNI\(_{\text{xyz}} = [0, 48, -10]\), \(P = 1.57 \times 10^{-4}\)), albeit at lower (uncorrected) thresholds.

Unlike the regional analyses, the searchlight analysis revealed domain-specific representations of cognitive control along the
cingulate sulcus, extending into SMA and motor cortex (z_{peak} = 2.81, MNI_{xyz} = [-2, 2, 46], P = 0.005). This localization, which falls along the boundary between aMCC and dMFC, agrees with meta-analyses showing the epicenter of control-related activity in this area across working memory, inhibition, and attention-shifting tasks\textsuperscript{41}, and with the posterior rostral cingulate zone\textsuperscript{42}, a region classically thought to be involved in response selection. Due to its proximity to and connectivity with functionally related brain regions\textsuperscript{17}, this area is a prime candidate for integrating different types of control signals from multiple sources, such as the expected value of control\textsuperscript{20} and value-guided behavioral adaptations\textsuperscript{19}.

Integrative views of cingulate function are in part supported by observations that overlapping activation is observed in aMCC and dMFC during manipulations of pain, cognitive control, and social and evaluative processing\textsuperscript{17}. To assess whether the domain-specific representations identified in the present study similarly overlap within the broader territory of the MFC, we performed a conjunction analysis of the searchlight maps (Fig. 4b). Results revealed that these representations were predominately dissociable; the three domains did not commonly overlap in any voxel. Minimal overlap was found in dMFC, with small clusters of activity coding for both pain and cognitive control (60 voxels, 0.57%), and for pain and negative emotion (93 voxels, 0.88%). A small degree of overlap was also observed for pain and negative emotion in vmPFC (17 voxels, 0.53%). The only overlapping effects in cingulate cortex were for pain and cognitive control, spanning the border between pMCC (6 voxels, 1.16%) and aMCC (2 voxels, 1.29%).

To evaluate evidence against overlap, we computed Bayes factors using the minimum z-score from the three-domain conjunction analysis\textsuperscript{43,44}. In this analysis, if the minimum statistic from all three domains is less than or near zero, then there is little support for overlap. Conversely, if the minimum statistic is large and positive, it is more likely that there is overlap across the domains. Values < 1 reflect evidence in favor of the null hypothesis of no representation in all three domains, and values > 1 reflect evidence in favor of overlap. A Bayes factor < 0.1 is generally considered strong evidence against overlap, and a factor > 10 is generally considered strong evidence for overlap. This analysis revealed substantial evidence against overlap in the MFC (Fig. 4c), with a maximum Bayes factor = 0.0898.

**Discussion**

Our results reveal generalizable representations of pain, cognitive control, and negative emotion in separable patterns of MFC...
activity. The limited overlap of generalizable representations across domains contrasts with conventional, univariate assessments of cingulate function, which show substantial overlap across domains\(^5\). Thus, our findings here highlight functional diversity within MFC, and they suggest that domain-specific representations exist in most parts of MFC, including aMCC and adjacent regions. Though domain-specific representations are limited to one domain (pain, negative emotion, and cognitive control), our design allows us to infer that they do generalize across multiple subdomains (for example, somatic thermal, somatic mechanical, and visceral pain). The generalizable representations we identify provide empirical constraints on what integrative theories of aMCC function must explain. In most of the MFC, it may not be necessary to explain pain- or affect-related and cognitive error-related signals with a single mechanism. Along these lines, it has recently been suggested that the aMCC functions to monitor for conflicts related to ever-present, survival-relevant goals\(^3\). Consistent with this proposal, we identified generalizable representations of pain in aMCC. However, these representations were qualitatively distinct from those evoked by negative emotional stimuli, including social rejection, that were not generalizable. This distinction makes it unlikely that the aMCC is engaged in the same way to achieve different survival-relevant goals. It is also consistent with other recent work identifying dissociations in MFC activity across tasks taken from different domains\(^1\).

On the other hand, our findings leave room for integrative theories that explain computational mechanisms in terms of a convergence of different neural populations that interact to achieve computational goals. That is, it is possible that the same computational function may be implemented in diverse neural circuits, depending on their inputs and outputs. Our data therefore do not argue against unified computational accounts of aMCC, but rather against a unitary neural implementation of those computations. The proximity of pain, negative emotion, and cognitive representations we identified provides a neural substrate for their comparison and integration\(^7\). It is possible that integration across domains could be identified in carefully controlled studies implementing within-subject designs across domains and subdomains. Further, although we included many studies and subdomains, our sampling was far from exhaustive, and testing specificity is an open-ended process. Future work combining a more diverse set of subdomains (for example, incorporating studies of chronic pain, positive and negative reward prediction error, and behavioral withdrawal) with model-based approaches will help further test the claims of integrative theories of control.

In conclusion, we identified domain-specific representations for pain and negative emotion in the aMCC and vmPFC. These representations generalized across participants and diverse subdomains (three per domain). These representations could only be identified by extracting generalizable brain patterns across studies and subdomains. Currently, conventional research investigating population-level neural representation has been conducted at the level of individual studies. Even when very large, studies that sample limited numbers of tasks (i.e., a single exemplar task for a psychological domain) are not capable of identifying generalizable brain representations in this way. Although cross-validation procedures, reliability analysis, and independent replication samples are becoming increasingly common to ensure the generalizability of results, it is evident that findings are often idiosyncratic to a particular study or experimental context, rather than truly reflecting the mental operations under study. Our results demonstrate how modeling the similarity structure of fMRI data drawn from multiple studies and subdomains can overcome this challenge and disambiguate latent brain representations of theoretical constructs.

Methods

Methods, including statements of data availability and any associated accession codes and references, are available at https://doi.org/10.1038/s41593-017-0051-7.

Received: 21 August 2017; Accepted: 29 November 2017;
Published online: 1 January 2018

References

1. Amodio, D. M. & Frith, C. D. Meeting of minds: the medial frontal cortex and social cognition. Nat. Rev. Neurosci. 7, 266–277 (2006).
2. Cosmides, L. & Tooby, J. Origins of domain specificity: the evolution of functional organization. in Mapping the Mind: Domain Specificity in Cognition and Culture (eds Hirschfeld, L.A. & Gelman, S.A.) 85–116 (1994).
3. Vogt, B. A. Midcingulate cortex: structure, connections, homologies, functions and diseases. J. Chem. Neuroanat. 74, 28–46 (2016).
4. Botvinick, M., Nystrom, L. E., Fussell, K., Carter, C. S. & Cohen, J. D. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 402, 179–199 (1999).
5. Ridderinkhof, K. R., Ullsperger, M., Crone, E. A. & Nieuwenhuis, S. The role of the medial frontal cortex in cognitive control. Science 306, 443–447 (2004).
6. Ilo, S., Stuphorn, V., Brown, J. W. & Schall, J. D. Performance monitoring by the anterior cingulate cortex during saccade countermanding. Science 302, 120–122 (2003).
7. Dosenbach, N. U. et al. A core system for the implementation of task sets. Neuron 50, 799–812 (2006).
8. Procyk, E., Tanaka, Y. L. & Joseph, J. P. Anterior cingulate activity during routine and non-routine sequential behaviors in macaques. Nat. Neurosci. 3, 502–508 (2000).
9. Kolling, N., Behrens, T. E., Mars, R. B. & Rushworth, M. F. Neural mechanisms of foraging. Science 336, 95–98 (2012).
10. Büchel, C. et al. Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. J. Neurosci. 22, 970–976 (2002).
11. Rainville, P., Duncan, G. H., Price, D. D., Carrier, B. & Bushnell, M. C. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277, 968–971 (1997).
12. Erkin, A., Egnier, T., Peraza, D. M., Kandel, E. R. & Hirsch, J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neurosci. 51, 871–882 (2006).
13. Bishop, S., Duncan, J., Brett, M. & Lawrence, A. D. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. Nat. Neurosci. 7, 184–188 (2004).
14. Tomlin, D. et al. Agent-specific responses in the cingulate cortex during economic exchanges. Science 312, 1047–1050 (2006).
15. Rudebeck, P. H., Buckley, M. J., Walton, M. E. & Rushworth, M. F. S. A role for the macaque anterior cingulate gyrus in social valuation. Science 313, 1310–1312 (2006).
16. Ebitz, R. B. & Hayden, B. Y. Dorsal anterior cingulate: a Rorschach test for cognitive neuroscience. Nat. Neurosci. 19, 1278–1279 (2016).
17. Shackman, A. J. et al. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat. Rev. Neurosci. 12, 154–167 (2011).
18. Critchley, H. D. et al. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 126, 2139–2152 (2003).
19. Behrens, T. E., Woolrich, M. W., Walton, M. E. & Rushworth, M. F. Learning the value of information in an uncertain world. Nat. Neurosci. 10, 1214–1221 (2007).
20. Shenav, A., Botvinick, M. M. & Cohen, J. D. The expected value of control: an integrative theory of anterior cingulate cortex function. Neuron 79, 217–240 (2013).
21. Eisenberger, N. I. & Lieberman, M. D. Why rejection hurts: a common neural alarm system for physical and social pain. Trends Cogn. Sci. 8, 294–300 (2004).
22. Haynes, J. D. A primer on pattern-based approaches to fMRI: principles, pitfalls, and perspectives. Neuron 87, 257–270 (2015).
23. Logothetis, N. K. What we can do and what we cannot do with fMRI. Nature 453, 869–878 (2008).
24. Kwistiani, D. et al. Distinct behavioural and network correlates of two interneuron types in prefrontal cortex. Nature 498, 363–366 (2013).
25. Krishnan, A. et al. Somatic and vicarious pain are represented by dissociable multivariate brain patterns. eLife 5, e15166 (2016).
26. Woo, C. W. et al. Separate neural representations for physical pain and social rejection. Nat. Commun. 5, 5380 (2014).
27. Vogt, B. A., Berger, G. R. & Derbyshire, S. W. Structural and functional dichotomy of human midcingulate cortex. Eur. J. Neurosci. 18, 3134–3143 (2003).
28. Kriegeskorte, N., Mur, M. & Bandettini, P. Representational similarity analysis - connecting the branches of systems neuroscience. Front. Syst. Neurosci. 2, 4 (2008).
29. Peyron, R., Laurent, B. & Garcia-Larrea, I. Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol. Clin.* **30**, 263–288 (2000).

30. Lieberman, M. D. & Eisenberger, N. I. The dorsal anterior cingulate cortex is selective for pain: results from large-scale reverse inference. *Proc. Natl. Acad. Sci. USA* **112**, 15250–15255 (2015).

31. Hutchison, W. D., Davis, K. D., Lozano, A. M., Tasker, R. R. & Dostrovsky, J. O. Pain-related neurons in the human cingulate cortex. *Nat. Neurosci.* **2**, 403–405 (1999).

32. McNamara, D., Rangel, A. & O’Doherty, J. P. Category-dependent and category-independent goal-value codes in human ventromedial prefrontal cortex. *Nat. Neurosci.* **16**, 479–485 (2013).

33. Peelen, M. V., Atkinson, A. P. & Vuilleumier, P. Supramodal representations of perceived emotions in the human brain. *J. Neurosci.* **30**, 10127–10134 (2010).

34. Levy, D. J. & Glimcher, P. W. The root of all value: a neural common currency for choice. *Curr. Opin. Neurobiol.* **22**, 1027–1038 (2012).

35. Montague, P. R. & Berns, G. S. Neural economics and the biological substrates of valuation. *Neuron* **36**, 265–284 (2002).

36. Roy, M., Shohamy, D. & Wager, T. D. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends Cogn. Sci.* **16**, 147–156 (2012).

37. Laird, A. R. et al. Investigating the functional heterogeneity of the default mode network using coordinate-based meta-analytic modeling. *J. Neurosci.* **29**, 14496–14505 (2009).

38. Fan, L. et al. The Human Brainnetome Atlas: a new brain atlas based on connectional architecture. *Cereb. Cortex* **26**, 3508–3526 (2016).

39. Paus, T. et al. Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. *Cereb. Cortex* **6**, 207–214 (1996).

40. Kriegeskorte, N., Goedel, R. & Bandettini, P. Information-based functional brain mapping. *Proc. Natl. Acad. Sci. USA* **103**, 3863–3868 (2006).

41. Van Snellenberg, J. X. & Wager, T. D. Cognitive and motivational functions of the human prefrontal cortex. in *Luria’s Legacy in the 21st Century* (Christiansen, A.-L., Goldberg, E. & Bougakov, D. eds.) 30–61 (2009).

42. Amiez, C. & Petrides, M. Neuroimaging evidence of the anatomo-functional organization of the human cingulate motor areas. *Cereb. Cortex* **24**, 563–578 (2014).

43. Gallistel, C. R. The importance of proving the null. *Psychol. Rev.* **116**, 439–453 (2009).

44. Dienes, Z. Using Bayes to get the most out of non-significant results. *Front. Psychol.* **5**, 781 (2014).

45. de la Vega, A., Chang, L. J., Banich, M. T., Wager, T. D. & Yarkoni, T. Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization. *J. Neurosci.* **36**, 6553–6562 (2016).

46. Torta, D. M. & Cauda, F. Different functions in the cingulate cortex, a meta-analytic connectivity modeling study. *Neuroimage* **56**, 2157–2172 (2011).

47. Jahn, A., Nee, D. E., Alexander, W. H. & Brown, J. W. Distinct regions within medial prefrontal cortex process pain and cognition. *J. Neurosci.* **36**, 12385–12392 (2016).

48. Yeo, B. T. et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J. Neurophysiol.* **106**, 1125–1165 (2011).

**Acknowledgements**

We thank S. Fukuda, T. Muratsubaki and J. Morishita for assistance with data collection; K. Ochsner for sharing data from studies of negative emotion; T. Braver and J. Gray for sharing working memory data; and R. Poldrack for sharing response selection data (available at [https://openfmri.org/](https://openfmri.org/)). This research was supported by grants R01 HL089850 to P.J.G.; P01 HL040962 to S.B.M.; grants AG043463 to K.O.; by the Direction de la Recherche Clinique of the University Hospital of Grenoble Alpes; and by the pharmaceutical labs Ferring and Cephalon. L.V.O. is funded by the KU Leuven Special Research Fund. T.E.N. is supported by the Wellcome Trust.

**Author contributions**

P.A.K. and T.D.W. designed the experiment and drafted the manuscript. P.A.K. conducted data analysis. P.A.K., T.E.N., and T.D.W. developed simulated experiments for evaluating statistical procedures. A.R., B.L.B., M.C., C.D.-M., H.G.L., E.A.R.L., L.V.O., M.K., P.D., P.J.G., S.B.M., T.D.W., and C.-W.W. contributed neuroimaging data. All authors provided feedback and revised the manuscript.

**Competing interests**

The authors declare no competing financial interests.

**Additional information**

Supplementary information is available for this paper at [https://doi.org/10.1038/s41593-017-0051-7](https://doi.org/10.1038/s41593-017-0051-7).

Reprints and permissions information is available at [www.nature.com/reprints](http://www.nature.com/reprints).

Correspondence and requests for materials should be addressed to P.A.K. or T.D.W.

**Publisher’s note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
Methods
Experimental design. We adopted a construct-validation approach to examine generalizability representations of three constructs that engage the MFC: pain, cognitive control, and negative emotion. By (i) identifying latent multivariate representations that are indicative of an underlying psychological dimension rather than idiosyncrasies of one particular study or subdomain (i.e., task) and (ii) examining the similarity of those latent representations across multiple psychological domains, this framework provides a more definitive test of shared representation in the aMCC and areas within the MFC compared to conventional single-study or single-method investigations.

This approach has been taken for decades in psychometric research to assess construct validity1. The idea is to define a latent construct—intelligence and anxiety are classic examples—and measure it with multiple distinct indicators. Using multiple indicators permits the extraction of common factors that underlie the construct. Intercorrelations among indicators of the same construct provide evidence for convergent validity, suggesting that the indicators measure the same construct. If different indicators uniquely load on different constructs, they provide evidence for discriminant validity. Together, establishing converging and discrimination provides strong evidence for construct validity1.

Applied to fMRI, indicators are patterns of brain activity evoked by different tasks, and the constructs are the functional psychological domains (for posterior, pain or working memory) that the tasks putatively measure. The vast majority of studies, even large-scale studies like the Human Connectome Project and UK Biobank14,35, use only one specific task variant as a single indicator for a domain. This poses a problem in inferring the similarity of psychological domains from the similarity of brain activity examples of pain task forms a latent negative emotion task in aMCC26, so it is because pain is represented differently from negative emotion, or because the particular variant of pain studied differs from the particular variant of negative emotion? A study with multiple varieties of pain and multiple varieties of negative emotion could address this question, if it showed that a brain representation common to multiple varieties of pain is distinct from a representation common to multiple varieties of negative emotion. This is the method we used in the present study, as detailed below.

Study and contrast selection. fMRI data were sampled from studies of acute thermal somatic stimulation53,54, acute visceral stimulation55,56, acute mechanical stimulation, working memory14,64, response selection14, response conflict6, induction of negative emotion using images of visual scenes62,63, social negative emotion14,64, the perception of others in pain14, and emotionally aversive vignettes14,64, the perception of others in pain14, and emotionally aversive vignettes from the International Affective Digital Sounds system65. Together these data showed that a brain representation common to multiple varieties of pain is distinct from the particular variant of negative emotion? A study with multiple varieties of pain or working memory) that the tasks putatively measure. The vast majority of studies, even large-scale studies like the Human Connectome Project and UK Biobank14,35, use only one specific task variant as a single indicator for a domain. This poses a problem in inferring the similarity of psychological domains from the similarity of brain activity examples of pain task forms a latent negative emotion task in aMCC26, so it is because pain is represented differently from negative emotion, or because the particular variant of pain studied differs from the particular variant of negative emotion? A study with multiple varieties of pain and multiple varieties of negative emotion could address this question, if it showed that a brain representation common to multiple varieties of pain is distinct from a representation common to multiple varieties of negative emotion. This is the method we used in the present study, as detailed below.

Due to variability in sample size across studies (range = 15–183), data were randomly subsampled by selecting 15 participants from each study (total = 270). Although no statistical methods were used to predetermine this sample size, it is similar to those reported in previous publications14–16 (see also Supplementary Table 7 for maximal univariate effects in the present sample). Because our focus was to compare across studies, we used only task-level indicators, and no attempt to infer from the particularity of pain or the particularity of negative emotion were made. No participants were excluded from the analysis. A subset of these data was previously used to validate the use of automated meta-analysis to decode cognitive states of pain, emotion, and working memory14.

This was not a randomized study; it was a meta-analysis of multiple studies. Participants were recruited independently for each of the 18 studies being analyzed. Data collection was conducted blind to the goals of the present study. A posteriori group assignment was based on the goals of each study and the experimental manipulation being used (for example, studies involving thermal stimulation of the forearm were considered members of the pain domain). Data analysis was not performed blind to the conditions of the experiments.

Informed consent was provided by all subjects according to local ethics and institutional review boards. Participants sampled from studies 5 (n = 15, 4 female; M age = 26.97), 6 (n = 15, 8 female; M age = 24.42), 17 (n = 15, 7 female; M age = 31.1), and 18 (n = 15, 9 female; M age = 24.4) provided informed consent as approved by the University of Colorado Boulder institutional review board. Participants in study 11 (n = 21, 9 female; M age = 30.5) provided informed consent in accordance with the New York University institutional review board. Descriptions of ethics approvals, image acquisition and analysis, and demographics are described briefly in Supplementary Table 7 and in full detail in the corresponding references (see also the Life Sciences Reporting Summary).

Contrasts from thermal pain stimulation were between high and low levels of pain (i.e., intervals between two levels of painful stimulation) for visceral stimulation studies were between rectal distension trials and baseline. For mechanical stimulation studies, contrasts were made between pressure application to the thumb and baseline. Contrasts for both working memory studies were between N-back blocks and a fixation baseline. For response-selection studies, contrasts were between trials in a go/no-go task engaging response selection (as defined in the Cognitive Atlas13) against baseline. Response-contrast conflicts were made between congruent and incongruent trials in studies using the Eriksen Flanker task14. Studies of visual negative emotion were compared to neutral IAPS pictures or negative pictures against baseline14. Social negative emotion studies compared viewing pictures of ex-partners versus friends14 and viewing images of others in pain14 versus baseline. Auditory negative emotion studies compared listening to unpleasant affective sounds to baseline.

fMRI analysis. We employed three converging methods to isolate generalizable brain representations: (i) we modeled how dissimilar patterns of brain activity were from another, called representational similarity analysis (RSA14–16); (ii) we directly compared the similarity of brain activity in studies coming from the same domain (but different studies and subdomains) to the similarity of brain activity in studies from different domains; and (iii) we used partial least-squares regression to characterize the spatial profile of generalizable brain representations in MFC.

Feature selection. Input data were defined a priori as voxels located within the anterior midline, defined as voxels within cingulate cortex and superior frontal gyrus (in the LONI Probabilistic Atlas14). Based on a prior model of MFC, we simulated data with a large number of regressors (154) and a smaller number of voxels (270). The vast majority of these regressors are strongly correlated within domains (pain, working memory) that the tasks putatively measure. The vast majority of studies, even large-scale studies like the Human Connectome Project and UK Biobank14,35, use only one specific task variant as a single indicator for a domain. This poses a problem in inferring the similarity of psychological domains from the similarity of brain activity examples of pain task forms a latent negative emotion task in aMCC26, so it is because pain is represented differently from negative emotion, or because the particular variant of pain studied differs from the particular variant of negative emotion? A study with multiple varieties of pain and multiple varieties of negative emotion could address this question, if it showed that a brain representation common to multiple varieties of pain is distinct from a representation common to multiple varieties of negative emotion. This is the method we used in the present study, as detailed below.

In the present study, we modeled dissimilarity matrices, which are a form of similarity data, as coefficients of multiple regression models (Fig. 1). Applied to fMRI, indicators are patterns of brain activity evoked by different tasks, and the constructs are the functional psychological domains (for posterior, pain or working memory) that the tasks putatively measure. The vast majority of studies, even large-scale studies like the Human Connectome Project and UK Biobank14,35, use only one specific task variant as a single indicator for a domain. This poses a problem in inferring the similarity of psychological domains from the similarity of brain activity examples of pain task forms a latent negative emotion task in aMCC26, so it is because pain is represented differently from negative emotion, or because the particular variant of pain studied differs from the particular variant of negative emotion? A study with multiple varieties of pain and multiple varieties of negative emotion could address this question, if it showed that a brain representation common to multiple varieties of pain is distinct from a representation common to multiple varieties of negative emotion. This is the method we used in the present study, as detailed below.

RSA: model specification. We estimated representational dissimilarity matrices (RDMs) by computing the correlation distance (1–Pearson’s r, excluding on-diagonal elements, which have a dissimilarity value of 0) of multivoxel patterns of brain activity. Each pattern was acquired from one of 270 subjects drawn from the full sample of 18 studies (n = 15 per study). Next, we constructed model-based RDMs to characterize different components of a psychological hierarchy (Fig. 1). At the lowest level, the 18 studies were individually modeled to account for study-specific idiosyncrasies. Next, the nine subdomains (visceral stimulation, thermal stimulation, emotional stimulation, mechanical stimulation, response conflict, stop/go response selection, working memory, visual negative emotion, and auditory negative emotion) were modeled to account for response patterns that generalize across studies. Finally, the three psychological domains (pain, cognitive control, and negative emotion) were modeled as independent predictors to account for response patterns that generalize not only across studies, but across subdomains as well, hence being generalizable within but not across the three domains. Individually formed binary RDMs were used to determine which individual indicators were mapped onto the same model and were grouped into one level of the hierarchy based on study (18 RDMs, subdomain 9 RDMs, or psychological domain 3 RDMs). The unique off-diagonal elements (intersubject dissimilarities) of these 30 RDMs, in addition to a constant RDM, were vectorized to form regressors in a linear model. Linear regression was used with this model to fit the observed intersubject dissimilarity data. Fitting regressors with RSA-based dissimilarity matrices exhibit complex dependencies, as a result we use bootstrap inference to obtain P values (see “Inferences on RSA model parameters” section below).

RSA: model properties and diagnostics. To assess the suitability of our models, we conducted simulated experiments using resting-state fMRI (rsfMRI) data (n = 270) from the 1,000 Functional Connectomes project14. This allowed us to test the RSA models’ false positive rates, as well as the biases and variances of parameter estimates, with data using no true effects but real fMRI noise. This is the approach recently taken by Eklund et al.14 to assess false positive rates in standard GLM analyses.

We used a Monte Carlo procedure to conduct 1,000 RSA-based analyses of rsfMRI data, each with randomly generated event-related fMRI models for the 270 participants, allowing us to estimate the distribution of RSA parameter estimates under the null hypothesis. To mirror the dependence structure (including study/site effects) of a priori model and baseline data, we selected rsfMRI participants from 18 different sites, sampling 15 participants from each site (total = 270). All data were subjected to standard preprocessing, including realignment to correct for motion, nonlinear warping to standard MNI space, spatial smoothing (4-mm FWHM), and high-pass filtering (128-s cutoff). Then, for each Monte Carlo iteration, for
each participant, we generated a series of 10 events with random onsets, modeled them with Dirac delta (impulse response) functions and convolved them with SPM’s standard hemodynamic response function to generate a single regressor of interest for each constant term we also included. This was estimated using a subspace of interstudy relationships spanned by the BIC analysis in each region of interest. Statistics: infernces on RSA model parameters. Parameter estimates (β̂) from the model provide estimates of generalizability, with the interpretation of a significant (nonzero) parameter estimate depending on the nature of the regressor. Study-specific regressors test generalizability across individual studies, potentially within a study, in the sense that they capture intersubject correlations in the spatial patterns of activity. Positive values indicate similar patterns across participants for the study modeled. Subdomain-level regressors test generalizability across two studies of the same subdomain, controlling for other model parameters. Positive values indicate similar patterns across studies of the modeled subdomain and, thus, evidence for a coherent subdomain. Domain-level regressors, which were of primary interest here, test generalizability across three distinct subdomains (six studies), controlling for shared patterns specific to the study and subdomain. Positive values indicate shared spatial patterns across subdomains and, thus, evidence for a coherent domain-related pattern. Thus, we refer to these parameter estimates as generalization indices (for example, Fig. 2), as they reflect the extent to which patterns of brain activation generalize across subdomains, studies, or subjects. Because the regressors were tested jointly in multiple regression modeling, significant domain-level parameter estimates imply that the pattern of brain activity shared across the domain was not reducible to a subdomain-specific or study-specific pattern.

Inference on parameter estimates (β̂) was made using bootstrap resampling of subjects. This procedure involved repeatedly resampling subjects, with replacement, for each study over 5,000 iterations for the regional analysis and over 1,000 iterations for the searchlight analysis (see below). In each resampling, a new RDM was constructed using RSA activation for the resampled subjects and the true activation for the remaining samples from the same subject were drawn multiple times in this approach, pairwise dissimilarity values from the same subject (with a dissimilarity value of 0) were excluded from the analysis. Bootstrap distributions for individual model parameters were compared against 0 using normal approximation for inference. These distributions were visually inspected and an estimate was considered statistically significant if it was more extreme than 3 standard deviations. For noted otherwise, the main results reported in the manuscript (both regional and searchlight analyses) were thresholded after correcting for multiple comparisons based on the false discovery rate (FDR corrected, q < 0.05). All tests are two-tailed unless otherwise specified.

Statistics: RSA model comparison. To formally compare the amount of evidence for domain-generalizable representations, model comparisons were made using the Bayesian information criterion (BIC). The reference model included terms for each study (18 parameters) and each subdomain (9 parameters), as well as a constant (28 parameters in total). Next, we fit three models that each included a single additional term for one of the psychological domains (29 parameters in total). Finally, a more fully specified model that contained all three psychological domains (31 parameters in total) was fit. These five models were fit for each region of interest and the full extent of MFC. BIC values were computed using the log-likelihood of fitted models and penalizing based on the number of free parameters. The number of samples was set the number of participants included in the dissimilarities (270) as opposed to the number of unique elements in the dissimilarity matrix, because of dependence between elements of the dissimilarity matrix. BIC values were converted to weights using the formulation from Wagenmakers and Farrell74. These weights characterize which model is most consistent with the data.

In the present work, we included k = 18 studies with n = 270 participants divided equally among them (15 per study). We used the constant term in the model to characterize linear similarity among a subspace of interstudy relationships spanned by k × k × (k − 1)/2 − 1 = 170 dimensions. Principle, the upper bound on the number of regressors for interstudy differences in an identifiable model is 170. However, we were primarily interested in specific interstudy relationships, particularly those common to subdomains (9 parameters for pairs of studies with the same subdomain) and those common to domains (three parameters for three sets of 9 studies that load on the same domain construct across three subtypes). Our full model thus contained 31 regressors: 18 for specific studies, 9 for subdomains, three for domains, and one intercept term. As the number of voxels per ROI was at least 302 > 31, there was no risk of degenerate (zero-residual) models.

RSA: model rank and variance inflation factors. To confirm the identifiability and efficiency of our models, we computed the rank of our design matrix and variance inflation factors (VIFs) for each regressor. The VIFs show the degree to which variance in each parameter estimate is increased due to partial colinearity with linear combinations of other regressors. The rank of our design matrix is 31, indicating that the model is full-rank, identifiable, and not overparameterized. VIFs were finite for all regressors, consistent with the fact that model was identifiable (Supplementary Fig. 2). VIFs varied across regressors based on the partially shared variance across study, domain, and subdomain, which was unavoidable because part of the covariance common to participants in each domain was shared with the subdomains and studies that fall within it. However, the VIFs were clearly in a range that indicated reasonable ability to make inferences on the unique variance explained by each parameter, given the sample size. The regressors that were of primary interest (i.e., the three domain-level terms) had VIFs = 1.66.
all 270 subjects forming the data matrix and dummy coded variables forming the output matrix (270 subjects by 30 parameters: 18 studies, 9 subdomains, and 3 domains, with values of +1/-1 based on inclusion/exclusion for each term). Parameter estimates were bootstrapped over 5,000 iterations, and z-scores were estimated based on the mean and standard error of the bootstrap distributions. We note that this approach is not designed to ensure that representations are uniquely specific to each domain; if some studies or subdomains have especially high covariance with a domain, they could have a large influence on domain-level patterns. For this reason, PLS-based estimation of patterns is used in conjunction with RSA and direct comparisons of intersubject correlations.

Statistics: searchlight thresholds and assessment of overlap. For the conjunction analysis and visualization of searchlight maps, an uncorrected threshold (P<0.05) was used to ensure that an overly conservative threshold did not obscure overlapping regions. To estimate the relative evidence for and against overlap of the domains, Bayes factors were computed using the minimum statistic compared to the conjunction null and a uniform distribution ranging from 0 to 10 as a prior distribution (theoretically plausible values of parameters estimates). This test evaluates whether there is more evidence in favor of overlap (i.e., that the minimum statistic of the three maps is substantially greater than zero) or against overlap (the minimum statistic of the three maps is relatively close to or less than zero). Bayes factors >3 provide evidence of overlapping representations, whereas values less than 0.33 provide evidence against overlap.

Correspondence of searchlight maps with existing parcellations. River plots were created to depict the correspondence (quantified as the cosine similarity) between the searchlight maps and existing anatomical and functional parcellations.

Life Sciences Reporting Summary. Further information on experimental design is available in the Life Sciences Reporting Summary.

Data availability. The fMRI data for studies 9–12 are available from OpenfMRI: https://openfMRI.org/dataset/ds000008/, https://openfMRI.org/dataset/ds000007/, https://openfMRI.org/dataset/ds000101/ and https://openfMRI.org/dataset/ds000102/. fMRI data for study 13 is available at NeuroVault, http://neurovault.org/ https://openfmri.org/dataset/ds000008/, https://openfmri.org/dataset/ds000007/, https://openfmri.org/dataset/ds000006/, https://openfmri.org/dataset/ds000005/. Code availability. For download at https://canlabweb.colorado.edu/files/MFC_Generalizability.tar.gz.

References

49. Cronbach, L. J. & Meehl, P. E. Construct validity in psychological tests. Psychol. Bull. 52, 281–302 (1955).
50. Campbell, D. T. & Fiske, D. W. Convergent and discriminant validation by the multitrait-multimethod matrix. Psychol. Bull. 56, 81–105 (1959).
51. Barch, D. M. et al. Function in the human connectome: task-fMRI and individual differences in behavior. Neuroimage 80, 169–189 (2013).
52. Miller, K. L. et al. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat. Neurosci. 19, 1523–1536 (2016).
53. Wager, T. D. et al. An fMRI-based neurologic signature of physical pain. N. Engl. J. Med. 368, 1388–1397 (2013).
54. Atlas, L. Y., Bolger, N., Lindquist, M. A. & Wager, T. D. Brain mediators of predictive cue effects on perceived pain. J. Neurosci. 30, 12964–12977 (2010).
55. Rubio, A. et al. Uncertainty in anticipation of uncomfortable rectal distension is modulated by the autonomic nervous system–a fMRI study in healthy volunteers. Neuroimage 107, 10–22 (2015).
56. Kano, M. et al. Influence of uncertain anticipation on brain responses to aversive rectal distension in patients with irritable bowel syndrome. Psychosom. Med. https://doi.org/10.1097/PSY.0000000000000484 (2017).
57. DeYoung, C. G., Shamosh, N. A., Green, A. E., Braver, T. S. & Gray, J. R. Intellect as distinct from Openness: differences revealed by fMRI of working memory. J. Pers. Soc. Psychol. 97, 883–892 (2009).
58. van Ast, V. A. et al. Brain mechanisms of social threat effects on working memory. Cereb. Cortex 26, 544–556 (2016).
59. Xue, G., Aron, A. R. & Poldrack, R. A. Common neural substrates for inhibition of spoken and manual responses. Cereb. Cortex 18, 1923–1932 (2008).
60. Aron, A. R., Behrens, T. E., Smith, S., Frank, M. J. & Poldrack, R. A. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (fMRI) and functional MRI. J. Neurosci. 27, 3743–3752 (2007).
61. Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X. & Milham, M. P. Competition between functional brain networks mediates behavioral variability. Neuroimage 39, 527–537 (2008).
62. Gianoaros, P. J. et al. An inflammatory pathway links atherosclerotic cardiovascular disease risk to neural activity evoked by the cognitive regulation of emotion. Biol. Psychiatry 75, 738–745 (2014).
63. Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C. & Wager, T. D. Large-scale automated synthesis of human functional neuroimaging data. Nat. Methods 8, 665–670 (2011).
64. Kross, E., Berman, M. G., Mischel, W., Smith, E. F. & Wager, T. D. Social rejection shares somatosensory representations with physical pain. Proc. Natl Acad. Sci. USA 108, 6270–6275 (2011).
65. Bradley, M. M. & Lang, P. J. The International Affective Digitized Sounds (IADS-2): Affective Ratings of Sounds and Instruction Manual. (University of Florida, Gainesville, FL, 2007). Tech. Rep. B-3.
66. Poldrack, R. A. et al. The cognitive atlas: toward a knowledge foundation for cognitive neuroscience. Front. Neuroinform. 5, 17 (2011).
67. Kriegeskorte, N. & Kievit, R. A. Representational geometry: integrating cognition, computation, and the brain. Trends Cogn. Sci. 17, 401–412 (2013).
68. Wold, S., Jöreskog, M. & Eriksson, L. PLS-regression: a basic tool of chemometrics. Chemomtl. Intell. Lab. Syst. 58, 109–130 (2001).
69. Shattuck, D. W. et al. Construction of a 3D probabilistic atlas of human cortical structures. Neuroimage 39, 1064–1080 (2008).
70. Lancaster, J. L. et al. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Hum. Brain Mapp. 28, 1194–1205 (2007).
71. Biswal, B. B. et al. Toward discovery science of human brain function. Proc. Natl Acad. Sci. USA 107, 4734–4739 (2010).
72. Elkind, A., Nichols, T. E. & Knutsson, H. Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. Proc. Natl Acad. Sci. USA 113, 7900–7905 (2016).
73. Schwarz, G. Estimating dimension of a model. Ann. Stat. 6, 461–464 (1978).
74. Wagenmakers, E. J. & Farrell, S. AIC model selection using Akaike weights. Psychon. Bull. Rev. 11, 192–196 (2004).
75. Nichols, T., Brett, M., Andersson, J., Wager, T. & Poline, J. B. Valid conjunction inference with the minimum statistic. Neuroimage 25, 653–660 (2005).
Experimental design

1. Sample size
   Describe how sample size was determined. Because data from multiple datasets were combined in a multi-study framework, balanced subsampling was performed (n = 15 per study) to help equate statistical power for comparisons between studies.

2. Data exclusions
   Describe any data exclusions. No data were excluded from the analysis.

3. Replication
   Describe whether the experimental findings were reliably reproduced. Although replication was not attempted, the main findings reflect effects that are reliable across 6 different studies.

4. Randomization
   Describe how samples/organisms/participants were allocated into experimental groups. This was not a randomized study, it was a mega-analysis of multiple studies. Contrasts were constructed within subjects and the goal was to compare effects across studies. Participants were recruited independently for each of the 18 studies being analyzed. A posteriori group assignment was based on the goals of each study and experimental manipulation being used (e.g., studies involving thermal stimulation of the forearm were considered members of the ‘pain’ domain).

5. Blinding
   Describe whether the investigators were blinded to group allocation during data collection and/or analysis. Investigators were not aware of group comparisons during data collection. No blinding was performed for data analysis.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.
6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

- The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
- A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- A statement indicating how many times each experiment was replicated
- The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
- A description of any assumptions or corrections, such as an adjustment for multiple comparisons
- The test results (e.g. P values) given as exact values whenever possible and with confidence intervals noted
- A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
- Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

/software

7. Software

Describe the software used to analyze the data in this study.

Analysis was conducted using CANLab and SPM software implemented in MATLAB. Code for implementing all analyses is available at https://github.com/canlab/ and www.fil.ion.ucl.ac.uk/spm/software/.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). Nature Methods guidance for providing algorithms and software for publication provides further information on this topic.

/materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.

No unique materials were used.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

No antibodies were used.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

No eukaryotic cell lines were used.

b. Describe the method of cell line authentication used.

No eukaryotic cell lines were used.

c. Report whether the cell lines were tested for mycoplasma contamination.

No eukaryotic cell lines were used.

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.

No commonly misidentified cell lines were used.

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

Non-human animals were not used.
12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

270 healthy human participants were involved in the research. The age and gender of participants in each of the 18 studies are detailed in Supplementary Table 7.
MRI Studies Reporting Summary

Form fields will expand as needed. Please do not leave fields blank.

1. **Experimental design**
   - Describe the experimental design.
   - Describe how behavioral performance was measured.

2. Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.
   - The number of trials per subject ranged from 8 to 768. Stimulus durations ranged from 2s to 18s. Scan length ranged from 5 min to 13.5 min. Details for each study are listed in Supplementary Table 7 and the original publications for each study.

3. **Acquisition**
   - Imaging
     - Specify the type(s) of imaging.
     - Specify the field strength (in Tesla).
     - Provide the essential sequence imaging parameters.
     - For diffusion MRI, provide full details of imaging parameters.
     - BOLD fMRI
     - 1.5 and 3 Tesla
     - EPI (standard and multiband) and spiral in-out sequences were used for data acquisition. Readers are referred to the original publications for more details.
     - Diffusion MRI was not collected.
   - State area of acquisition.
     - Whole brain scans were used.

4. **Preprocessing**
   - Describe the software used for preprocessing.
     - SPM and custom code were used for preprocessing, the particular version depending on the study. Readers are referred to the original publications for more details.
   - Normalization
     - If data were normalized/standardized, describe the approach(es).
     - The templates used depend on the study, but all are in ICBM152 space.
     - Non-linear normalization to MNI space was performed.
   - Describe your procedure for artifact and structured noise removal.
     - Regression of motion parameters was performed in all studies (either 6 parameters based on translation and rotation or 24 with the inclusion of their derivatives, successive differences, and squared successive differences).
   - Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.
     - Outlier timepoints were excluded in some studies. These were identified based on Mahalanobis distance using a chi-square test.
10. Define your model type and settings.

11. Specify the precise effect tested.

12. Analysis
   a. Specify whether analysis is whole brain or ROI-based.
   b. If ROI-based, describe how anatomical locations were determined.

13. State the statistic type for inference.
   (See Eklund et al. 2016.)

14. Describe the type of correction and how it is obtained for multiple comparisons.

15. Connectivity
   a. For functional and/or effective connectivity, report the measures of dependence used and the model details.
   b. For graph analysis, report the dependent variable and functional connectivity measure.

16. For multivariate modeling and predictive analysis, specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.

   Multivariate RSA models were specified and fitted using least squares regression. Subject was treated as a random effect.

   Dissimilarity between brain activity (1 - Pearson's correlation coefficient) was modeled as a function of study, psychological subdomain, and domain.

   ROI-based and whole brain searchlight
   Existing parcellations were used for ROI-based analyses.
   Voxel-wise statistics were used.
   FDR correction was used.

   Connectivity analysis was not performed.
   Graph analysis was not performed.

   For multivariate models, the independent variables comprised dissimilarity matrices (1 - Pearson's correlation coefficient) estimated on data from all subjects (n = 270). Feature extraction was done in three ways: using local searchlights in the medial frontal cortex (MFC), using a priori ROIs in the MFC (Vogt parcellation), and using a set of ROIs that spans the whole brain (Brainnetome atlas). No dimension reduction was performed. RSA-based models were estimated using least squares regression. Partial Least Squares regression was also used to predict psychological domains from patterns of brain activity. Inferences were made on parameter estimates using bootstrap and Monte Carlo methods.