Supporting Information

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Affective vs. Sensory Aspects of Pain in dACC

If "pain" is the term most closely associated with dACC activity, what does this finding suggest about the dACC's function? Is it a dedicated physical pain module? One prominent account of dACC suggests that it is involved in the affective, but not the sensory, aspect of pain processing (12). This account proposes that the dACC supports the distressing part of pain but is not involved in tracking the location or intensity of the pain inputs. Lesion data from humans and animals support this claim (43–45). Moreover, animal research has shown that individual neurons within the dACC have almost no stimulus localization information (46–48). Neurosynth results support this dissociation as well. In addition to term-based reverse inference maps, Neurosynth has broader topic-based maps that use a collection of related terms and weights them by their centrality to the topic.

There are two pain-related topics in the database. For one of these topics (topic no. 80), the top five terms are a mix of generic and more affective pain words ("pain," "painful," "stimulation," "chronic," "noxious"). For the other (topic no. 131), the top five terms are more focused on the sensory aspects ("somatosensory," "stimulation," "tactile," "touch," "primary"). Many terms are common to both topics ("pain," "painful," "stimulation," "somatosensory," "nociceptive," "sensory," "perception," "primary," "sensation"), but the topics are weighted differently. It is thus of note that the reverse inference map for the somatosensory-focused pain topic does not include activity in the dACC or anterior insula (AI) but instead shows effects in the somatosensory cortex and posterior insula. In contrast, the more affectively focused pain topic includes both the dACC and AI.

Paracingulate Sulcus

There is substantial sulcal variability within the dACC. Although the dACC was historically assumed to consist of the cingulate gyrus and the cingulate sulcus, which sits above it, Paus et al. (49) reported that a second sulcus, the paracingulate sulcus (PCS), is present in a subset of the population and thus extends the dACC further in the dorsal direction. This possible additional sulcus is relevant because, for some individuals, the ventral portion of the SMA/pre-SMA (Fig. 1) may actually be the PCS. The critical question, then, is whether effects we have designated as outside the dACC (e.g., the maximal point of forward inference for the term "dACC"; coordinates 0, 18, 49) might be in the dACC after all.

There is no way to definitively rule out this possibility in the current study. Neurosynth doesn't have coding for individual participant morphology. Moreover, almost no fMRI studies account for these individual differences. The vast majority of fMRI studies overlook most individual differences in neuroanatomy and depend on the probabilistic neuroanatomy averaged across a group of participants and then on standard atlases that typically don't take these individual differences into account. Even if we knew definitively that observed effects for terms like "dACC," "executive," and "conflict" were from PCS, the current data would still constitute strong data that the majority of the dACC (i.e., the cingulate gyrus and cingulate sulcus) is selective for pain over the various other accounts of dACC function.

However, we think it is unlikely that the Neurosynth results observed in the ventral SMA/pre-SMA were really PCS effects. The statistic typically used to report PCS prevalence is the percentage of individuals who have a PCS of any kind in at least one hemisphere. Across six MRI studies, ∼72% of participants met this criterion (42, 49–53). However, three factors reduce the likelihood that effects observed in the relevant studies in the Neurosynth database are PCS, rather than SMA/pre-SMA.

First, functional activations in this region from individuals with unilateral PCS are likely only resulting from actual PCS 50% of the time (and SMA/pre-SMA the other 50% of the time). Second, there are two structural forms of PCS. The "prominent" form extends through the entire dACC region; however the "present" form begins in the rostral ACC and ends near the anterior border of the dACC. Thus, only the prominent variant of the PCS covers the region in the ventral SMA/pre-SMA under consideration here. Finally, men are significantly more likely than women to have unilateral or bilateral PCS. This gender difference is of consequence because, across PCS morphology studies, the samples are biased toward more males (60%) whereas, in the Neurosynth studies relevant here (e.g., those using the term "dACC"), the samples averaged only 48% male. Thus, population estimates from the morphology studies overestimate the prevalence of the PCS in our Neurosynth sample.

To better estimate the true likelihood that effects in the region we have labeled ventral SMA/pre-SMA are actually from PCS activations, we used data, from a large study ($n = 171$) by Yücel et al. (42), that provide all of the relevant cross-tabulations on how many subjects have prominent or present PCS unilaterally or bilaterally or are missing it altogether. Starting a bit higher than PCS studies in general, 89% of individuals in this study have at least one unilateral PCS of some kind. However, only 60% of participants have prominent PCS, the only form that could produce the activations in question. Moreover, only 16% exhibit bilateral prominent PCS, with 32% showing left unilateral prominent PCS and 12% showing right unilateral prominent PCS. Given that unilateral prominent PCS contribute only a 50% probability of producing observed midline effects, these three variants (bilateral, left unilateral, and right unilateral) suggest a 38% likelihood of observed ventral SMA/pre-SMA effects actually coming from the PCS [i.e., 16% + 0.5 × (32% + 12%)].

Finally, men were overrepresented in this sample (58%) and were significantly more likely to show evidence of at least unilateral prominent PCS than women (68% to 50%). After computing the reduced contributions from unilateral prominent PCS, men and women showed 43.5% and 31% likelihoods, respectively, of producing ventral SMA/pre-SMA effects from the PCS. Adjusting for the gender differences across research populations suggests that, in our Neurosynth sample, there is only a 37% chance [i.e., (male: 43.5% × 48%) + (female: 31% × 52%)] that these effects resulted from PCS tissue and a 63% chance that effects in the region in question came from the SMA/pre-SMA.

Additionally, these six morphology studies (42, 49–53), including the one by Yücel et al. (42), have indicated the existence of a PCS that is left-lateralized. Across these studies, about 35% of participants showed evidence of a prominent PCS in only the left hemisphere whereas only 17% of participants showed evidence of a prominent PCS in only the right hemisphere. If effects we have labeled as SMA/pre-SMA were really PCS, one might expect them to be left-lateralized. Instead, effects tend to either be cleanly bilateral or somewhat right-lateralized.

Across the thousands of participants in the studies examined from the Neurosynth database, a nontrivial number undoubtedly have PCS in the location we have labeled SMA/pre-SMA. Nevertheless, for the reasons given in this section, we think that the effects we observed in this region can more confidently be attributed to the SMA/pre-SMA than to the PCS.

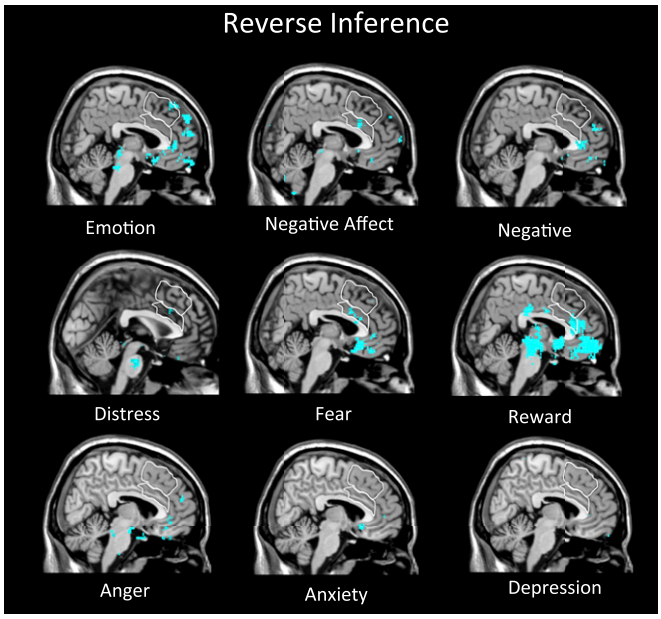

Fig. S1. Neurosynth reverse inference maps for emotion-related terms. Distress-related terms, including "negative affect," "distress," and "fear" yield reliable reverse inference effects in the dACC (but not terms such as "emotion," "negative," "anger," "anxiety," or "depression"). Maps use Neurosynth's standard FDR criterion of $P < 0.01$.

Table S1. For each term used in analyses, the number of studies within the Neurosynth database (as of 6/15/15)

Term	No. of studies
Amygdala	1,158
Anger	68
Anterior cingulate	1,552
Anxiety	288
Auditory	1,004
Basal ganglia	389
Cognitive	2,474
Cognitive control	377
Conflict	246
Control	2,781
dACC	87
Depression	344
Detection	485
Distress	53
Effort	137
Emotion	699
Error	326
Executive	531
Fear	272
Hippocampus	806
Inhibition	432
Motor	1,910
Negative	1,076
Negative affect	60
Noxious	85
Pain	410
Painful	158
Posterior cingulate	677
Pre SMA	105
Reward	560
Salience	222
Somatosensory	534
Stop signal	64
Stroop	162
Supplementary motor	521
Tactile	163
Task relevant	140
Thalamus	725
Visual	2,347
Working memory	815