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VIEWPOINT

Inflammatory bowel disease: perspectives from cingulate cortex in the first brain

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Abstract
The article by Agostini et al. (2013) in this issue of Neurogastroenterology and Motility evaluated patients with Crohn's disease (CD) for volumetric changes throughout the brain. They observed decreased gray matter volumes in dorsolateral prefrontal cortex and anterior midcingulate cortex (aMCC) and disease duration was negatively correlated with volumes in subgenual anterior cingulate (sACC), posterior MCC (pMCC), ventral posterior cingulate (vPCC), and parahippocampal cortices. As all patients were in remission and suffered from ongoing abdominal pain, this study provides a critical link between forebrain changes and abdominal pain experience independent of active disease and drug treatment. The aMCC has a role in feedback-mediated decision making and there are specific cognitive tasks that differentiate aMCC and pMCC that can be used to evaluate defects in CD. The sACC is an important area as it has impaired functions in major depression. As depressive symptoms are a feature in a subset of patients with active inflammatory diseases including IBD, treatment targeting this subregion should prove efficacious. Finally, vPCC has a role in ongoing self-monitoring of the personal relevance of sensory stimuli including visceral signals via sACC. This pathway may be interrupted by vPCC atrophy in CD. Cingulate atrophy in CD leads to targeting chronic pain and psychiatric symptoms via cingulate-mediated therapies. These include psychotherapy, guided imagery and relaxation training, analgesic dosages of morphine or antidepressants, and hypnosis. Thus, a new generation of novel treatments may emerge from drug and non-traditional therapies for CD in this formative area of research.

Keywords *cognition, depression, midcingulate cortex, pain, posterior cingulate cortex, subgenual anterior cingulate cortex.*

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INTRODUCTION

It is well known that the second brain in the gut[1] interacts with the first brain in the cranium. Indeed, early studies[2,3] showed that electrical stimulation of anterior cingulate cortex (ACC) in the first brain induces ulcers and lesions therein block ulcers caused by restraint stress in rats. The links between cingulate volumetrics and Crohn's disease (CD) patients in remission were explored in an important study by Agostini and colleagues[4] in this issue of *Neurogastroenterology and Motility* and the findings cement further the close ties in the Brain-Gut axis.

This article evaluated patients with CD in remission for 12 months and not receiving corticosteroids, biologics, and/or psychotropic medications. This patient group and healthy controls underwent structural MRI followed by voxel-based morphometry (VBM) to identify regional differences in gray matter (GM) volumes in the whole brain. The CD patients exhibited decreased GM volumes in dorsolateral prefrontal cortex and anterior midcingulate cortex (aMCC) and

disease duration was negatively correlated with GM volumes in subgenual ACC (sACC), posterior MCC (pMCC), ventral posterior cingulate cortex (vPCC), and parahippocampal cortex. As all patients were in remission and suffered from abdominal pain for at least 6 months, this study provides a critical link between forebrain changes and abdominal pain experience independent of active disease and drug treatment.

The literature surrounding the role of limbic cortex (i.e., cortex that directly regulates autonomic functions and stores emotional memories) in inflammatory bowel disease (IBD) including CD suggests there are three areas that need a more detailed consideration of the structural and functional links with the first brain; organization of cingulate cortex according to structure/function subregions, interactions with structures that conduct visceral nociceptive information to and from the gut, and impairments of parts of cingulate cortex that are associated with stress, anxiety, and depression. These considerations naturally lead to new and cingulate-focused strategies for treating pain and psychiatric symptoms in IBD.

Cingulate organization and functions

The term 'anterior midcingulate cortex' used by Agostini *et al.*[4] will be a new one for most gastroenterologists who still work with the concept of ACC proposed by Brodmann[5] more than 100 years ago. As no imaging study has ever shown a function common to this large stretch of limbic cortex, it was necessary to seek the structural and functional organization in a model with descriptive and predictive value. This was accomplished by introducing the midcingulate concept. This region has been verified with a wide range of methods showing that MCC is not a part of ACC, but rather a qualitatively unique region[6] and the Agostini *et al.*[4] study once again shows the value of this neurobiological model of cingulate cortex. While investigators still refer to 'BA24' when locating sites of atrophy, Brodmann did not identify an aMCC and area a24' is not a Brodmann area. Let us consider sACC, aMCC, pMCC, and vPCC in which this article observed either atrophy or a correlation with disease duration to see what functions and tests might be of value to further assessing symptoms and treatment of CD. Figure 1 provides a co-registration of the sites reported by Agostini *et al.*[4] to cingulate cortex in a postmortem case.[7] The one aMCC site and area 8 site of atrophy are outlined with black and the four sites associated with disease progression are outlined with red.

The aMCC had reduced volume in the CD patients. This region has a role in feedback-mediated decision

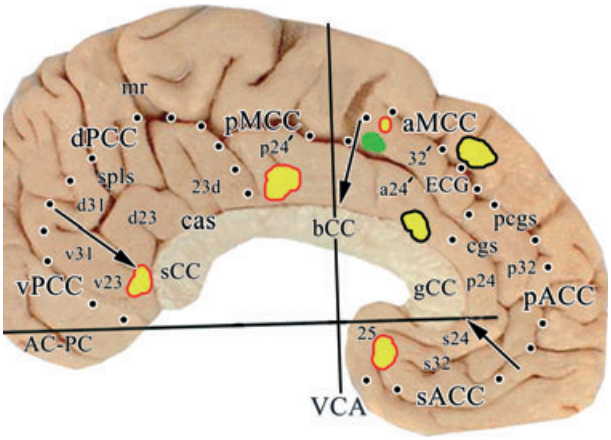

Figure 1 A postmortem case with cingulate regions (ACC, MCC, PCC) outlined with dots and subregion borders marked with arrows. Each area was determined from histological sections and the borders are not shown for simplicity. The sites of interest from the Agostini *et al.*[4] study were co-registered to this brain with atrophy in yellow with black highlight in aMCC, while those negatively correlated with disease duration in sACC, pMCC, and vPCC shown in yellow with red highlight. Further histological details can be found in Vogt.[54] Davis *et al.*[27] reported atrophy in IBS in area 32′ shown here in green. As IBS has no evidence of gut inflammation, this conjunction of results may indicate a site that is vulnerable to psychogenic mechanisms in both IBS and CD. Abbreviations: AC-PC, anterior-posterior line; cas, callosal sulcus; cgs, cingulate sulcus; gCC, bCC, sCC, genu, body, and splenium of the corpus callosum, respectively; ECG, external cingulate gyrus; mr, marginal ramus of the cingulate sulcus; pcgs, paracingulate sulcus; VCA, vertical plane at the anterior commissure.

making that is tested with various forms of Stroop or flanker interference tasks.[8] Enriquez-Geppert *et al.*[9] used conflict manipulated by congruency of flanking stimuli relative to a target (congruent *vs* incongruent) and motor inhibition by within-trial response change (keep response *vs* stop-change) and showed that high conflict on incongruent trials activated pMCC and stop-change trials modulated aMCC. Thus, there are now specific cognitive tasks that differentiate aMCC and pMCC and these can be used to evaluate specific cognitive defects in CD. Moreover, the aMCC is also responsive during pictures and scripts that generate fear[7] and fear may play a role in the aversive nature of CD symptoms. Therapies that seek to reduce fear and anxiety may be of particular value in CD as noted below.

The sACC had a site with volumetric changes that negatively correlated with disease duration and Agostini *et al.*[4] refer to their study as preliminary because they did not evaluate participant's emotional functions. This is an extremely important area for future research as this cingulate subregion stores negative emotions[10] and has impaired glucose metabolism[11] and emotional processing[12] in major depression. Furthermore, electrical stimulation therein alleviates depression[13] and

ACC undergoes atrophy in major depression in carriers of the short allele of the serotonin transporter.[14] Since Hauser *et al.*[15] reported anxiety and depression in active IBD including CD, but not during remission, there may be a persistent underlying change in limbic cortex that is too small to generate measurable psychiatric changes reflected in their study instrument (Hospital Anxiety and Depression Scale).

The vPCC has a role in ongoing self-monitoring of the personal relevance of sensory stimuli.[16] A six-stage model whereby vPCC extracts personally relevant information from an ongoing stream of sensory information has been proposed[17] and this pathway may be interrupted by atrophy in vPCC in CD. This site could serve as a target for therapeutic intervention; particularly because it is interconnected with sACC in establishing self-relevance and emotional content of sensory experience likely including visceral afferents.

Visceral and cutaneous pain and cingulate cortex

Visceral nociceptive afferents terminate in the spinal cord which transmits this information to the midline thalamus[18] and from there to cingulate cortex.[19] Christianson *et al.*[20] observed that acute gut inflammation associated with infections of the GI tract generate peripheral nociceptor and spinal sensitization and result in visceral hyperalgesia. Enhanced release of neuropeptides from primary sensory nerve endings and mast cells has been implicated in the sensitization of primary afferent pathways which in turn can result in morphological changes in sensory and motor innervation of the colon.[21] Acute noxious visceral stimuli more frequently activate ACC[10] than MCC as does anticipation of noxious retrosigmoid distension in irritable bowel syndrome (IBS[22]). CD patients report significant pain during acute flares, and a substantial portion of patients with quiescent CD continue to report pain. Thus, pain in IBD more often than not persists despite resolving inflammation and achieving clinical remission[23] and may be associated with structural changes in ACC and MCC.

May[24] reviewed brain atrophy in phantom pain, chronic back pain, irritable bowel syndrome, fibromyalgia, and headache and found that brain atrophy for each overlaps in cingulate cortex. To this list of ACC/MCC-vulnerable areas in chronic pain must be added CD. May[24] concluded that GM changes in chronic pain patients are the consequence of frequent nociceptive input and should be reversible when pain is adequately treated. The central role of MCC in acute pain was emphasized by Erpelding *et al.*[25] who used VBM in healthy controls to show that interindividual variations in cutaneous sensations are linked to different parts of MCC with increased warm detection threshold correlated with thinning in aMCC and increased heat pain sensitivity correlated with thickening in pMCC. These findings raise a number of issues. Firstly, are there preexisting, interindividual cortical changes in visceral pain as well as cutaneous sensitivities before disease onset in CD. It may be possible that a longitudinal study of individuals before the onset of CD could parse these phenomena. Secondly, there may be links between cutaneous and visceral cortical impairments that have yet to be analyzed given the conjunction of findings between the Agostini *et al.*[4] and Erpelding *et al.*[25] studies. For example, are visceral pain sensitivities associated with changes in cutaneous receptive fields such as enhanced caudal body sensations? This latter suggestion is supported by the fact that both visceral and cutaneous nociception are transmitted by the spinothalamic tract to the midline thalamus[18]; the latter of which projects to ACC and MCC.[19] Finally, Kwan *et al.*[26] observed that aMCC is not activated by urge or pain generated by rectal distension in IBS compared with healthy controls and Davis *et al.*[27] showed atrophy in area 32′ in IBS (green site in the figure). As IBS is not associated with inflammation and has a central-predominant (psychogenic) etiology, the conjunction of the Davis *et al.*[27] and Agostini *et al.*[4] sites in aMCC area 32′ suggests that CD may have a psychogenic vulnerability not previously appreciated.

Gut inflammation and stress evoke cingulate-mediated psychiatric illness

Agostini *et al.*[4] pose an immune system hypothesis to explain aspects of CNS disruption in their patients. Animal studies report increased cytokine levels in the brain after peripheral inflammatory challenges, suggesting a local synthesis of cytokines as part of a systemic immune response during active disease and peripheral inflammation interacts with the brain via humoral and neural pathways.[28–30] Circulating cytokines can cross the blood-brain barrier to propagate inflammatory signals by activating endothelial cells, perivascular macrophages, and glial cells.[31]

Importantly, cytokines may contribute to behavioral alterations that resemble depression as manifested in medically healthy individuals. Capuron *et al.*[32] compared interferon-alpha induction of depressive symptoms in healthy and depressed patients and there was considerable overlap in symptom expression between cytokine-induced depression and idiopathic depression. Differences in isolated symptom domains suggested that cytokines may preferentially target

neurocircuits relevant to psychomotor activity (a key cingulate function), while having a limited effect on cognitive distortions regarding self-appraisal. In terms of CD, this may reflect a critical distinction in sACC and vPCC functions relating to inflammatory-mediated responses.

Volumetric changes may predate CD onset. Graff *et al.*[33] suggest that depression can significantly antedate the diagnosis of IBD at a higher rate than expected from comparative base rates, anxiety and depressive symptoms are elevated during periods of active disease, and psychiatric issues arise in the context of potential adverse effects of medications including corticosteroids. Once again, we turn to cingulate cortex where it has been reported that sACC glucose metabolism correlates with cortisol levels in monkeys in familiar or threatening contexts.[34] A review by Rampton[35] of animal models and acute human studies reported that experimental psychological stress activates mast cells that sensitizes gut nociceptors, increases epithelial permeability, increase access of luminal bacteria to the lamina propria, and local activation of the immune response with release of cytokines. An excellent review by Haroon *et al.*[36] provides details about the mechanisms linking gut inflammation to the development of depressive symptoms.

The association of IBD and psychiatric illnesses is well known.[37] Many studies demonstrate the advantages of psychotherapeutic treatment, including faster recovery, improved quality of life, and reduced health care use. In a study of IBD adolescent patients, Childhood Depression Inventory scores are related to disease activity, lack of interest and energy, and decreased appetite.[38] Finally, many studies demonstrate correlations between IBD and psychiatric illnesses in adults including depression and anxiety,[39] panic disorder,[40] and suicidal thoughts[41] and atrophy of sACC may contribute to all of these symptoms. Finally, anhedonia is a core feature of major depression and Keedwell *et al.*[42] examined its neural basis by correlating anhedonia severity with responses to personally relevant happy and sad stimuli. Responses to personally relevant, rewarding stimuli in anhedonically depressed individuals showed an abnormal increase in sACC. It appears that anhedonic individuals attend more closely to rewarding stimuli in an attempt to generate a happy mood and this pathway may be blocked by sACC atrophy in CD.

Cingulate-targeted treatment of IBD symptoms

Targeting cingulate cortex for treatment of IBD is a relatively new strategy and is supported by the findings of Agostini *et al.*[4] and others cited above. Although there are still few objective imaging studies to validate the efficacy of non-traditional approaches in cingulate cortex, some options are now apparent and require further consideration.

1) A prospective study of patients with CD showed a greater reduction in inpatient hospital stay and number of days off sick in those given psychotherapy and relaxation training with corticosteroids than in those given steroid therapy alone.[43] Although the brain target of therapy has not been assessed with imaging, this may provide a means of recalibrating sACC and vPCC changes in CD.
2) Treating pain symptoms early may be critical to reducing atrophy in sACC and vPCC in CD given the role of vPCC in assessing personal relevance and sACC in storing memories with negative valence.[24] Younger *et al.*[44] showed that analgesic dosages of morphine in patients with chronic low back pain change brain structure in a longitudinal MRI study. Increased GM volume was detected in pregenual ACC and aMCC and a dose-correlated volumetric increase occurred in right vPCC. Follow-up scans conducted ~5 months after drug cessation demonstrated that many of the morphine-induced changes persisted.
3) Mizrahi *et al.*[45] used guided imagery with relaxation training to improve anxiety and quality of life in patients with IBD; however, the active central nervous system sites of therapeutic intervention are not known.
4) A review by Streeter *et al.*[46] suggested that yoga practices reduce allostatic load in stress response systems to restore optimal homeostasis. Depression and chronic pain are exacerbated by stress, have low heart rate variability, and show symptom improvement in response to yoga-based interventions. The Agostini *et al.*[4] study showed a correlation between atrophy and disease duration in vPCC and Khalsa *et al.*[47] reported that posterior cingulate blood flow increases with meditation suggesting a means of reversing the vPCC atrophy in CD.
5) Hypnotherapy has been employed in pilot studies in IBD,[48] but no functional imaging is available. Mawdsley *et al.*[49] reported that hypnosis significantly decreased pulse rate, reduced median serum interleukin-6 concentration, rectal mucosal release of substance P, histamine and interleukin-13, and blood flow. Although these studies did not assess pain relief, hypnosis is used to relieve pain associated with major surgeries and its clinical effect is likely mediated by ACC projections to the periaqueductal gray.[50] This approach provides an important

alternative to treating pain and gut inflammation in IBD and functional imaging and connection studies are needed.

6) Goodhand *et al.*[51] showed that antidepressants used to treat concomitant mood disorders in IBD reduced relapse rates, use of steroids, and endoscopies 1 year after treatment. This effect is likely mediated by sACC because drug-responders taking paroxetine or fluoxetine show increased blood flow in sACC.[52,53]

In conclusion, the Agostini *et al.*[4] article raises specific mechanisms of disease progression in CD and suggests a number of cingulate targets that can be addressed in future efforts to alleviate pain and psychiatric symptoms during active disease or remission. Pending objective imaging assessments of many potential therapies, these should lead to new approaches to targeting cingulate cortex in CD and more generally IBD.

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