Journal Club

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Anticipatory Brain Activity in Irritable Bowel Syndrome

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Review of Berman et al. (http://www.jneurosci.org/cgi/content/full/28/2/349)

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders. It is considered a chronic functional disorder because of the lack of an identifiable structural or biochemical basis. However, functional brain imaging studies have identified abnormal brain responses to visceral stimuli (such as rectal distention) in IBS patients (for review, see Ohman and Simren, 2007), suggesting that IBS involves a dysregulation of the communication between the central and enteric nervous systems. Furthermore, patients suffering from functional pain disorders often show symptom-related anxiety, and this may affect their ability to anticipate and cope with impending pain stimuli. Therefore, expectation-related brain responses to potentially painful stimuli may contribute to IBS symptoms.

A recent study by Berman et al. (2008) suggests that IBS patients have a deficit in corticolimbic inhibition, and this may be associated with symptom-related anxiety and hypervigilance. The authors propose a mechanism through which deficient coping mechanisms lead to dysfunctional homeostatic and motivational–affective processing of expected and actual visceral sensations. Normally, a homeostatic afferent processing network is downregulated during anticipation, and an antinociceptive network is activated during stimulus delivery, which leads to a higher pain threshold. The former network includes areas such as insula, anterior cingulate, amygdala, and dorsal brainstem, whereas the latter network involves the right lateral orbital frontal cortex and supragenual anterior cingulate cortex (ACC).

Using a cued rectal distention stimulus paradigm, brain activity was examined under six conditions: rest, cue, mild/moderate/sham rectal distention, and rating. Compared with controls, IBS patients showed less anticipatory inactivation of the homeostatic afferent processing network, and more extensive increases in dorsal ACC and brainstem activity during distention [Berman et al. (2008), Fig. 2 (http://www.jneurosci.org/cgi/content/full/28/2/349/F2)]. Further analysis showed that less anticipatory inactivation of specific brainstem areas, the locus ceruleus complex and parabrachial nucleus, correlated with lower discomfort thresholds, higher negative affect, and greater activation of bilateral rostral ACC and right lateral orbital frontal cortex during rectal distention. The authors concluded that higher anxiety in IBS patients leads to overactivity in the arousal circuit and thereby failure to trigger coping mechanisms during anticipation of pain via corticolimbic inhibition.

Although the interpretation suggested by Berman et al. (2008) may be plausible in light of a proposed model of IBS implicating ineffective cortico-limbic-pontine inhibition of visceral inputs within the homeostatic processing network (Mayer et al., 2006), several other studies have provided conflicting findings, both in terms of expectation-related activity and IBS-related rectal distention activity. For instance, a seminal paper by Ploghaus et al. (1999) found that in healthy individuals, brain responses to anticipation and actual painful experience could be discriminated anatomically. Anticipation was associated with activation of more rostral regions of the ACC and insula, whereas the actual pain response activated the caudal ACC and mid-insula. This finding suggests that a specific cortical network is activated during anticipation. These results directly contradict the findings of Berman et al. (2008), suggesting that BOLD (blood oxygen level-dependent) activity increases rather than decreases during anticipation in rostral ACC and insula. Normal anticipatory brain responses must be elucidated before we can interpret differences in patient populations.

In addition to conflicting with previous expectation-related results in healthy subjects, the brain responses during rectal distention found by Berman et al. (2008) conflict with some previous findings in IBS patients. For instance, Kwan et al. (2005) used a percept-related functional magnetic resonance imaging (MRI) design to explore brain activity related to the feeling of the urge to defecate and pain perception. Compared with controls, IBS patients showed an absence of activation

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in right ACC and dorsal anterior insula, suggesting abnormal interoceptive processing. These findings were supported by a recent structural MRI study that found cortical thinning of these ACC and insula regions in IBS (Davis et al., 2008). Together, these findings contrast with the present study, in which greater activity was found in dorsal ACC and brainstem, suggesting increased ascending afferent information. Moreover, Kwan et al. (2005) found that IBS patients exhibited increased activity in primary somatosensory cortex, medial thalamus, and hippocampus, whereas the present study did not include these areas in their region of interest definitions. Whole-brain analysis may be more appropriate to provide a more complete account of this complex issue.

Although the current study is a valuable contribution toward our understanding of IBS, certain aspects of the protocol design limit the interpretation of the results and could be improved in subsequent studies. First, the anticipation period, which was a critical feature of the study, is quite short when compared with the stimulation periods. This is statistically problematic because there is a substantial imbalance of statistical power (one data point for anticipation vs five data points for stimulation). Furthermore, because the hemodynamic response function for a brief stimulus normally extends for ~12 s, even if the expectation-related brain activity occurred within the 3 s repetition time, this signal would bleed into the subsequent distention period. A more reasonable design would have been to use a longer anticipation period to properly capture the full anticipatory experience and its resultant hemodynamic response, such as those used previously: for example, Porro et al. (2003) used a 42 s anticipation period preceding painful stimuli.

A second problem with the protocol design in Berman et al. (2008) is that the interpretation of the 25 mmHg condition is obscured by the fact that this pressure level straddles the discomfort thresholds of controls versus patients. This is problematic because some patients may have experienced this pressure level as uncomfortable, whereas it is highly unlikely that any controls experienced discomfort. Other studies have used a more refined method of defining pressure levels individually, on a subject-by-subject basis.

In conclusion, the authors provide important evidence relating symptom-related anxiety in IBS patients to abnormal cortical coping responses. These alterations may contribute to the pathology and persistence of this challenging disorder and may also hold the key to refining prospective treatment options. However, because of the diversity in methodology and results from previous studies, the current findings need to be interpreted cautiously.

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