Alterations in Brain Functional Connectivity in an Animal Model of Colitis

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Introduction

The brain-immune system relationship is a complex one with evidence that alterations in one elicits changes in the other and vice versa. Patients with Ulcerative Colitis (UC) have been shown to have increased psychological stress which involves an integration of both subcortical and cortical brain structures. A previous fMRI study in UC patients reported significantly reduced BOLD signal in UC patients vs. controls in the amygdala, thalamic regions, and cerebellar areas(1). In this current project, we seek to determine if brain changes in relevant responsive brain areas previously shown in UC patients also show activation differences in an animal model of colitis.

Methods

Sprague Dawley rats received 20 mg of intracolonic trinitrobenzene sulfonic acid and MR images were acquired in a 4.7T magnet 7 days following induction of colitis. The MR imaging consisted on resting state scan and an anatomical image for reference-to-atlas registration. Neuropathic & Inflammatory PCR arrays were used to discover the altered genes expression associated fMRI brain activity in 4 brain regains such as hippocampus (HC); thalamus (Thal), amygdala (amyg) and periaqueductal gray (PAG).

Results and Discussion

Seed regions used in correlation analysis were selected based on results for patients with IBS and UC. These included the prefrontal cortex (PFC), anterior cingulate cortex (ACC), PAG, somatosensory cortex (SMS Ctx), thal, insular cortex (Ins Ctx), HC, and amyg. Control and colitis groups showed significant increases and decreases in functional connectivity in the ACC, PFC, PAG and SMS Ctx, with overlapping patterns of connectivity and some regions varying between these conditions (Fig. 1). Of note is the lesser functional connectivity with the PFC with TNBS treatment, an increased connectivity with SMS Ctx with colitis and reduced functional connectivity in PAG. Statistical comparison maps show differences in functional connectivity with each seed region of interest which spans many distributed brain regions. Our preliminary data also showed that there were several genes with altered expression after 7 days TNBS colitis vs control rats (5:5) via Neuropathic & Inflammatory PCR array analysis. These altered genes expression associated with fMRI's brain regions activity.

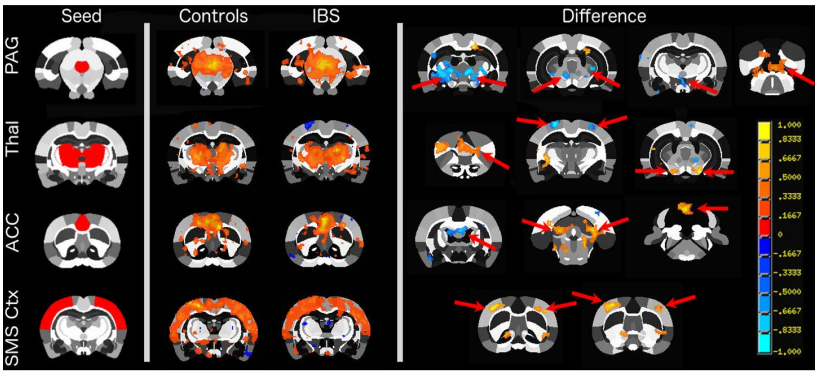

Figure 1. Seed specific alterations in limbic cortical networks induced by IBS treatment. PAG: IBS significantly reduced functional connectivity between PAG and mesencephalic reticular formation, ventral tegmental area (VTA), posterior hypothalamus. Thal: IBS increased functional connectivity between Thal and PFC and VTA, whereas the SMS Ctx showed reduced connectivity with Thal. ACC: functional connectivity between ACC and medial anterior thalamic region was reduced by IBS treatment, while increased connectivity was observed in superior colliculus and cerebellum. Statistical comparison is for each condition > 0 or IBS vs control for clusters larger than 40 voxels ($p<0.05$, uncorrected).

Conclusions

Colonic inflammation elicits changes in brain connectivity in several autonomic relevant brain regions that in turn induce large scale alterations of topological indices of network connectivity. The global and local network analysis did not show any significant differences between control and colitis rats, although there was a trend towards greater strength of connectivity in colitis vs control rats. This may suggest differences in functional connectivity may not be associated with a broader and robust change in functional network topology.

These results may help to further understand alterations in functional brain connectivity that occurs in patients with UC associated with certain gene expression. Furthermore, differences in functional brain connectivity could provide significant and relevant biomarkers of changes in the brain-gut axis that are present in patients with UC.

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References

[1] Agonstini, *et al.*, Inflamm Bowel Dis. **17,**1759-1777 (2011).