

OPEN PEER REVIEW REPORT 2

Name of journal: Neural Regeneration Research

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Title: Gut microbiome: implications for neurogenesis and neurological diseases

Reviewer's Name: Bruno P. Imbimbo

Reviewer's country: Italy

COMMENTS TO AUTHORS

This manuscript reviews the present knowledge on the link between gut microbiota and neurogenesis and the potential mechanisms underlying this relationship. This is an important topic for the clinical potential on pharmacological and probiotic intervention on gut microbiota to treat several neurological diseases in which neurogenesis plays a crucial role. I have a few points to put on the attention of the Authors:

Major Points

1. Authors should mention that excessive calorie intake accelerates the age-dependent decline of neurogenesis, while calorie restriction and physical exercise have the opposite effect and that these effects can be mediated by gut microbiota (Cavallucci et al. *Nutrients and neurogenesis: the emerging role of autophagy and gut microbiota. Curr Opin Pharmacol* 2020; 50: 46-52).
2. Authors should mention the important recent findings that in mice intestinal bacteria maintain adult enteric nervous system through TLR2-induced neurogenesis (Yarandi et al. *Intestinal Bacteria Maintain Adult Enteric Nervous System and Nitroergic Neurons via Toll-like Receptor 2-induced Neurogenesis in Mice. Gastroenterology* 2020; 159: 200-213).
3. Authors may also mention that in mice chronic stress may impair the neurogenic effects of fluoxetine, a selective serotonin reuptake inhibitor, through an effect on gut microbiota (Siopi et al. *Changes in Gut Microbiota by Chronic Stress Impair the Efficacy of Fluoxetine. Cell Rep* 2020; 30: 3682-3690).
4. When speaking on fecal microbiota transplant, Authors may mention the pilot AMBITION study in 5 Alzheimers patients (NCT03998423) recently interrupted because of SARS-CoV-2 has been detected in fecal material.

Minor Points

5. On page 8, please provide a reference to support the sentence "microglia-mediated pruning are also proposed to be involved in Alzheimer's disease".
6. On page 9, please provide a reference to support the sentence "Clostridium butyricum, a butyrate-producing probiotic, significantly improved neurological deficits and neuronal degeneration in a mouse study of traumatic brain injury".
7. On page 9, I believe it should be "Yang et al,..." , not "Liu et al,..." .
8. On page 10, differently, from what stated by the Authors, study of Reference # 41 was not performed in germ free animals. In addition, Authors should be more precise stating that while *Bifidobacterium breve* 6330 influenced BDNF in normal animals, it had no significant effect on BDNF in those which were maternally separated".
9. On page 14, when speaking of the study on probiotic VSL#3, please specify that it was in rats.