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Title: Bowel motor dysfunctions associated with digestive and extra-digestive diseases: morphological changes of intestinal epithelial barrier and neuromuscular compartment as a common feature?

Reviewer's code: 02549885

1. The entire manuscript writes about bowel functional (bowel motor and secretory functions), and the core tip section emphasizes bowel motor and secretory functions. The authors should explain why you write only bowel motor dysfunctions without mentioning secretory functions in the title section?

As suggested by the Reviewer, the title has been changed to "Bowel motor and secretory dysfunctions associated with digestive and extra-digestive diseases: morphological changes of intestinal epithelial barrier and neuromuscular compartment as a common feature?".

2. Studies shown that changes in the intestinal microbiota could cause bowel functional disturbances, but why the intestinal microbiota effect has not been analyzed in this manuscript.

We fully agree with the Reviewer, since several evidence from the literature suggests that changes in gut microbiota composition could promote the development of functional bowel disorders [Cryan et al., 2019 Lancet Neurol. S1474-4422(19)30356-4; Enck et al., 2018 Ann Nutr Metab. 72 (4) :296-306; Nagao-Kitamoto et al., 2016 Intest Res. 14 (2) :127-38; Nouvenne et al., 2018 Acta Biomed. 89 (9): 47–51; Rajilić-Stojanović et al., 2011 Gastroenterology 141(5) :1792-801; Ringel, 2017 Gastroenterol Clin North Am. 46(1) :91-101; Simre´n et al., 2013 Gut. 62(1) :159-76; Quigley et al., 2013 Gastroenterol Hepatol 9(9) :560-9]. However, the main purpose of the present review was to provide an overview of available knowledge on the morphological and molecular changes

occurring in intestinal epithelial barrier and enteric neuromuscular compartment associated with digestive and extra-digestive diseases. In addition, we think that the impact of intestinal microbiota alterations in bowel functional disturbances in patients with digestive and extra-digestive diseases could represent an interesting topic to widely discuss in an original review article. Indeed, an integrated overview about the relationship between alterations in gut microbiota composition and bowel functional disturbances associated with digestive and extra-digestive diseases is missing. Accordingly, we decided to add a comment about the impact of changes in gut microbiota in bowel functional disturbances in "Conclusions and future perspective" section of the revised manuscript (see page 20 lines 336-343 and page 21 lines 349-350).

3. What's the difference between your review and other reviews in the field of bowel functional disturbances?

At present, most of the available reviews have focused their attention on data regarding morphological and molecular changes occurring in intestinal epithelial barrier (IEB) and neuromuscular compartment, as well as their role in the onset of bowel motor dysfunctions in specific digestive or extra-digestive diseases regarded as distinct pathological entities. However, an overview addressing in a critical and holistic manner the common traits of morphofunctional alterations, shared by these diseases, characterized by heterogeneous ethiopatogenesis, is presently lacking. On this basis, the present review has been conceived to provide a comprehensive and critical overview of available knowledge on the morphological and molecular changes occurring in IEB and enteric neuromuscular compartment in digestive and extra-digestive diseases, such as inflammatory bowel diseases (IBDs), irritable bowel syndrome (IBS), intestinal infections, metabolic syndromes and neuropsychiatric disorders. In addition, our intent was to highlight whether these alterations might represent a common condition underlying the onset/progression of bowel functional disturbances in both digestive and

extra-digestive diseases. This assessment might help to identify novel targets of potential usefulness to develop novel pharmacological approaches for the therapeutic management of such disturbances.