

Format for ANSWERING REVIEWERS

January 16, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript No 5970 -Review.doc).

Title: The Dark side of the Mood: The role of negative affects in the pathophysiology and clinical expression of Irritable Bowel Syndrome (IBS).

Author: Maria Rosaria A. Muscatello, Antonio Bruno, Giuseppe Scimeca, Gianluca Pandolfo, Rocco A. Zoccali

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5970

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers.

Reviewer # 1

(1) Language has been simplified and long sentences shortened.

(2) A brief review on therapeutic targets/approaches for IBS also targeting mood and emotions has been added.

(3) Specific comments:

- Abstract, line 6: "moderate" was changed with "modulate"

- Abstract, lines 10-16 (now lines 8-13): the single sentence, difficult to follow, has been rewritten and divided in more concise statements

- Abstract, line 13 (now line 11): "...associated to in relation to..."? has been corrected

- Review Page 3, lines 5-6 (now lines 4-5): "...and incomplete evacuation and urgency..."? has been substituted with "and altered stool passage (urgency or feeling of incomplete evacuation)"

- Review Page 3, line 7: "...structural biochemical abnormalities..."? It has been deleted, and the sentence has been reformulated also adding supplemental references as suggested by the Reviewer #2

- Review Page 3, lines 12-13 (now line 13): probably: "...health care and /or cultural factors...": corrected, as suggested

- Page 3, lines 15-20: Single sentence; simplify and divide: done

- Page 4, line 3: "...understanding of the pathogenesis...": corrected

- Page 4, line 8 (now page 3, line line 2 from the bottom): "...that the disorder is..." What disorder? IBS? Review and be more precise. The disorder was IBS, this has been specified

- Page 4, line 24 (now line 12): "modulate" instead of "moderate"

- Page 4, lines 4-5 (now line 20): "...In animal models if rodents..."? It was "of" rodents; however, it has been simplified as "in rodent models"

- Page 5, line 21 (now line 3-4 from the bottom): "...disturb the development og GI physiologic maturation."? Consider review. The sentence has been reformulated as follows: "events such as prenatal undernutrition and painful experiences might interfere with GI physiologic maturation"

- Page 5, line 28 (now lines 3-4): "...anger, on the pathophysiology....": corrected

- Page 7, line 8 (now page 6, line 7): "...the rise time..."? and Review Page 7, line 9 (now line 9): "...the recovery function of the response..."? clarify. The sentence refers to objective measures of emotions, and specifically to electrophysiological parameters used to evaluate emotional intensity. We tried to be more explicit adding the following: "...where the last three parameters refer to different aspects of affective chronometry or the time course of emotional responding"
- Page 7, line 16 (now page 6, line 15): "...salient..."? It refers to "emotionally salient stimuli"
- Page 8, line 1-5 (now Page 6, lines 6-9 from the bottom): Not clear, consider review. The sentence has been changed as follows "Both PA and NA can be conceptualized either as a transient state or as a trait, defined as individual differences in general affective level."
- Page 8, last line: Delete "(p. 75)" and Page 9, line 22 (now page 7, Zautra's quotes): Delete "(p. 301)" page numbers have been deleted
- Page 12, lines 12-13 (now page 10, lines 1-2): "...childhood ...in adulthood"? It has been reformulated as "...childhood maltreatment resulted significantly associated with psychopathological outcomes in adult life."
- Acronyms as "ANS" and "ENS have been used
- Page 14, line 18 (now page 12, line 3) : Should be "mediates", not "mediated". Corrected
- Page 16, lines 11-12 (now page 13, lines 12 and followings): What do the authors mean by "smaller hippocampal volume partially mediated the effects..."? The "hippocampal volume" cannot mediate a response; perhaps there is a relation between hippocampal volume and early-life adversity/depression. Explain better. The interesting finding by Rao et al. (2010) in a sample of adolescents at-risk for depression was that smaller hippocampal volume was observed before the manifestation of clinical symptoms. This evidence was particularly strong in those who experienced high levels of adversity during childhood. Thus, the Authors suggested that smaller hippocampal size may be an inherited trait predisposing individuals towards the development of those psychiatric disorders that are triggered or worsened by stress, thus partially mediating the effect of early-life adversity on depression during longitudinal follow-up.

Reviewer #2

- Introduction: We added "new" aspects in the pathophysiology of IBS into the third paragraph of the introduction chapter, and integrated new references, as suggested by the Reviewer.
- Regarding sexual or physical abuse, it has been clarified that it can be a key predisposing factor for the development of IBS, however it is has occurred in only a minority of all IBS patients.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



Rocco A. Zoccali - Professor of Psychiatry
 Department of Neurosciences - University of Messina
 Policlinico Universitario Via Consolare Valeria 1 Messina 98125 - Italy
 Fax: +39-090-695136
 E-mail: rocco.zoccali@unime.it