Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-2024-2262

Reviewer A

My main issue here is the quality of the English. The paper is very difficult to read. I'm not clear if the authors have English as their first language.

Whilst the overall structure is fine, the writing within each section lacks structure and clarity. There are other reasonably contemporary reviews that are better written and this article doesn't really add much to what has already been published elsewhere. This reads like an undergraduate essay not an expert review in a high quality journal

The figures are good.

There is a lot of interesting content here but I'm afraid it does not read well enough for publication.

Reply: Thank you very much for your thoughtful review and valuable comments regarding our manuscript. We have carefully studied the comments and made revisions that we hope will be recognized. The English has been revised (by a professional mother tongue speaker). In this article, we delve into the cough regulatory network, particularly the brain regions and neurotransmission circuits of central regulation, and related aspects such as the body rhythm gut-brain axis. Emphasizing the underlying neural mechanisms leading to cough dysregulation in disease are heterogeneous, affecting personalized treatment for many related diseases and the significance of effective treatments and areas for further. The revised version additionally highlights some clinical aspects and the goal of treatment that suppresses unnecessary coughing (excessive pathologic) without interfering with necessary coughing behavior. In the revised version, we have adjusted part of the structure of the article, especially Part 5 "The quest for effectiveness in treatment", and we have modified errors or misunderstandings to make the review concise, clear, and correct. We have added some content, such as some clinical aspects in Part 5: the clinical significance of cough hypersensitivity and the aspects of cough related to it.

6 Remove 'of diseases' from sentence

Reply: Thank you for your attention to detail. We have modified our text as advised.

Changes in the text: We have deleted "of diseases" in the sentence **(see Page 1, line 5-6)**.

23 I wouldn't start with talking about COVID…. cough can be a sx of a wide range of viruses and underlying conditions (and be a primary condition in itself). I would look at things more broadly here rather than anchoring int subsequent discussion in covid. Was a big deal a few years ago. A lot less so now.

Reply: Thank you for your helpful comments.

Changes in the text: We have modified the focus of this section to ensure attention to a broader range of content. **(see Page 1, line 21-27)**

59 I think reference needs to be made here (I note discussed in detail later..) that cough reflex has peripheral and central components.

Reply: Thank you for your comments. We have modified it to make it more explicit, and we aim to focus on highlighting the role of the central section.

Changes in the text: We have changed "The center can modulate cough in several ways, including altering the perception, location, and quantification of afferent stimuli, mediating cognitive and emotional responses to these, and managing descending pathways. Cough can be reflexively evoked or autonomously triggered, suggesting the existence of multiple regulatory mechanisms that reflect the complexity of cough behavior" to "Cough can be reflexively evoked or autonomously triggered, involving both peripheral and central regulation, that reflect the complexity of cough behavior. The center can modulate cough in several ways, including altering the perception, location, and quantification of afferent stimuli, mediating cognitive and emotional responses to these, and managing descending pathways" **(see Page 3, line 59-63)**.

65 You can use less words…..e.g. 'In the field of cough research, more extensive and profound studies have been conducted on chronic cough' could be shortened to 'most research has looked at chronic cough'…..simpler and more readable English. This applies throughout and a review by a native English speaker may be helpful.

Reply: Thank you so much for your suggestions on our manuscript. We have modified our text as advised.

Changes in the text: We have changed "In the field of cough research, more extensive and profound studies have been conducted on chronic cough" to "In the field of cough research, most studies have looked at chronic cough" **(see Page 3, line 65-66)**.

121-usually refer to a delta and c fibres…..

Reply: Thank you for your helpful comments.

Changes in the text: We have deleted "vagal branches" and instead inserted "Aδ and C-fibres" **(see Page 5, line 120).**

176 GABAA should be GABAA

Reply: Thank you for the suggestion.

Changes in the text: We have modified our text as advised **(see Page 6, line 175)**.

187 this sentence is an example of poor English. Gobbledygook. Out of place here. Try and write in plain English and avoid jargon. There are multiple examples throughout the review.

Reply: Thank you for your comments. We have tried to make the language as plain and easy to read as possible

Changes in the text: We have changed the sentence"The proper utilization of cough models and the advancement of novel models have facilitated the improved translation of research discoveries on cough mechanisms into efficacious approaches for managing cough." to "The efficient transformation of research discoveries on cough mechanisms into cough therapies relies on the proper utilization and innovation of cough models" **(see Page 7, line 184-186).**

344 Need to be clear that there is little direct evidence linking cough to these mechanisms.

Reply: Thank you for pointing out how important it is to clarify this. Currently, there are fewer studies on the correlation between the gut-brain axis, the body-brain axis and cough, but as a topic that urgently needs to be researched, we think it warrants some discussion. We note that studies are showing direct or possibly indirect associations between cough and these mechanisms. For example, immune damage and microbiota dysbiosis related to cough, as well as the aforementioned neurodegenerative diseases (see 3.4.1 Voluntary cough) are closely related to cough behavior and modulation. The gut microbiome plays a key role in neurodegenerative diseases. However, relying on the current study to establish a definitive causal relationship between these mechanisms and cough remains challenging. We have clarified this point in our review.

Changes in the text: We modified the end of this section **(see Page 13, line 363-366).**

Reviewer B

This manuscript seems to have well organized a wide range of contents from the traditional definition of cough to the mechanism, reflex, and treatment of cough. However, I would like to comment on a few contents.

1) The concept of cough hypersensitivity and the clinical significance including the tool for evaluating it are somewhat lacking. It would be good to add more contents on the clinical significance of cough hypersensitivity in cough and the aspects of cough related to it. It would also be good to add more details on cough trigger factors and the relationship between this and the cough reflex pathway and neurobiology.

Reply: Thank you very much for your thoughtful review and valuable comments regarding our manuscript.

Changes in the text: We have added the clinical significance of cough hypersensitivity and the aspects of cough related to it **(see Page 14-15, line 404-416, see Page 13-14, line 371-399)**. The concept of cough hypersensitivity and the way to evaluate it **(see Page 14, line 385-387, see Page 2, line 29-31, see Page 4, line 110-117, see Page 14-15, line 410-414)**. Refined the cough trigger factors and the relationship between this and the cough reflex pathway and neurobiology (**see Page 5, line 125-127).**

2) It would be good to add clinical significance to the risk that may occur when cough suppression treatment is limited as a physiological reflex.

Reply: Thank you so much for your suggestions on our manuscript.

Changes in the text: We have added the related contents of the risk of cough suppression treatment. (**see Page 3, line 73-75, see Page 16, line 443-446)**

3) It would be good to add the contents that the perspective and research on the aspect of cough treatment and well-controlled, which ultimately requires suppressing only unnecessary cough without suppressing necessary cough, are needed.

Reply: Thank you for your helpful comments.
Changes in the text: We refined Part 5 (The quest for effectiveness in treatment) and Part 6 (Conclusion) to highlight the quest for suppressing only unnecessary cough without suppressing necessary cough from the aspect of cough treatment and well-controlled (**see Page 14-15, line 400-416, see Page 15, line 420-421, see Page 12, line 437-446)**.

Reviewer C

This review article provides a comprehensive and in-depth discussion on the central regulatory network of cough. Overall, the manuscript is well-structured and presents valuable insights. I have only minor suggestions to further improve clarity and organization:
1. I recommend authors incorporate clearer summaries of key mechanisms in a structured, tabulated format.
Reply: We thank Reviewer C for this positive assessment on the value and readability of the review. We adjusted and improved the table (Table 1) of brain regions involved in the summary of cough-related regulatory mechanisms to make it more suitable for the summary of cough signal transmission pathways in Figure 1.
Changes in the text: Table 1 (**see Page 29).**

2. Page 2, lines 64-69. Please briefly mention the role of CNS in terms of current classification of cough.
Reply: Thank you for your comments. We briefly describe the role of the central nervous system The classification of coughs based on durations corresponds to international guideline recommendations.
Reference1: Irwin RS, French CL, Chang AB, Altman KW; CHEST Expert Cough Panel*. Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2018 Jan;153(1):196-209. doi: 10.1016/j.chest.2017.10.016. Epub 2017 Nov 10. PMID: 29080708; PMCID: PMC6689094.
Reference2: Kardos P, Dinh QT, Fuchs KH, Gillissen A, Klimek L, Koehler M, Sitter H, Worth H. German Respiratory Society guidelines for diagnosis and treatment of adults suffering from acute, subacute and chronic cough. Respir Med. 2020 Aug-Sep; 170:105939. doi: 10.1016/j.rmed.2020.105939. Epub 2020 Apr 25. PMID: 32843157.
Changes in the text: We have added the sentence "Modulation of the central nervous system has an important effect on cough duration, and this effect may be bidirectional, which involves the physiological and pathological mechanisms of cough" in this paragraph **(see Page 3, line 66-68).**

3. Page 2, lines 69-73. This part seems more suitable for the next section, 'physiological and pathological mechanisms of cough'.
Reply: Thank you for your helpful comments.
Changes in the text: We have moved this part to the beginning of the next section, "Physiological and pathological mechanisms of cough" **(see Page 3, line 70-75).**

4. Page 3. 3.1. Please provide some explanations of for the cough that occurs in the absence of external stimuli.
Reply: Thank you very much for your suggestion.
Changes in the text: We have added explanation of cough in the absence of external stimuli **(see Page 4, line 93-96).**

5. Table 1. Please clarify the categorization for the first column and add horizontal lines delineating the regions matching to their respective functional domains.
Reply: Thank you for your helpful comments. We have modified the Table 1 as advised.
Changes in the text: Table 1 **(see Page 29).**

Reviewer D

This is a comprehensive and much-needed review of cough's (mostly) central mechanisms.

Major comments

As a clinician I would like to include some clinical aspects, i.e. differentiation between cough as a symptom of many diseases and cough as a disease on its own; RCC is mentioned several times in the paper, but not explained. Are there differences in the complex central mechanisms between asthmatic cough, COPD exacerbation cough, ILD cough on the one hand, and UCC/RCC on the other?

The paper needs a native speaker check. For example, it contains several incomplete sentences
Reply: Thank you very much for your thoughtful review and valuable comments regarding our manuscript. In the new version of the paper I have fixed all the mistakes that the referee reported. The English has been revised (by a professional mother tongue speaker).
Changes in the text: We have added an explanation to the first mention of the RCC **(see Page 13, line 356-358).** Discussion of cough as a symptom and the disease on its own **(see Page 14, line 400-404)**. And discussion of central mechanisms for some different coughs **(see Page 11-13-14, line 371-399).**

Minor comments

Row 23-24 "In recent years, cough has emerged as one of the most prevalent symptoms of COVID-19, caused by the SARS-CoV-2 virus " this is only true for acute COVID, but not for long-covid as cited (1)
Reply: Thank you for pointing out the error.
Changes in the text: We have corrected as advised **(see Page 1, line 24).**

Row 27-29 "unlike a physiological cough, a persistent or pathological cough is often linked to various conditions such as respiratory infections, asthma, and chronic obstructive pulmonary disease". This definition is not correct: acute cough in common cold is not persistent, usually lasting only 10-14 days

Reply: Thank you very much for your suggestion.

Changes in the text: We have modified this sentence to make it more logical that pathological or persistent coughs correspond to the examples. For example, the acute cough in common cold corresponds to pathological cough **(see Page 1, line 21-24).**

Row 30-31 "A prominent characteristic of patients with cough hypersensitivity is the presence of specific triggers for coughing,(3)" – define cough hypersensitivity first

Reply: Thank you for your helpful comments.

Changes in the text: We have added the definition **(see Page 2, line 29-31).**

Row 33-34: please define allotussia and hypertussia

Reply: Thank you for the suggestion.

Changes in the text: We have added allotussia and hypertussia definition **(see Page 2, line 31-33).**

Row 73 …can compromise airway protection and further affect health" add e.g. aspiration pneumonia, atelectasis, etc.

Reply: Thank you for your insightful comments.

Changes in the text: We added the examples you mentioned at the end of the sentence **(see Page 3, line 74-75)**.

Row 78 Pure reflex movements – once precipitated - are inherently uncontrollable

Reply: Thank you for perfecting this sentence.

Changes in the text: We have modified the sentence as advised **(see Page 3, line 78)**..

Row 81 voluntarily or voluntarily intervenes in..

Reply: Thank you for pointing out the error.

Changes in the text: We have modified the error **(see Page 3, line 80-81).**

Row 93-94 "on cough threshold and the urge-to-cough has been conducted via provocation tests, with little or no direct testing of the urge-to-cough and cough threshold in the normal state." My understanding is that cough provocation tests, i.e. capsaicine or citric acid trigger only the peripheral receptors but not the central mechanisms.

Reply: I apologize for the misunderstanding in my expression. What we mean here is to illustrate the limitations of the test methods regarding cough threshold and urge-to-cough, which are not conducted in a natural state free from artificial interference, and the process and the results are susceptible to interference by multiple artificial factors. Such as psychological factors, perception differences of specified tussive agents mentioned later.

Changes in the text: We have modified the sentence to make it clearer **(see Page 4, line 91-98)**.

Row 216-217 “Numerous studies have shown that placebos and many complementary medicine-based treatments are effective in suppressing cough” Reference(s)?

Reply: Thank you for your helpful comments.

Changes in the text: We have adjusted the expression and added references **(see Page 8, line 210-211)**.

219-220 “they still cause a transient urge-to-cough, which commonly provokes a voluntary cough” Can we call cough, following urge to cough by capsaicin induction, still call “voluntary”? Is it not different from a voluntary cough induced by prompting the patient to cough during a physical exam?

Reply: I apologize for the misunderstanding in my expression. This complete sentence “When the doses of inhaled capsaicin in healthy individuals are insufficient to cause coughing, they still cause a transient urge- to-cough, which commonly provokes a voluntary cough. to-cough, which commonly provokes a voluntary cough”, we want to express that when the stimulus does not reach the cough threshold, it does not directly produce a cough, but rather produces a transient urge-to-cough, which in turn autonomously decides whether to cough or not.

Changes in the text: We have modified this sentence to make it more explicit **(see Page 8, line 212-214)**.

Row 347-348 “…and activation of the body–brain circuit in the absence of immune damage has no effect on cytokine levels” - correct sentence?

Reply: Thank you for your helpful comments.

Changes in the text: We have modified this sentence to make it corrected **(see Page 12, line 330-332)**.

Row 357-358 “…in that neurons expressed in the vagal ganglia respond selectively to proinflammatory stimuli…” Is “neurons expressed” the right term?

Reply: Thank you for your helpful comments.

Changes in the text: We have removed the extra words to make it correct **(see Page 12, line 340-342).**

Row 339 and elsewhere: “in jugular vein neurons” Is this the right term for ganglion jugulare or jugular ganglion?

Reply: Thank you so much for your suggestions on our manuscript.

Changes in the text: We have made two revisions **(see Page 5, line 130 and Page15, line 429).**