Replies to reviewers and the Editor

We are grateful for the constructive comments on our paper.
(new revised text the marked in red font in the revised manuscript).

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an opinion article manuscript, which critically reflects conventional psychiatric classifications and taxonomy. It offers innovatve approach to construction of a novel trans-diagnostic entity named "complex stress reaction syndrome". It is clear from this paper that the authors, in line with the literature, are not confident in the categorical approaches for psychiatric diagnosis.

Reply:

We are glad that the reviewer appreciates our novel approach.

As far as the opinion of authors goes beyond conventional approaches for constructing of psychiatric taxonomy, they need extended discussion on the alternative concepts of psychiatric validity, more specifically the controversies between validation of nosological structures (typical for medicine) as compared to prototype, cluster and dimensional diagnosis of mental disorders. In other terms it is critical to highlight the difference between diagnostic and nosological validity (https://doi.org/10.1007/978-3-030-55140-7_3) and to make explicit stand which of the two is adopted in the definition of the novel CSRS.

Reply:

We thank the reviewer for theses important comments. In following, we have discussed n the revised manuscript all points raised by the reviewer and included appropriate references in a dedicated Discussion section where we make our stand clear as requested by the reviewer:

The CSRS within the debate on psychiatric nosology

Our opinion goes beyond conventional approaches for construction of psychiatric taxonomy. Alternative concepts of psychiatric validity include controversies between validation of nosological structures (typical for medicine) as compared to prototype, cluster and dimensional diagnosis of mental disorders (49). While the field of psychiatry moved towards more medically oriented nomothetic knowledge, alternative groups which we follow in our empirical and review papers, suggest that the field has to move away from this type of knowledge towards a more ideographic and subjective approach to psychopathology (49).

The main differences between the validity of dimensional diagnostics and that of traditional nosology are apparent in several aspects: (1) in traditional approaches, mental pathology is regarded as a strict drift from acceptable norms while the transdiagnostic views, similar to ours, suggest an axis between normal and psychopathological conditions (2) in dimensional approaches co-existing psychopathological states appear in parallel along with personal strengths and capacities for resilience, unlike traditional nomenclature (3) dimensional approaches to the convergent and divergent validity of a cluster or co-existence of different pathologies without meeting a full criteria of any category in the conventional systems, such as the CSRS, do justice to the patient and the entire individual clinical picture he\she describes to the clinician, while traditional approaches prefer multiple comorbidities (4) the dimensional approaches such as the CSRS, unlike convention systems, emphasize subjective complaints of the patient (*symptoms*) rather than *signs* judged by the clinician. By that, these dimensional approaches are shifting the focus from the powerful societies of professionals towards the patient's subjectivity, and they recognize that

professionals too, have their own subjective perspectives to consider before endorsing a diagnosis based only on signs.

Specifically, the CSRS has shown high reliability, as in two different countries and with two different methodologies the same results were found (25). Additionally, the CSRS has shown high convergent and divergent validity as a combination of several identified stress symptoms, without meeting any full conventional category. These findings suggest a complex and unique type of reactivity to multiplicity of stressors. Other combinations suggested earlier, as Complex Anxiety and Depression (50) or Complex Post Traumatic Stress Disorder, showed validity for inclusion of just two conventional categories (51) while others showed a too wide range of inclusion, ruling out the potential judgement of divergent validly (10).

We acknowledge the importance of biological validation of psychiatric illness, but this still cannot be utilized for a treatment per any specified condition until the field of neuropsychiatric science advances considerably. The CSRS implies symptoms more than signs and subjectivity more than objectivity. The treatment derived from the CSRS would be patient-specific and session-specific, as human experience may go back and forth on the axis of elevated symptomology vs. resilience and coping. Therefore, the notion of session-specific treatment requires the clinician's diagnostic effort at every given session to reevaluate the patient's symptomology for progression vs. regression and to offer treatment accordingly. We propose that the human experience transits along time that elapses and a condition may be judged for a given patient, in a given environment at a given moment, considering how the observed syndrome has been individually experience-shaped (52–55).

It was noted earlier (49) that the empirical validation used as the basis of conventional categories has been mostly regression statistical analyses with a weak basis for causality. Contrary to any etiological arguments, we argue that the CSRS represents an association between multiplicity of stressors and a mixed

clinical picture, which is worth to treat to avoid further increase in the patient's stress reactivity and future limitations of his\her resilience capacities.

We locate CSRS within the blend of the Biopsychosocial (BPS) model (56) and the Person-Centered Medicine (PCM) approach (57), as the novel CSRS is related to exogenic stressors (BPS) and occurs as a subjective complex stress reaction of the patient (PCM). Thus, as outlined here and according to our binational research design and findings (25), the CSRS falls within the post-modern dimensional approaches more than within any strict nosology, for better prevention and treatment. CSRS was designed and investigated from a humanistic perspective, arguing that mental health is not represented by the lack of psychopathology, while psychopathology, in turn, is a condition with an indication to treat and may be reversible.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: In this editorial and in an earlier article in the World Journal of Psychiatry (reference no. 22), the authors propose "a new category within the conventional classification systems: the Complex Stress Reaction Syndrome, for a condition of multiplicity of stressors, which showed a mixed clinical picture for daily life in the post COVID-19 era, in the general population." They base their findings on their literature review and a population-based study they had conducted in Israel & Italy.

However, I think that several issues must be considered before accepting the authors' proposal of a new mental health category that has become more evident after the COVID-19 pandemic. The mental health consequences of the COVID-19 pandemic including the diversity of psychiatric symptoms reported by people does not appear to be qualitatively different from reports of past epidemics and

natural disasters (Esterwood et al. Psychiatr Q. 2020; WHO 2022-Mental health in emergencies).

What was probably different about the COVID-19 pandemic was its scale and the fact that it was covered extensively by the social, electronic, and print media. That this coverage itself could have contributed to the psychological consequences was apparent to all who have been exposed to the barrage of information or disinformation about the pandemic. I am not sure whether this has been examined properly.

There has been an explosion of reviews and surveys about the mental health consequences of the COVID-19 pandemic in the past 2 years. Although, there is enough evidence to suggest that the mental health of the population deteriorated following the lockdown (e.g., Pierce et al. 2020 Lancet Psychiatry), there is some suggestion that the extent of deterioration was less than anticipated (Witteveen et al. 2023 PLoS Med; Sun et al. 2023 BMJ; Hjorthøj & Madsen 2023 BMJ). The consequences were mainly limited to depression and disproportionately affected women and younger people. Although these contrary findings may be controversial, there is greater consensus about the poor methodologically quality of the studies introduces a significant element of bias. This has been acknowledged by the authors. Therefore, a great deal of caution is needed before drawing any conclusions from this evidence-base.

Most of these surveys were conducted the general population and involved what was essentially sub-threshold symptoms. Epidemiological studies have shown that anxiety, depression, functional somatic, and even obsessional symptoms can coexist at the population or the community level (Simon et al. 1999; Goodwin 2015 Dialogues Clin Neurosci). This is based on Watson's two-dimensional model of positive and negative affect. Negative affectivity forms the basis of a universal dimension of distress. Strictly speaking, this cannot be called comorbidity because that requires the co-occurrence of two independent threshold disorders. Nevertheless, this coexistence of multiple symptoms is already included in

categories such as mixed anxiety depressive disorder. It is expected that stress-related symptoms will form a part of the mix in patients exposed to the pandemic. Many individuals will have had exacerbations of pre-existing disorders during the pandemic. In other vulnerable individuals, the pandemic would have unmasked latent psychiatric pathology. This would explain the presence of symptoms of eating disorders, obsessions and compulsions, substance abuse and other symptoms. However, much like the category of mixed anxiety depressive disorder (Moller et al. 2016), there will be doubts about the validity of any category with a mix of diverse psychiatric symptoms.

Lastly, adding the symptoms of long COVID to this category will create the same psychological versus physical dispute that we have witnessed with chronic fatigue syndrome or myalgic encephalomyelitis. Studies have already started appearing, which suggest that the long COVID syndrome is more likely to associated with psychosocial factors rather than COVID infection (Selvakumar et al. 2023 JAMA Netw Open). Although the authors' proposal is a worthwhile one, I think they will have to find a way to resolve these issues about the existence of a new transdiagnostic category in the aftermath of the COVID-19 pandemic.

Reply:

We thank the reviewer for the detailed and important comments. We have added a new section in the Discussion that addresses the reviewer's points and cites the references suggested:

The origins of CSRS

CSRS emerged from the robust transdiagnostic clinical picture during and following the pandemic (38). The WHO indicates a prevalence of 22% of a mixed picture including depression, anxiety, PTSD, and general distress, fatigue, irritability and anger in the general population following the experience of war or natural disaster (39). Transdiagnostic approaches to classifications were proposed

even prior to the COVID-19 pandemic (1–4). Here we argue that the impact of multiple stressors in daily life is a neglected issue in traditional classifications.

What was probably different about the COVID-19 pandemic compared to previous catastrophes was its global scale and the fact that it was covered extensively by the social, electronic, and print media. This factor may be regarded as an additional stressor in daily life beyond disasters. Whether media use is a source of social support, especially for young people ((27, 40, 41) or a daily life stressor in the form of bombardment of information (42), is still a topic under scientific debate and probably age-related with large inter-individual variance.

Although there is enough evidence to suggest that the mental health of the population deteriorated following the pandemic (e.g., (43)), there is some suggestion that the extent of deterioration was less than anticipated (44, 45). In any case, epidemiological studies have shown that anxiety, depression, functional somatic, and even obsessional symptoms can coexist at the population or the community level (38, 46, 47), supporting our transdiagnostic views and the CSRS.

Inclusion of long COVID symptoms in the CSRS may create the same psychological versus physical dispute that we have witnessed with chronic fatigue syndrome or myalgic encephalomyelitis, but we include in the CSRS just neuropsychiatric symptoms, while systemic components of long COVID are excluded. In support of our view, studies that have already started appearing suggest that the long COVID syndrome is more likely to be associated with psychosocial factors rather than the COVID infection itself (48).

Thus, the origins of CSRS are rooted in the multi-faceted stress of the pandemic and its impact on mental health including its residuals in the post COVID era. The relevance of concomitant stressors included in daily life, under regular, non-catastrophic conditions, and their association with a mixed clinical picture, is gradually becoming apparent.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Psychiatry, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Before final acceptance, the author(s) must add a table/figure to the manuscript. There are no restrictions on the figures (color, B/W) and tables. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Reply:

The revised manuscript now includes a figure, as requested by the company Editor-in-Chief. It also includes cutting-edge references found by a dedicated search in the RCA.