Multiple Chemical Sensitivity: Catching up to what kind of science?

Commentary on Molot, J., Sears, M., Anisman, H. (2023). Multiple Chemical Sensitivity: It's time to catch up to the science, Neurobiological and Biobehavioral Reviews, https://doi.org/10.1016/j.neubiorev.2023.105227

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The recent review of Molot et al. (2023) appropriately emphasizes Multiple Chemical Sensitivity (MCS) as a growing healthissue and the necessity of dedicated healthcare and medical education. The authors explain MCS mainly as the result of the sensitization of transient receptor potential (TRP) receptors, notably TRPV1 and TRPA1, and oppose this explanation to psychological processes as a causal explanation. We argue that: 1. critical evidence from double-blind exposure studies showing patients' inability to discriminate between actual and sham exposure questions this claim; 2. the interpretation of the role of TRP-receptors fails to appreciate the importance of chemicals as stressors for MCS patients and may confound cause and effect; 3.the evidence supporting a causal role of psychological processes is largely neglected; 4. the opposition between biological and psychological causes is not helpful in trying to understand MCS. Most importantly, treatment suggestions based only on the hypothetical role of TRP-receptors may aggravate the burden of MCS on both patients and society.

(1) Sensitization of TRP-receptors may indeed be an interesting avenue to better understand mechanisms involved in MCS, as studies using capsaicin inhalation challenge and brain imaging convincingly suggest. However, Molot et al.'s review largely overlooks the literature that challenges the pathogenic role of chemical substances in MCS (for an overview, e.g., Haanes et al., 2020). Double blind provocation studies have repeatedly shown that affected individuals are not able to distinguish between chemicals and sham exposure, and that they do not experience more MCS-associated symptoms when exposed. Although some studies may suffer from methodological weaknesses, the bulk of the evidence strongly suggests that a toxic effect of chemical products is neither necessary nor sufficient to account for MCS.

(2) The evidence reviewed by Molot et al. is only correlational: sensitization of TRP-receptors may be *associated* with MCS but a *causal* link with the occurrence of MCS-symptoms has not been established so far. What is clear, however, is that patients with MCS experience chemical substances, either odorous or not, as important sources of stress, avoidance behavior and substantial loss of quality of life. Molot et al. emphasize that psychological factors such as stress, depressive mood and anxiety are also associated with sensitized TRP-receptors. In addition, the typically observed heterogeneity and diversity of potential triggers (including chemically unrelated agents) renders a monocausal chemical explanation of MCS rather unlikely. While this is no direct evidence that these psychological factors cause sensitization of TRP-receptors in MCS, this alternative hypothesis seems just as valid as the one defended by the authors, given the available evidence so far.

(3) Disentangling cause and effect requires experimental studies demonstrating the effect of causal mechanisms. This was done in a series of studies by Van den Bergh et al. (2017a) (see Table 1 for an overview), in healthy participants because in patients causes and consequences are intrinsically confounded. These studies showed that experimental induction of symptom expectancies through behavioral conditioning caused symptom reports in response to chemicals, while controlling for the effect of the substances themselves (within-chemical control). Interestingly, these effects were most pronounced in persons with psychological characteristics akin to those of MCS patients and in patients with functional somatic symptoms with elevated psychiatric comorbidity, which is in line with epidemiological findings on psychopathology being a risk factor for the development of MCS. In addition, whereas acquired symptoms were initially only found in response to chemicals with an unpleasant odor, framing chemicals with a pleasant odor as potentially dangerous subsequently facilitated acquiring symptoms to such chemicals as well (Winters

et al., 2003). Further, acquired symptoms generalized to newly presented chemicals. This is convincing evidence that expectancy induction can cause the acquisition of symptoms in response to chemicals unrelated to the chemical effects themselves and that these effects are moderated by factors that also characterize MCS patients.

(4) Opposition between biological and psychological origins has been the stock-in-trade of discussions about MCS. The review we address makes no exception, stating for example that "the lack of awareness and understanding of the evidence for biological mechanisms perpetuates the perception that the etiology of MCS is psychogenic" (p.9). This dichotomy between biological and psychological mechanisms is scientifically untenable. A vast array of evidence makes clear that all symptom experiences come about in the brain. This implies that symptoms are based on a (probabilistic) integration of peripheral input and information generated by the brain. Symptoms are therefore always influenced by factors labeled as psychological (e.g., previous experiences stored in the nervous system). These factors may become the most powerful determinants (Van den Bergh et al., 2017b), particularly in chronic conditions such as MCS, in which past toxic exposures, negative affect, and/or negative expectations about chemicals are predominantly present (Nordin, 2020; Van den Bergh et al., 2017a). Importantly, symptoms of MCS are real and they can have dramatic impacts on individuals' life regardless of their underlying determinants.

Finally, Molot et al. rightly criticize the stigma patients with MCS are facing and the barriers to access healthcare. However, putting forward biological determinants as causal factors while turning down other ones fosters dualistic thinking and may actually increase stigma. Conversely, we promote a comprehensive view of MCS that gives equal credit to biological, psychological and social determinants in line with the WHO's biopsychosocial perspective

when defining health. This has major consequences for treatment. Molot et al. suggest that individuals should protect themselves against chemicals, and that policy makers should regulate them, despite questionable evidence that they cause symptoms of MCS. This strategy bears the risk of increasing worries and negative expectations about chemicals. In line with the experimental studies showing a critical role of expectations (Van den Bergh et al., 2017a), one may rather suggest an important role for exposure therapy, a well-established evidence-based treatment method that is able to disconfirm expectancies. As for now, recommendations based only on a potential critical role of TRP-receptors in MCS seem premature. It is recommended that clinical practice and future research should refrain from taking one-sided perspectives and embrace a biopsychosocial view of MCS.

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