Electrohypersensitivity is always real

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Given the rapid increase of electromagnetic fields in our environment, the recent review paper by Belpomme and Irigaray, 2022 (doi: 10.1016/j.envres.2022.113374) is timely in trying to integrate and discuss the available evidence to understand electrohypersensitivity (EHS), also called idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) or symptoms associated with EMF (SAEF-EMF) (Haanes et al., 2020). There is no doubt that EHS can be a severely disabling condition, has a relatively high prevalence and needs better scientific understanding and more effective treatments. However, we have serious concerns about 1. the metatheoretical perspective of the paper, 2. the biased and selective review of the literature, 3. the claims that are made about the meaning of reported data/findings, 4. the rationale used to arrive at a conclusion, and 5. the conclusion itself.

As to the metatheoretical perspective, Belpomme and Irigaray seem to endorse an old-fashioned reductionist biomedical model that considers diseases only as "real" when they can be reduced to a physiological dysfunction of the organs that seem to be designated by the symptoms. For example, they urge to consider EHS as "*a real syndrome*" (p.3) or "*a real pathological disorder caused by EMF exposure*" (p.10) because some links have been found to physiological alternations (Belpomme and Irigaray, 2022). This implicitly suggests that diseases are "*not real*" if this reduction is not possible. In line with this, they "*indubitably refute the hypothesis of a nocebo effect*" and stand against considering psychological determinants of EHS (p.8). These statements express a long-abandoned mind-body dualism, while at the same time neglecting substantial advancements in understanding nocebo mechanisms, and more broadly symptom perception processes (Van den Bergh et al., 2017b), see further). Since decades, however, medicine has subscribed to a biopsychosocial model that considers any disease as resulting from a "web of causation" in which factors at biological, psychological and social level and their interactions contribute to the symptom profile, suffering and disability (Engel, 1977). Obviously, EHS is real by the mere fact that it comes with disabling symptoms and substantial suffering, regardless of whether there is an established association with somatic abnormalities. Therefore, individuals with EHS should receive efficient and appropriate treatment. The latter, however, requires a deep and correct understanding of the causal mechanisms involved.

In that respect, the authors rely on a biased and selective review of the literature. Since they "*… consider (it)* ***a priori*** *as scientifically unjustified to speculate that the electromagnetic claims of all the patients are unfounded and that their subjective symptomatic feeling could relate to some non-EMF psychosomatic or nocebo health effects*" (p.4), the literature on nocebo processes in EHS is simply neglected. This *a priori* position is clearly at odds with the major advances that have been made in the past two decades in understanding the psychological and neurobiological processes underlying placebo and nocebo effects (for reviews, see (Colloca and Barsky, 2020; Tavel, 2022). Also for EHS, there is substantial evidence showing that experimentally induced expectations of harmful EMF lead to elevated and potentially lasting symptom reports (Bräscher et al., 2020, 2017; Witthöft and Rubin, 2013). Despite the suggestion by the authors that multiple chemical sensitivity (MCS) and EHS share a common pathophysiological mechanism, the results of an extensive research program on MCS are also neglected. However, results showed that experimental induction of expectations provoked elevated symptom reports to harmless chemicals, reproducing most of the clinical characteristics of individuals with MCS through nocebo manipulations (see (Van den Bergh et al., 2017a), Table 1, for a review of findings).

In general, putting nocebo mechanisms in opposition with "real" physiological mechanisms neglects evidence that in any disease the relationship between physiological dysfunction and symptom reports is strongly mediated by symptom perception processes. Symptoms may originate in physiological dysfunction and subsequently be determined by nocebo mechanisms, explaining why in chronic diseases symptoms typically show a rather poor relationship with critical physiological parameters (Fitzcharles et al., 2021). Symptom perception processes are also strongly involved in the observation that no link with a physiological dysfunction can be established in about one third of the consultations in primary care and between one third and half of the consultations with specialists (Van den Bergh et al., 2017a). The brain activation patterns underlying those symptom experiences are increasingly being determined (e.g. Bogaerts et al., submitted; (Benedetti and Piedimonte, 2019; Jepma et al., 2018)). They involve mostly the prefrontal cortical networks and the striatal and

brainstem circuits (Wager and Atlas, 2015). Interestingly, symptom reports during sham EMF exposure in individuals with EHS can be linked to similar brain activation patterns (Landgrebe et al., 2008). In sum, there is strong evidence that nocebo and – more broadly – symptom perception processes are ubiquitously present in medicine to impact and modify the symptom profiles of patients, regardless of whether or not they suffer from diseases underpinned with identified somatic abnormalities.

In addition to neglecting evidence of a nocebo effect in EHS, the author's coverage of provocation studies hardly meets the scientific principles of a systematic review: no search criteria, no inclusion criteria, and no systematic quality ratings are mentioned. This may explain why the author's conclusions are in stark contrast with the conclusions reached by scientifically sound reviews of provocation studies. Briefly, after a systematic literature search, strict application of inclusion criteria and quality checks, Rubin et al. (Rubin et al., 2010) reviewed 46 blind or double-blind provocation studies involving 1175 EHS cases. Despite the conviction of EHS sufferers that their symptoms are triggered by exposure to EMF, no robust evidence could be found for it under controlled conditions. Among the studies that checked the percentage of participants who were able to detect EMF, low numbers were found that were equal for patients (2.9%) and healthy controls (2.4%) and likely due to chance. Importantly, sham exposures appeared sufficient to trigger symptoms in the laboratory similar to those usually reported by individuals with EHS. These conclusions confirm the results of a meta-analysis combining several studies (Röösli, 2008), of a systematic review (Röösli et al., 2010), and of studies by Baliatsas et al. (Baliatsas et al., 2015, 2014). Although some studies show methodological limitations, as underlined by Belpomme and Irigaray, the bulk of the evidence strongly supports the view that self-reported symptoms of EHS do not result from actual EMF exposure, while strong indications are repeatedly observed that perceived exposure and worries about them contribute to the symptoms. Accordingly, unbiased elaboration of the available empirical evidence shows that the core claim of these persons, namely that symptoms emerge in the presence of EMF and subsequently wane after removal of EMF, is actually not caused by EMF exposure itself. Pre-existing symptoms (e.g. medically unexplained, see above) can retrospectively be attributed to EMF, or symptoms can be

explained by a nocebo effect, but in both cases beliefs about the presence and harmfulness of EMF seem to be the critical process, not the actual exposure to EMF (Boehmert et al., 2020).

Another problematic aspect of the paper is how physiological effects are interpreted in the context of exposure to EMF. They are considered as biomarkers or "*objective pathophysiological changes*" (p. 1) establishing that the EHS is "real" and – thereby – precluding the role of psychological processes such as nocebo. In a systematic review, Rubin et al. (Rubin et al., 2011) identified 29 single or double-blind experiments in which participants with IEI-EMF were exposed to different levels of EMF and in which objectively measured outcomes were assessed. Five studies identified significant associations between EMF exposure and heart rate and blood pressure, pupillary reflex and altered EEG during sleep, but the latter results were similar in the EHS group and the healthy control group. However, other studies failed to replicate those findings suggesting that there is no reliable evidence that persons with EHS experience unusual physiological reactions due to exposure to EMF (Huang et al., 2022; Malek et al., 2015). Also, other physiological changes such as low-grade inflammation and indications of oxidative/nitrosative stress are inconsistently found but, as the authors acknowledge themselves in another recent paper about EHS, they lack specificity "*since they are also found in common diseases such as cancer, diabetes, obesity, Alzheimer's disease and other suspected environment-related pathological disorders*". The conclusion that they "*nevertheless, … strongly testify to the somatic non-psychological signature of EHS*" (Belpomme et al., 2021) is astonishing because the authors thereby – again – neglect the vast evidence that psychological processes can cause somatic abnormalities, that nocebo processes can have objectifiable physiological effects and are themselves related to objectifiable processes in the brain (see above).

Furthermore, exposure to EMF for an individual with EHS is not just exposure to man-made electromagnetic fields, it is particularly also exposure to a stressful stimulus. Plenty of evidence exists that the experience of stress impacts EEG, EMG, skin temperature, skin conductance and heart rate variability (HRV), variables that are mentioned by the authors as indicators of "objective abnormalities".

One can easily understand that persons with EHS become chronically stressed while seeing their lives gradually disintegrating, which evidently may show up in many objective physiological changes. For example, chronic stress is associated with oxidative stress, immune changes and neuroinflammation (Bottaccioli et al., 2019). But these effects are then the result of the health condition and not the cause. No studies so far have tested and shown that objective pathophysiological changes are mediating EHS symptoms. It is simply assumed that, if there are pathophysiological changes in individuals with EHS, they must be the cause of the symptoms. In sum, it seems that the claim of having identified biomarkers is largely overstated and the importance of observed "*objective pathophysiological changes*" is misinterpreted.

Another problem is that the authors failed to clearly distinguish between two important questions: (1) whether EMF can cause biological changes and potential harm in some individuals; (2) whether self-reported symptoms of individuals with EHS are due to actual radiation from EMF. These two questions are confounded throughout the paper and the authors seem to consider evidence in response to the first question as evidence to also answer the second question. Obviously, answering the first question (a public health question) is complex and difficult, especially if the effects would be small and interact with a variety of characteristics of the exposure source, exposure conditions and individual difference factors. It requires animal studies in the laboratory, translational studies and large-scale prospective epidemiological studies. Up to now, we cannot reliably say that EMF is harmless (let alone that it is logically impossible to prove that EMF or any other exposure has no effects) and further systematic and sound research will be needed for years in order to arrive at a solid body of evidence. However, evidence reviewed by the authors about potential harm of exposure to EMF is irrelevant to answer the second question: if a person is reporting bodily symptoms emerging in presence of EMF, the critical question is whether EMF are the causal factor. Therefore, controlled provocation studies are so important. As described above, existing empirical evidence shows that the actual presence of EMF is not critical for symptoms to occur, while perceived exposure seems to play a more important role.

Finally, the concluding but unwarranted claim by authors, namely that symptoms of EHS are caused by physiological abnormalities due to EMF, is potentially harmful in itself. Especially the warning for "*emerging and growing worldwide EHS and MCS global plagues*", and the call upon public health authorities to "*decrease EMF-exposure*" (p.11), is problematic in at least three ways. First, from an epidemiological perspective, there is simply no empirical evidence for this sensationalist statement that the number of people affected by EHS or MCS is dramatically on the rise. According to recent studies, prevalence rates are actually rather decreasing (Huang et al., 2018a). Second, professing plagues in the absence of evidence may do harm in terms of fostering nocebo effects. For example, reading websites of individuals with MCS emphasizing the ubiquitous presence of harmful chemicals leads to elevated symptom reports in response to harmless chemicals (Winters et al., 2003). Also, symptom prevalence was shown to covary with patterns of media coverage and subsequent risk perception (Chapman et al., 2013; Huang et al., 2018b). Third, if nocebo and erroneous attribution processes are the main cause of the symptoms, the advice to reduce and/or avoid as much as possible the sources of EMF will actually increase the problem. Cognitive and behavioral therapy (CBT) was put forward as a promising treatment for EHS (Rubin et al., 2006; Van den Bergh et al., 2020). However, protection against EMF counteracts the goals of CBT, which promotes progressive exposure to symptoms and their alleged causes. We therefore strongly advise the authors to acknowledge the full scientific evidence when further commenting on EHS.

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