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Comment on "The Effects of Long-Term 40-Hz Physioacoustic Vibrations on Motor Impairments in Parkinson's Disease: A Double-Blinded Randomized Control Trial. Healthcare 2020, 8, 113"

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We enthusiastically read the recent article published by Mosabbir and colleagues [4]. The authors assessed the effects of long-term 40-Hz physioacoustic vibrations on motor impairments in Parkinson's disease (PD) and they reported that all the aspects of PD motor impairments improved. Our goal is to share some thoughts, different opinions about the interpretation of results and some suggestions for future studies.

We found that not properly considering the effects of 40 Hz gamma frequency band on CNS, the reason behind the 40 Hz frequency being the most effective in the range of gamma frequency band (25-140 Hz) and missing the Impact mechanisms of the 40 Hz on brain cells has led to the authors ignoring a potential interpretation of data. Also, we will suggest some other potential treatments along with physioacoustic vibrations for PD which are supported by scientific evidence.

The authors said the reason they chose 40 Hz is the neuroprotective effect of this frequency that is shown by consistent evidence. But they did not mention any of that evidence which seems to be absolutely necessary in order to explain results. In one previous study laccarino and colleagues worked on how gamma frequency entrainment increases amyloid load and modifies microglia on Alzheimer's

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disease [1]; They aimed to figure out possible molecular mechanisms of gamma on Alzheimer's disease and the effect of these mechanisms on other neurological diseases to find possible therapeutic interventions.

Considering that there is an abundance of studies that show which oscillations in the gamma range can be derived by visual stimulation, in laccarino and colleagues' study they use different frequencies (20, 40, or 80 Hz), random flicker, constant light-on (light), or dark for 1h on 5XFAD mice. The results showed that light flickering at 40 Hz raised the power in the local field potential (LFP), whereas exposure to other intervals of flickering (20 or 80 Hz), dark and constant light-on (light) did not.

Also, in the laccarino and colleagues' study, they showed 40 Hz has a direct effect on microglia and their type of activity. Given that a 40 Hz stimulation increased microglia cell body diameter by 165.8% and a 40 Hz light flicker decreased Microglia primary process lengths by 37.7% in comparison with dark controls. This morphology indicates enhanced engulfment activity in microglia. Another significant finding in the study was the increase of the A-bearing microglia after a 40 Hz flicker compared to dark controls. These results indicate that the phagocytic activity of microglia plays an important, protective and therapeutic role in Alzheimer's disease. These results were confirmed in another study conducted by Martorell and colleagues which was done with multi-sensory gamma stimulation [3]. The role of microglia in neurodegenerative disorders has long been the focus of neuroscientists. There are a number of theories and data that show the positive and negative effects of microglia in neurological diseases. But among these ramifications of microglia in CNS disorders, phagocytosis has been shown to have a more neuroprotective effect rather than a negative one. The effects of the phagocytic role of microglia (positive or negative) has been a topic of discussion in relation to PD and a beneficial effect of phagocytosis stimulation in PD was supported by some recent studies [5, 2]. as a result, modulating the phagocytic process of microglia can be a potential treatment target in PD.

Considering the content thus far, we can now provide some potential suggestions to go with conclusions in Mosabbir and colleagues' study. Firstly, the authors stated that previous methods that utilized whole-body vibration (WBV) using platform-based interventions showed inconsistent evidence for treatment. They suggested some likely reasons for it but despite mentioning the use of random waves and the ones below 20 Hz in previous methods, they missed the effect of a 40 Hz wave delivered to the brain among other gamma and random waves that was documented in previous studies (as we mentioned before).

Secondly, they stated that previous investigations have failed to illustrate the effect mechanism of physioacoustic therapy method (PAT) and other vibration therapies, therefore the mechanism is not yet fully explored and remains unclear. Perhaps by generalizing the results of the use of 40 Hz to other neurological disorders (Alzheimer's), they could have reached a potential conclusion that besides explaining the mechanism (Activation of the phagocytic form of microglia by a 40 Hz gamma frequency(, would also be able to answer why other frequencies fail to show the therapeutic effect of a 40 Hz wave.

Here are some other suggestions for potential future studies: (i) Using the PAT method on animal models of PD that can help us understand the effect mechanism of 40 Hz on CNS. (ii) Applying other methods of treatment on Alzheimer's disease using the same 40 Hz, including visual and auditory stimulation, multi-sensory stimulation, and comparing them to each other. (iii) Using an electroencephalogram (EEG) in PAT and other stimulation methods in order to figure out the most affected part of the CNS while applying a 40 Hz wave. We hope these cases would help us increase our knowledge of PD and its treatment in the future.

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