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How Placebo can work as a treatment for Depression

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Abstract

Placebo is like a shadow but unlike a shadow simultaneously. Though biologically no reason to change one's body is given, placebo will gradually ease the pain, as if the medicine is given to the patient. Placebo has been a popular option in major hospitals due to its speciality of absence of side effects that can be produced by the medicines or surgeries. Furthermore, placebo can be utilised especially well to cure mental disorders compared to other pathogenic diseases since mental disorders are rather subjective and don't necessarily require treatments for infection. To apply this idea to real life, I reflected on how the belief of listening to the scientifically-proven mood-boosting music could actually lead to an improvement in the students' emotions, which aligns with what I sought out to investigate but not directly. I randomly selected 10 students, which is a relatively small sample size, in my school, in the same age group between 16 to 18. To assess their basic emotional status, I conducted the Oxford Happiness Questionnaire (OHQ) before and after the experiment to compare any change from listening to music, and Patient Health Questionnaire-9, before the experiment to measure the severity of student's depression using a Google Form; both are self-assessed report. Half of the sample listened to the music that has been scientifically shown the correlation between listening to the music and improvement in emotion swings from Brain.fm, while the other half listened to the placebo, a frequency-based music, which isn't scientifically proven to impact one's emotions. The results showed that the higher the severity of depression, the greater improvement in OHQ showed after the experiment for both placebo and the other group. Furthermore, placebo and the other group that listened to the real mood-improving music showed similar results in the change of OHQ after the experiment.

1. Introduction

Major Depression Disorder (MDD) is a mood disorder expressed by persistently low mood, loss of interest, and reduced productivity. According to the Centers for Disease Control and Prevention (CDC), the rate of MDD in adolescents and adults increased from 8.2% to 13.1% between 2013-2014 and August 2021-August 2023 (Brody and Hughes, 2025), with contributing factors such as COVID-19 inducing social isolation and increased exposure to social media; COVID-19 that physically induced individuals to isolate themselves from the society rapidly increased the risk of MDD, likewise, expanding use of social media that drives people to compare themselves with the celebrities in the social media prompted the increase of MDD. With an increasing incidence of MDD over the past few years, with 56% increasing rate between 1991 and 2021, due to some social factors such as COVID-19 pandemics and excessive use of social media, placebo effect could also be viewed as an alternative to either prevent the MDD, or to help through with MDD.

This study explores if the placebo effect could play a role in improving depressive symptoms in MDD. It investigates whether expectation solely can influence mood, and how this differentiates from established treatments like psychotherapy or antidepressants. This research focuses on how perceived treatment may influence brain function and emotional state.

I chose Brain.fm to use for the experimental group in my sample as this website provides audio platforms that have been scientifically proven to help with emotion regulation, meditation, and focus; the audio file combined with the platform for emotion regulation and meditation was used for the experimental group. For the placebo group, I was looking for the frequency-based music, which majority of people assume to relate to our mood shift, even if it's not validated by research; 432Hz music was used as it's widely used for healing and meditation session, which was also the most similar audio as the experimental group's audio.

To measure the severity of each participant's depression, I used Patient Health Questionnaire-9 (PHQ-9), which is a self-report questionnaire that infers basic symptoms of MDD, such as lacking interest, low self-esteem, and thoughts of self-harm. However, since it's a self-reported data, the reliability may not be ensured. Interviews with each participant were also conducted before and after the experiment to assess their psychomotor issues, such as the speed they speak in, how many times they make eye contact, etc.

2. Literature Review

Introduction to the Major Depression Disorder

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. (Depression (Major Depressive Disorder) - Symptoms and Causes, n.d.) An individual is diagnosed the Major Depression Disorder when they experience a constantly depressed mood, anhedonia, feeling of guilt, lack of energy, poor concentration, or suicidal thoughts (Bains & Abdijadid, 2023). Depression influences the medial prefrontal cortex (MDFC), medial and caudolateral orbital cortex, amygdala, — part of the limbic system responsible for processing emotions especially fear and aggression— , hippocampus — part of the limbic system that contributes to learning, memory storage, and spatial navigation —, and ventromedial parts of the basal ganglia, which controls the movement, cognition, and reward processing (Zubieta et al., 2005). This justifies the common symptoms of MDD such as decrease in productivity, mood swings, and suicidal thoughts. This can arouse possible severe symptoms across phenotypes such as negative bias, threat dysregulation, and inattention-cognitive dyscontrol, which are common in people with MDD (Goldstein-Piekarski et al., 2021).

3. Causes of MDD

Not only the neural circuits are negatively impacted by the MDD, the entire structure of the brain is also damaged. The volume of gray matter, which plays a big role to process the information, emotions, and movement, and to store the memories; MDD potentially reduces the volume of grey matter due to neuronal loss, eventually via unnecessary apoptosis of neurons. The condition of MDD specifically leads to atrophy and loss of neurons in glia in limbic regions and circuits (Duman, 2009). This loss of neurons can be explained by the hormone called corticotropin-releasing hormone which is released when experiencing MDD, which acts as a stress response in our body (Yan et al., 1998). It targets neurons located in the

hippocampus, ultimately leading to excitotoxic neuronal death. Reduction in glial cells, synaptic proteins, and the size of neurons are also shown due to MDD. One of the glial cells that differs from the other glial cells is called oligodendrocyte, which is accountable for forming fatty sheath around axons, which is also called myelination. However, reduction in the number of oligodendrocytes leads to demyelination, preventing the insulation of axons for smooth signal transfer. Depression also causes repeated stress, which encourages dendritic remodelling in our brain. Reformation of dendrites in neurons apparently would be reflected by a decrease in the volume of neuropil, which occupies the majority of the grey matter. This can further lead to a decrease in rate of electrical signal conduction. As well as grey matter, the volume of white matter of the corpus callosum is also reduced in MDD; white matter is a group of aggregated nerve fibres. The MDD showed lessened volume of white matter CBF in the bilateral anterior cerebral artery regions and the left middle cerebral artery region, causing a cognitive impairment ((He et al., 2022). In the aspect of neurochemical systems, depression leads to abnormalities of serotonergic, dopaminergic noradrenergic, cholinergic, glutamatergic, GABA-ergic, glucocorticoid and peptidergic function.

4. Treatments for Major Depression Disorder

Speaking of the antidepressants, there are various methods to treat MDD. Hypotheses that suggest the causes of MDD are mainly split up to be two hypotheses: monoamine hypothesis that focuses on the deficit in the amount of monoamines and neurotrophic hypothesis that focuses on the neurotrophic and endocrine factors. First of all, the monoamine hypothesis emphasises lack of cortical, limbic serotonin (5-HT), norepinephrine (NE), and dopamine (DA) neurotransmitters. According to the study, stress prompts the change in brain neurochemicals, mostly monoamines. Whereas, neurotrophic hypothesis believes that depression is related to the loss of neurotrophic support – less support for neurons – and effective therapies can increase synthesising new neurons and connections between synapses in the cortical areas, for instance, hippocampus (McCance & Huether, 2023).

There are older versions of antidepressants which are prevalent these days: monoamine oxidase inhibitors (MAOIs), or tricyclic antidepressants (TCA). These are avoided to use recently due to a higher risk of side effects such as hypotension or weight gain. MAOIs are dominant to treat atypical depression, while TCAs are more effective when used for melancholic depression. The mechanism of MAOI is to irreversibly stop the enzyme monoamine oxidase, which breaks down the monoamine neurotransmitters. Monoamine is necessary as it regulates core brain functions, emotions, and our behaviours. Monoamine oxidase tends to exist as isomers MAO-A and MAO-B; they mainly metabolise dopamine. By blocking these enzymes, synaptic availability of serotonin, dopamine, and norepinephrine, which balance the emotions we feel, is increased, which shows the antidepressant effect. However, TCA is used to increase the amount of monoamines, which block presynaptic serotonin and norepinephrine transporters in the CNS to increase the concentration of these chemicals in the synaptic cleft (Bobo, 2023). These hormones then contribute to better mood regulation and physical functioning.

Single-receptor antidepressants, which also are known as selective serotonin reuptake inhibitors (SSRI), are introduced. Based on the mechanism, serotonin is reabsorbed by the neurons. Similar to MAOIs, SSRIs work by preventing the reuptake by the serotonin transporter at the presynaptic axon terminal, which means the amount of serotonin available increases to progress further messages between neurons. As more serotonin remains in the synaptic cleft, it stimulates postsynaptic receptors, neurons

receiving a signal, for a longer period of time. It has little effects on other neurotransmitters, leading to fewer side effects than TCAs and MAOIs which have a great effect on the neurotransmitters (Chu & Wadhwa, 2023b).

Not only the medications that physically cause biological changes within our body can treat MDD, but also therapy can; psychotherapy, which builds an interpersonal relationship with the therapists, is used to treat depression conditions. It utilises the idea of neuroplasticity, which means how the brain changes its structure and functions as its senses are triggered. Psychotherapy can further modify genetic expression and the structure of the brain by reinforcing the connections and interactions between neurons. During psychotherapy, memory reconsolidation can also be used to encourage the people with MDD to behave in different ways than they have tried to. By bringing an experienced event up to a patient, it initiates a downstream molecular flow and results in an increased rate of transcription and translation of plasticity-related proteins; this helps with remodelling the synaptic connections. Furthermore, by constantly reminding the patient of a certain experienced event, it induces the establishment of long-term memory, which requires a long interaction between hippocampal regions of the medial temporal lobes and medial prefrontal cortex. By asking the patient to elaborate their experience, this evokes the patient to also elaborate their emotional states involved in the past memories, it further increases the consistency between the middle prefrontal cortex and limbic regions, which provokes emotions such as confidence and stability. Psychotherapy also involves empathy-related processing; it's known as Mirror Neuron System (MNS), a dispersed network of brain cells that releases when a person perceives another person performing a similar action done by himself. This stimulates the prefrontal cortex in our brain, which improves the emotion regulations and perspective talking that can ease the mood swings that are easily experienced by the people undergoing MDD (Cammisuli & Castelnuovo, 2023).

What the placebo effect is

The placebo effect refers to assessable improvement in a patient's condition due to their belief that they are being treated rather than the treatment itself; it involves neurotransmitters such as endorphins, cannabinoids, and dopamine. This research suggests that placebo responses are related to physiological mechanisms, such as activation of opioid and dopamine pathways, which are involved in reward and emotion regulation. Placebo effect activates the u-opioid receptors, which contributes to the stress regulation and pain modulation (Zubieta et al., 2005).

The question is, how can placebo help depression? First of all, opioid receptors are binding sites for neurotransmitters that help with pain regulation and emotional responses. Well, biochemically, placebo caused a higher mu-opioid receptor activity in areas of the brain such as the subgenual anterior cingulate cortex and amygdala (Zubieta et al., 2005).

Neuroplasticity is the ability of the Central Nervous system to change its activity in response to stimuli by adjusting its structure, functions, or communications. The appraisal account model implies that placebo can occur due to the brain using its precognitive learnt associations, which helps forecast and shape the future wellbeing and emotional status. Placebo engages the network of the brain that is active during rest such as fronto-limbic areas that include left dorsolateral prefrontal cortex, anterior cingulate cortex, and ventral striatum, considered as the priority in the placebo condition (Atlas and Wager, 2014).

Placebo also encourages the growth in dendrites of neurons and connections between neurotransmitters via providing new synapses. Additionally, placebo provides the blockade of the N-methyl-D-Aspartate receptor on glutamate, which is the excitatory neurotransmitter, neurons, stimulating the release of Brain Derived Neurotrophic Factor; this increases synthesis of new synapses and dendrites, improving the electrical signals (Seymour & Mathers, 2024).

Speaking of synaptogenesis, synaptic loss can bring a decrease in the volume of cortical and limbic brain regions such as prefrontal cortex and hippocampus; reduction of connectivity of hippocampus and PFC can further lead to disturbance in mood disorders, which rationalises the symptoms of depression (Duman & Aghajanian, 2012). As depression originates from the formation of abnormal circuits in our brain, placebo can induce cerebral circulation and functional neuro-radiological change that is suggestive of neuroplasticity in fronto-limbic areas (Seymour & Mathers, 2024b).

5. Methodology

This experiment explores whether expectation of mood improvement influences self-diagnosed wellbeing. My study was conducted in the high school located around Bandar Enstek, Negeri Sembilan Darul Khusus, Malaysia. This boarding school consists of the students aged from prep school up to Sixth Form, coming from around 28 different countries.

To discover the method to provide the placebo effect, several different ways were considered: Timtam candies given as dummy pills, or tea given as prescription on a regular basis. However, direct injection of substances to the participants regardless of their harmlessness could cause various issues such as ethical issues, parental consents. Furthermore, attempting the placebo effect on the prep school students whose brains have not been fully developed might be negatively stimulating for them. Hence, I decided to choose the sample from the Sixth Form randomly; 10 participants were chosen randomly. Since my boarding school has set up the daily schedule from 8 am to 4 pm, this keeps most of the participants' schedule uniform.

To assess their emotional status, I used PHQ-9 to measure the severity of depression in each participant before the experiment to see if the improvement in Oxford Happiness Questionnaire (OHQ) varies according to their intensity of depression. I also conducted interviews before and after the experiment to see basic symptoms that MDD might show, such as avoiding eye contact, or extremely varying speaking speed. I chose PHQ-9 and OHQ as measurements to assess participants' emotional status since no professional diagnosis could be given and quantitative data are needed to plot the graph; furthermore, observing their psychomotor issues might be subjective and the two chosen questionnaires are the most widely used. Google forms were used to conduct the survey with my participants, as attached as Appendix A and B. Based on the participants' responses, quantitative data could be collected. Even though the participants are not diagnosed to have MDD, it assesses how close each individual is to the spectrum of depression; however, as it's self-reported data, it might still bring bias. According to each participants' emotional status, to what extent the placebo effect would be effective would also be found.

To provide the placebo effect, the frequency-based 432Hz music was chosen as it's commonly known to have a mood improving, meditating effect, while it hasn't scientifically been substantiated; it also sounds relatively similar to the music that experimental group is listening to. Participants were divided

into two groups; 5 randomly chosen students were asked to listen to experimental music from Brain.fm, while the other group was asked to listen to 432Hz music. Participants were asked to listen to music for one week everyday. Though both groups received auditory stimuli, the key independent variable was the type of music participants were listening to. I also sent out a parental consent letter regarding the safety of the participants and the ethical assurance. To spot any change in each participant's mood, OHQ was completed on a daily basis throughout the entire experiment after listening to music.

6. Results and Discussion

Figure 1: The difference in OHQ before and after experiment vs PHQ-9 for each PHQ-9 index for placebo group

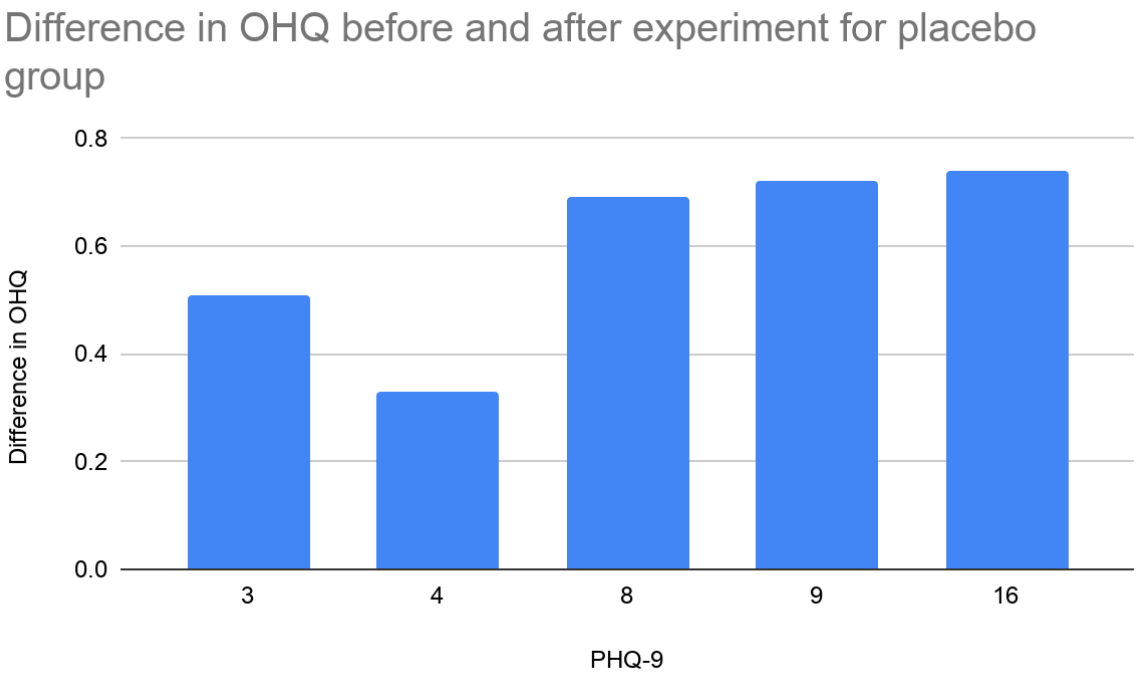

Figure 1 shows how the score of the Oxford Happiness Questionnaire differs from pre-experimental status to the last day of the experiment, only including the placebo group of participants. There is a fluctuation in data between the PHQ-9 index of 3 and 4, but the difference in OHQ before and after the experiment increases as the PHQ-9 value increases up to PHQ-9 value of 16. It reaches a maximum increase of 124.2% from the PHQ-9 index of 4 to the PHQ-9 value of 16. This can also indicate that placebo effect would work better with the patients that are experiencing severe symptoms of MDD as the participants with higher PHQ-9 scoring experienced greater improvement in mood condition based on change in OHQ value. However, since the experiment is not repeated, error bars are not provided.

Figure 2: Difference in OHQ before and after experiment for experimental group vs PHQ-9 for each PHQ-9 index for experimental group

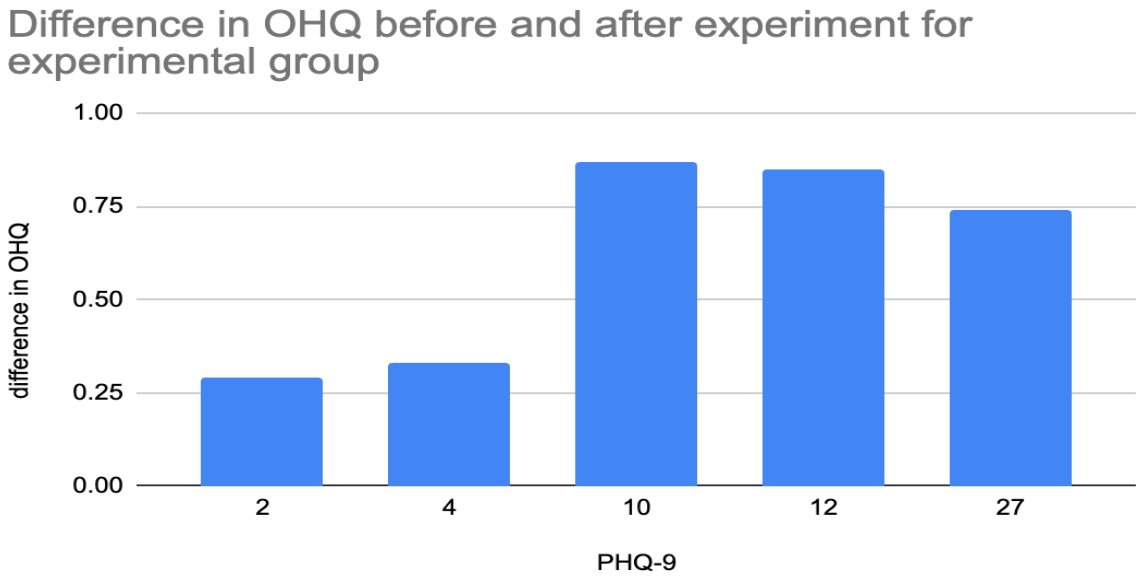

Figure 2 shows the difference in OHQ before and after the experiment for the experimental group depending on the PHQ-9 index. Similar to the placebo group, as the PHQ-9 index value increases, meaning that actual treatment also works better on the participants with higher PHQ-9 index. It shows a sudden increase between PHQ-9 values of 4 and 10, showing an increase of 2.6 times. However, unlike the placebo group, as the PHQ-9 index increases over 10, the difference in OHQ decreases; this can indicate that actual soundtrack might only work for the individuals that are not experiencing extremely severe depression.

Figure 3: Change in OHQ for experimental and placebo group over the experiment

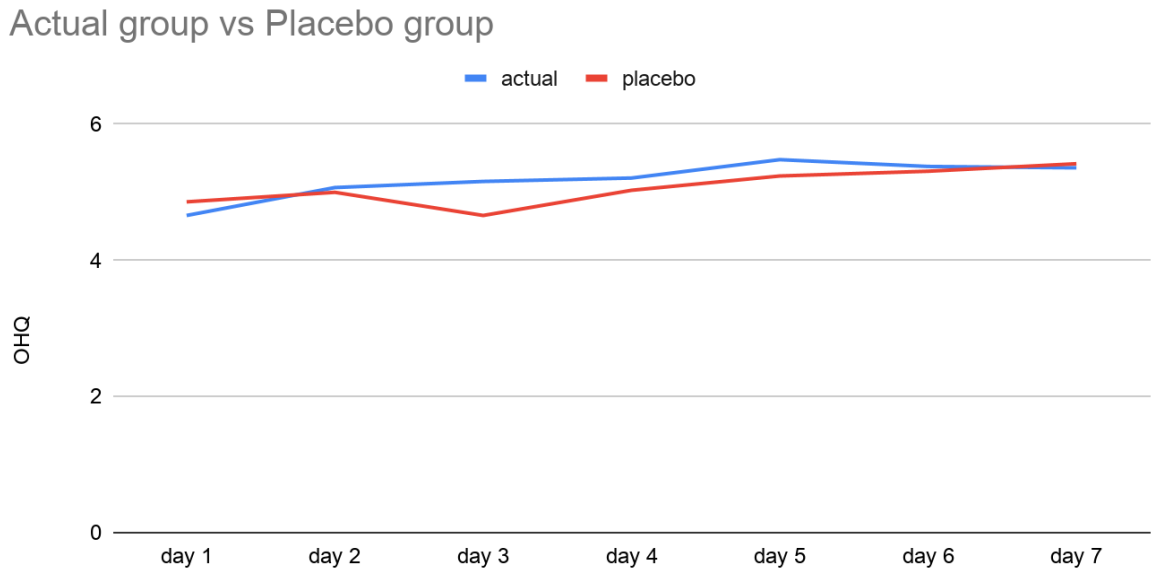

Figure 3 then shows how the scoring of the Oxford Happiness Questionnaire changed over the period of experiment. Both groups of participants who listened to the actual mood-improving music and

the placebo music display increasing scoring of OHQ over the week, meaning that mood-improving music is a reliable source and placebo music had nearly the same effect as the actual mood-improving music. In fact, the placebo group showed the greater scoring of OHQ on the last day; the group who listened to the mood improving music showed an average score of 5.42, while the placebo group showed an average score of 5.22. This result shows that the group of participants that had the belief they were receiving an auditory stimulus and the other group that listened to an actual auditory stimulus showed relatively similar rate of improvement in OHQ value, meaning that placebo group showed similar improvement in mood condition compared to the actual group. The results show that the placebo effect can positively affect the mood condition to a similar extent to the effect from the actual mood-improving music. It could be concluded that the placebo effect shows the potential to replace the actual treatment that has a risk of side effects, which also aligns with my hypothesis.

7. Limitation of this research

While the methodology could be viewed as a safe and ethical method as it didn't harm participants in any way and the parental consents have been recorded, however, the period of experiment might not have been long enough since the mood shift hasn't been proven in a long term. Furthermore, more reliable results might be obtainable if the group of participants were bigger, and if the range of age in participants were larger. The sample group wasn't diagnosed as MDD, meaning the experiment doesn't necessarily show the comparison between an actual and placebo treatment.

However, the other control variables that could have affected the participants' mood shift, such as school schedule, or atmosphere were mostly controlled. Since the participants and I are all situated in the same boarding school, under the same school schedule from 8:00 am to 4:00 pm, it could be said that control variables were well controlled.

Furthermore, the sample size is pretty small as only 10 participants were involved in the experiment as it was pretty challenging to find students that would listen to the music forcefully everyday. Since there were only two groups of participants, there is no control group that didn't receive auditory stimuli, making it difficult to confirm that placebo is the only factor affecting the result. Additionally, the duration of the experiment was relatively short as a week. Hence, the data might not be fully reliable as the OHQ value might change only if the participants listened to the music for a longer period of time. Lastly, the way to assess the participants' mood condition is based on the self-reported data, which might include some risk of bias. Moreover, the study hasn't been repeated nor conducted for a long period of time (1 week), hence statistical testing and error bars couldn't be given. This makes the data shown less valid and reliable. However, since the placebo group in my experiment showed a positive change in emotional status over time, it doesn't necessarily mean that the diagnosed MDD patients will also show an enhancement in their emotional state. This might be caused by some symptoms such as profound disbelief, especially patients who have suffered from unstable relationships with their surrounding people; it's challenging to directly believe the fact that they are told.

8. Conclusion

The purpose of the study was to explore if placebo is even valid, and if placebo could be applied for the neurological disorders, such as MDD. This experiment showed that placebo music, in the form of

frequency-based music, could have a similar effect as the actual music known to regulate one's emotions, which demonstrated the potential of placebo that could be further utilised to help with MDD.

As the method for placebo in my experiment didn't involve a group of patients that have been diagnosed as MDD, it was challenging to ascertain as to whether my experiment results showed an effect of clear placebo compared to an actual treatment. Furthermore, other variables such as the time in a day they listened to the music, how much of delay there was for the participants to respond to the questionnaire after listening to music were not controlled in the experiment, which could have affected the individuals' mood. Moreover, the assessment of the emotional state of individuals was conducted via OHQ, which doesn't show a direct correlation with their tendency for MDD. The assessment was conducted in this way in order to minimise the risk of the experiment that could harm participants emotionally. Hence, this experiment partially answered my question as the placebo effect showed a similar effect as the scientifically proven mood-improving soundtrack, though it didn't involve the diagnosed MDD patients. To a certain extent that considers the safety for the MDD patients, the experiment could be conducted towards the patients to see any difference in the results compared when the experiment was done to the participants without MDD. Further investigation could be executed to show which type of placebo would work the best; for instance, the experiment could compare the effects of gustatory, auditory, or visual placebo treatment.

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