

## Hypnosis and music interventions (HMIs) inactivate HIF-1: A potential curative efficacy for cancers and hypertension <sup>☆</sup>



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### ABSTRACT

Hypnosis and music interventions (HMIs) have shown positive influence on cancers for nearly 200 years, but the underlying mechanisms were rarely explored systematically. The hypothesis suggests a potential curative efficacy of HMIs on cancers by inhibiting hypoxia inducible factor-1 (HIF-1), which is a key mediator of cancer development, especially under hypoxic conditions. HMIs are sufficient to attenuate the pain and anxiety degree of individuals, improve multiple psychological and physiological parameters, and consequently, lead to increased oxygen saturation *in vivo*. Furthermore, abundant oxygen *in vivo* inhibits the activation of HIF-1 and potentially blockades kinds of HIF-1-induced oncogenic signaling pathways. The hypothesized efficacy of HMIs is very similar to anti-cancer medicines targeting HIF-1. The implication of the hypothesis in preventing hypertension is also discussed. In summary, the hypothesis clearly suggests the potential involvement of the convenient, safe, non-pharmaceutical, and low-cost HMIs in preventing HIF-1-mediated diseases, including cancers and hypertension.

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### Introduction

*Hypnosis and music interventions have a long history of assisting cancer treatment*

Hypnosis is a suggestive intervention alleviating individuals' sufferings and is a non-pharmacologic tool combating anxiety of cancer patients [1,2]. In the history of cancer treatment, the earliest hypnosis event was conducted approximately 200 years ago, and nowadays hypnosis is considered as an effective way to assist cancer therapy [3]. Music is also used to adjust the human's mood in the daily life and has strong effects on mental and bodily activity [4,5].

Hypnosis and music interventions (HMIs) play positive roles in cancer treatment, such as complementing the modern therapeutic approaches, improving psychological and physical parameters, and alleviating pain and anxiety of cancer patients [3,6–11]. For

example, HMIs significantly alleviate the frequent symptom “hot flashes” in breast cancer patients [12–15]. Presently, more and more patients are willing to use HMIs to aid their treatment, and a growing number of clinical trials are currently carried out to evaluate the therapeutic efficacy of HMIs for cancers [3,6,7,12,14,16–18].

Nonetheless, the clinical application of HMIs is still a controversial topic and receives bias in some areas [3,7,17]. One important puzzle is that the curative mechanisms, by which HMIs benefit cancer patients, have not yet been demonstrated clearly. Herein, we intend to propose the anti-cancer efficacy of HMIs by inhibiting hypoxia inducible factor-1 (HIF-1) which plays an important role in oncogenesis.

*HIF-1 is an essential transcriptional factor mediating the growth of tumor cells*

Tumors contain hypoxic regions with much lower oxygen concentration compared to normal tissues, while the transcription factor HIF-1 enables tumor cells to grow in the hypoxic micro-environment [19–22]. HIF-1 up-regulates kinds of cellular responses to hypoxic stress and is essential for the life cycle of tumor cells [19,20]. First, HIF-1 alters the metabolism of hypoxic tumor cells from oxidative phosphorylation to glycolysis in order to increase energy supply [23]. Second, HIF-1 aggregates cancer

*Abbreviations:* HIF-1, hypoxia inducible factor-1; HMIs, hypnosis and music interventions; bpm, beats per minute.

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development by inducing multiple downstream genes involved in the proliferation, invasion, metastasis, and angiogenesis of tumor cells [19,24–26]. Third, the increased activity of HIF-1 is notably associated with higher cancer risk and higher cancer morbidity [19]. However, inhibiting HIF-1 has potent anti-cancer effects [27–29], and we therefore collect the relevant evidence demonstrating how HMIs inactivate HIF-1 and benefit cancer treatment.

## The hypothesis

### The definitions of HMIs

HMIs are defined as the combination of hypnosis and relaxing music, and several key points of HMIs are listed below, respectively.

The definition of hypnosis [2,3,6,13,14,16,17,30,31]:

1. Participants need a quiet environment and a separate room, lying on bed or sitting in a sofa.
2. Participants listen to a professional hypnotist or a hypnosis tape, trying to relax the whole body and remain still and calm.
3. The former part of the hypnosis is a process of hypnotic induction, which should be compatible with the age, interest, and cognitive levels of participants and promote participants to gain physical and mental relaxation.
4. The latter period of the hypnosis is consisted of relaxing, encouraging, comfortable, analgesic, and other positive suggestions.
5. The whole process of hypnosis is often accompanied by relaxing music.

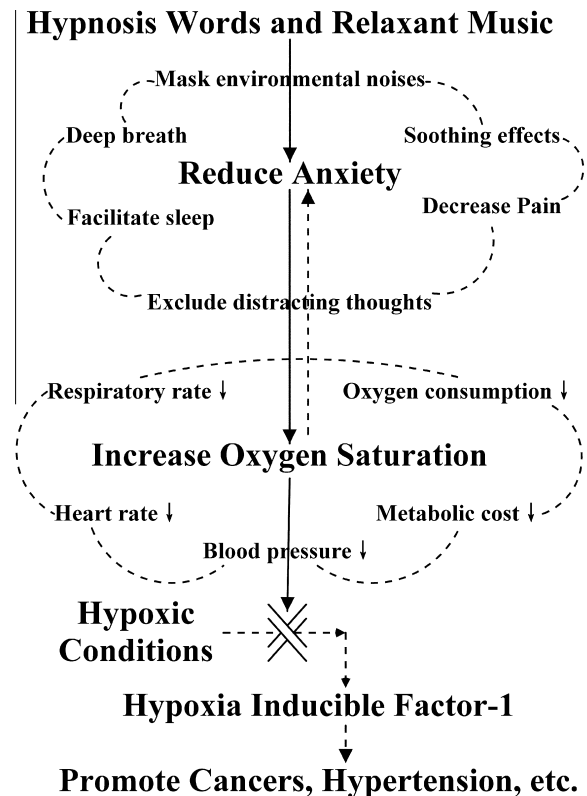
The definition of relaxing music [5,7,8,10,32,33]:

1. The music should be appropriately selected by a registered music therapist, and participants are familiar with and appreciate the music.
2. The music (without lyrics) should be melodic, sedative, and non-motivational.
3. The melody of the music is controlled by volume and pitch.
4. The frequency of the music is about 60–80 beats per minute (bpm).
5. The decibel range of the music is about 30–40 dB.
6. Buddhist music, classical music, folk music, piano music, and harp music are preferentially recommended. Several types of music could be selected, and let participants take turns to listen.

The duration of each HMIs session is about 15–30 min, and multiple listening sessions give participants more positive relaxation and lead to greater health benefits [7,9]. Successful HMIs is to achieve the thoroughly hypnotic relaxation, both mentally and physically.

### HMIs potentially inactivate HIF-1

Previous research has ever demonstrated that HMIs can influence the chemical activity of some molecules *in vivo* [8]. As illustrated in Fig. 1, we hypothesize a curative mechanism by which HMIs inactivate HIF-1 and subsequently contribute to the prevention of cancers. The hypothesized effects of HMIs are very similar to the therapeutic efficacy of some anti-cancer medicines inhibiting HIF-1. On the other hand, because HIF-1 is also correlated with hypertension, we will further discuss the implications of the hypothesis in preventing hypertension, including a short-term as well as a long-term effect.



**Fig. 1.** Hypnosis words and relaxant music reduce the anxiety levels of individuals mainly by inducing deep breath and soothing effects, masking environmental noises, facilitating sleep, excluding distracting thoughts, decreasing stressful behaviors, and decreasing pain score. The reduced anxiety levels result in decreased respiratory rate, heart rate, blood pressure, metabolic cost, and oxygen consumption, leading to increased oxygen saturation *in vivo*. Increased oxygen saturation *in vivo* in turn alleviates the anxiety levels of individuals, and potentially blocks hypoxia inducible factor-1-mediated diseases, including cancers and hypertension.

## Evaluation of the hypothesis

*HMIs alleviate the anxiety degree of individuals including cancer patients*

Cancer patients, even survivors who have finished the clinical therapy, often experience side effects, pain, fatigue, and fear of recurrence [3,6,7,14], which causes a great deal of anxiety. Anxiety leads to negative health outcomes, longer recovery periods, resistance to treatment, and nightmares, while HMIs are well-established means of decreasing anxiety caused by pain and stress [7,30,34,35]. For example, HMIs reduce anxiety in the painful therapeutic procedures such as biopsy and surgery for cancer patients [3,14,36,37].

We have listed ten examples in Table 1, indicating the positive effects of HMIs on attenuating anxiety degree. HMIs mask environmental noises, decrease stressful behaviors, have soothing effects, and facilitate sleep [38,39]. HMIs also inhibit distracting thoughts, lead to deep breath, enhance the functions of lung and heart, and improve the anxiety-related physiological parameters [1,3,5,40].

*HMIs lead to increased oxygen saturation *in vivo**

Alleviated anxiety induced by HMIs has positive influence on the physiological parameters *in vivo* [31,34,49]. As briefly summarized in Table 1, HMIs reduce respiratory rate, heart rate, blood pressure, metabolic cost, and oxygen consumption, and consequently increase oxygen saturation *in vivo* [50,51]. The main reasons may lie in the following aspects:

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