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Placebo 'serotonin' increases heart rate variability in recovery from psychosocial stress ☆

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HIGHLIGHTS

- Placebo suggestion can enhance physiological stress recovery.
- Placebo 'serotonin' increased vagally-mediated heart rate variability.
- Support for placebo-induced activation of top-down regulatory systems

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ABSTRACT

Objective: To investigate placebo effects on heart rate (HR) and heart rate variability (HRV) in recovery from a psychosocial stressor.
Methods: A healthy sample underwent two mental arithmetic stress tests in one experimental session. After undergoing the baseline test, participants were randomized into control or placebo groups. Prior to the second stress test, the placebo group received an intranasal dose of 'serotonin' (placebo) with the suggestion that it would enhance recovery. HR and HRV were assessed throughout procedures.
Results: There was an increase in vagally-mediated HRV in the placebo group. The change in HR did not differ between groups.
Conclusions: Placebo suggestion can enhance autonomic recovery after psychosocial stress. Findings are consistent with the notion of top-down mechanisms of placebo effects, but further research would need to specifically examine the role of top-down regulatory pathways as possible mediators of placebo-induced changes in autonomic function.

1. Introduction

Once dismissed as a nuisance factor in clinical trials, the placebo effect is now acknowledged as a genuine psychobiological phenomenon [1]. Placebo protocols can stimulate endogenous neurobiological systems [2–4], generate psychophysiological responses [5–7], and even change the brain [8]. Responding to placebo treatments may represent a sort of endogenous healthcare system [1].

There are a number of ways of generating placebo effects [1,9]. Placebo-induced expectations, in which the suggestion of symptom improvement or therapeutic benefit is delivered with placebo treatment, has been investigated most extensively in experimental pain [8,10,11]. Consequently, much is known about the capabilities and mechanisms of placebo effects in this area, but for other areas such autonomic nervous system (ANS) activity there is a relative dearth of research [12,13]. While there are established links between the ANS and pain regulation networks [14], the specific modulation of ANS function by placebo suggestion represents a different question.

Heart rate variability (HRV), the beat-to-beat variation in heart rate, is a measure of the ANS that indexes cardiac regulation [15]. HRV is believed to represent the fluctuations in autonomic inputs to the heart, with the parasympathetic and sympathetic systems working in dynamic equilibrium to regulate an organism's reaction to and recovery from stress [16]. The *neurovisceral integration* model describes a regulatory network with top-down pathways between the prefrontal cortex (PFC) and the ANS, and HRV is thought to measure the PFC regulation of vagal activity [16].

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In a similar manner, expectation-induced placebo effects are also thought to arise from top-down regulatory pathways that originate in the PFC [2,17]. Suggestions of benefit are thought to generate cognitive expectations, which then stimulate endogenous homeostatic processes [11]. Considerations of this kind suggest that HRV might be a suitable index of ANS activity in response to a suggestive placebo manipulation.

Prior work has found HRV metrics to be somewhat unresponsive to placebo suggestion; however, HRV has typically been assessed as a potential mediator of primary outcomes measures rather than being the focus of the manipulation [18–20]. Given HRV's role in regulating an organism's response to stress [16], it would appear that attempts to modulate HRV would be best served in the context of stress. One study has shown that placebo suggestion can influence HRV parameters after a painful stressor [21]. However, given the established interplay between pain and ANS networks [14], the use of a pain task to generate a stress response may be problematic, in such that data may not necessarily translate into non-pain paradigms, or to *psychological* stress.

In experimental settings, the effects of psychological stress can be investigated with the use of psychosocial stressors such as noxious social evaluative tasks, which can generate a physiological stress response [22]. Further, perhaps the most validated HRV measures are those indexing the vagally-mediated return to homeostasis in recovery from a stressor [15,23]. Thus, attempts to influence HRV specifically with a placebo protocol but without the confounds associated with pain processes, may be best accomplished with the use of a psychosocial stress task and the suggestion of enhanced recovery from the stressor.

The current report investigated whether a suggestion based placebo protocol could enhance recovery from experimentally induced psychosocial stress. An intranasal spray of 'serotonin' (the placebo) was administered with the suggestion that it would enhance recovery from a mental arithmetic stress test. Heart rate (HR) and HRV were measured during baseline and post manipulation phases. A control group underwent the same procedures except they did not receive the intranasal spray or the accompanying verbal suggestion. It was hypothesized that those in the placebo group would have an increase in HRV and a reduction in HR in the recovery period after the second stress test; relative to the first stress test and the control group.

2. Methods

Note, this study is part of a larger investigation into the placebo personality [24].

2.1. Participants

A sample of 63 volunteers (21 males and 42 females) was recruited via notices posted on university intranets, social media sites, and the distribution of flyers. No course credit was offered for participation. To be eligible, participants had to be able to read and write English, have no chronic medical or psychological conditions, and, if female, not be pregnant. Those eligible to take part were invited to participate and were sent consent forms before being scheduled for one 75-minute laboratory session. Of the 152 who initially expressed interest in the study, 91 (60%) returned the screening questionnaire and 75 of them (82%) were eligible with 17 excluded based on the criteria described above. Of the remaining 75, 11 either did not respond to the invitation or were unable to be scheduled for a laboratory session. A total of 64 participants completed the experimental session, but one male participant had to be excluded upon completion as debriefing indicated he was not blind to the study purpose.

2.2. Design, randomization and blinding

This was a randomized controlled experiment. Participants were block-randomized into placebo or control conditions by blind selection from an envelope. The researcher carried out randomization procedures after they had delivered the introductory overview to the participant and left the lab (Fig. 1). The research assistant (RA) remained in the lab and was not privy to the randomization process. The approach avoided the possibility of knowledge regarding group allocation affecting interactions between the participant, the RA, and the researcher during any Phase I procedures. The researcher delivered the placebo manipulation in Phase II, which enabled the RA to remain blind to group, and thus neutrally administer both stress tests. Participants were told the purpose of the study was to investigate the relationship between serotonin, stress reactivity and stress recovery (deceptive cover story).

2.3. Procedures

The RA carried out all Phase 1 procedures, starting with the baseline questionnaire (see measures), and a baseline 'resting' (seated) measure of HR and HRV (Base 1). The RA then administered the first stress test, a 5-minute mental arithmetic test adapted from a previous study [25]. Participants were told this was a 'mental arithmetic IQ test' and were asked sequentially to subtract a number (163) from a starting number (8500) as quickly as possible. Participants could not progress until they gave the correct answer. If they paused, they were prompted to carry out the task as quickly as possible. After the stress test a 5-minute recovery period commenced (Recover 1). All participants underwent the same procedures for Phase I.

Phase II commenced with another baseline HR and HRV reading (Base 2). The RA then left the lab and was replaced by the researcher who remained in the lab for the duration of Phase II. Participants were then told whether they were in the 'serotonin' (placebo) group or the 'comparison' (control) group by the researcher and shown a brief video in which information regarding procedures was delivered by a credible source (an Associate Professor in the Medical School). For those in the control group the emphasis of the video was on how important control groups were in experimental trials. Those in the placebo group were told that they would receive an intranasal dose of serotonin just before and just after the second stress test and this would enhance their recovery from the stress test. Consistent with the aim to utilise an explicit suggestion protocol, detailed information was provided about the stress response, how HRV was a measure of this, indexing autonomic regulation and sympathetic and parasympathetic activity, and that this would be measured by the heart rate monitor they were wearing. Serotonin was described as a neurotransmitter that plays a key role in stress recovery and its administration via the intranasal spray would reduce heart rate and stress, thus enhancing recovery from the stressor.

After this video, the researcher explained the administration and re-iterated its effects before administering one spray of the 'serotonin' (5% sterile saline solution) in each nostril. The control group were advised that they would undergo a second stress test. The control group did not receive an intranasal spray to avoid the possibility of this treatment ritual affecting responses [26]. The RA then re-entered the room and administered the second stress test. Participants were not advised of the nature of this test until it commenced. The second stress test was the same as the first, with the exception of the starting number (8600) the subtracting number (177) and the presence of the researcher (behind a screen), which was designed to counteract habituation by elevating the stress of the second test without deviating too much from Phase I procedures. Immediately after the stress test the RA left the room and placebo group participants received a top-up dose of 'serotonin' (same procedure) and were told this would 'enhance their recovery during the five minute recovery period' (the control group again received nothing), before all participants commenced the second 5-minute recovery period (Recover 2). Finally, participants were given a $20 voucher and thanked for their time.