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A personality mathematical model of placebo with or without deception: an application of the Self-Regulation Therapy

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1 Introduction

A series of studies show that placebo has an important impact on the improvement in various disease symptoms [1]. However, placebo has important ethical limitations since it is based on deception [2]. Besides, a series of pioneering studies show that placebo is effective even without deception. In fact, the placebo without deception improves the symptoms of irritable bowel syndrome, allergic rhinitis, headache and back pain, major depression, attention-deficit hyperactivity disorder (ADHD) and cancer-related fatigue [3]. Two mechanisms that have been proposed to explain the placebo effect: Expectations, and Classical Conditioning [4]. However, it is possible that the same mechanisms act to both deceptive placebo and without deception. For instance, a study on the placebo without deception to treat pain proves that the conditioned patients experienced a therapeutic effect for longer periods (4 days) even though when they know they are receiving placebo. Thus, the placebo without deception can be independent of expectations [5]. In other studies, increasing positive expectations improves the placebo without deception result [6]. It is very likely that the two mechanisms, the classical conditioning and the increase in expectations, contribute to the placebo effect of no deception [7]. On the other hand, the Self-Regulation Therapy (SRT) is a therapeutic procedure based on suggestion. It combines positive expectations and classical conditioning to reproduce the effects of drugs [4]. Therefore the SRT can be considered a placebo without deception procedure. This study compares the effectiveness of the SRT and deceptive placebo for the reproduction of the effect of a stimulant drug, methylphenidate (MPH), as well as the dynamical response to both SRT and deceptive placebo can be reproduced with a personality mathematical model presented.

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2 Methodology

A within-subject, crossover, double-blind, placebo-control design was employed in this study. Two healthy male volunteers participated in this study, with ages of 56 and 57 years old. A single-case experimental ABC design was used. In each phase, one of three conditions was administered: placebo, 5 mg or 10 mg of MPH. The order of administration (MPH or placebo) was determined by random assignment, unknown both for the participants and the research assistant. In a previous study [8], Participant 2 used the SRT to reproduce the effect of MPH, whose result will be considered in this study. In all phases the participants filled in a sheet of adjectives every 10 minutes over a 3-hour period. These adjectives measure the General Factor of Personality (GFP), which represents the organism's general activation. It is a Five-Adjective Scale of the General Factor of Personality, and the five adjectives are adventurous, daring, enthusiastic, merry and bored [9]. The participants had already experienced the effects of MPH on previous occasions. At the end of the experiment they tried to guess what had been taken in each phase.

3 Results

Fig. 1 depicts the GFP scores during the 3-hour period of Phase Placebo and 10 mg condition for Participant 1. He had correctly guessed that he took 10 mg of MPH (the most intense effect of the two MPH conditions) but thought that the placebo was 5 mg. This was a deceptive placebo. The shape of both curves is very similar (inverted U) as well as the peak, but the effect is clearly faster (the slope is more pronounced) in the 10 mg of MPH condition. Fig. 2 depicts the GFP scores during the 3-hour period of Phase Placebo, 5 mg (the most intense effect of the two MPH conditions) and SRT conditions for Participant 2. This participant had correctly guessed the placebo condition and thought that the 5 mg was 10 mg MPH. The three curves are very similar (inverted U). It only fits to stand out that SRT effect is slightly more intense than placebo. By comparing the placebo response of the two participants, we observe that the peak of the effect is similar for both of them, but that the shape of the curve is different. Thus, in the case of Participant 2, the shape of the placebo curve was very similar to that of the SRT, with a very fast onset, indicating that the placebo effect in Participant 2 is a more accurate reproduction of the effect of the drug.

4 The personality mathematical model

The model presented is a stimulus-response model, where the stimulus can be MPH, SRT or Placebo. It si written as:

$$\left.\begin{array}{rcl} \frac{dm(t)}{dt} & = & -\alpha \cdot m(t) \\ m(0) & = & M \\ \frac{ds(t)}{dt} & = & \alpha \cdot m(t) - \beta \cdot \int_0^t e^{\frac{x-t}{\tau}} \cdot s(x) \cdot y(x) dx \\ s(0) & = & 0 \\ \frac{dy(t)}{dt} & = & a(b - y(t)) + p \cdot s(t) \cdot y(t) \\ y(0) & = & y_0 \end{array}\right\} \quad (1)$$

Note that (1) is a coupled a system of two differential equations and one integro-differential equation. The $m(t)$ variable is evolution of the stimulus before entering in the metabolizing organism system, being M the stimulus initial amount and α is the stimulus assimilation rate. The $s(t)$ variable represents the stimulus, i.e., the amount in organism of the stimulus, assuming that the its initial value is zero, due to the experimental conditions, being β is the stimulus metabolizing rate. The $y(t)$ variable represents the GFP dynamics; and b and y_0 are respectively its tonic level and its initial value. Its dynamics is a balance of three terms, which provide the time derivative of the GFP: the homeostatic control ($a(b - y(t))$), i.e., the cause of the fast recovering of the tonic level b, the excitation effect ($p \cdot s(t) \cdot y(t)$), which tends to increase the GFP, and the inhibitor effect ($\beta \cdot \int_0^t e^{\frac{x-t}{\tau}} \cdot s(x) \cdot y(x)dx$), which tends to decrease the GFP and is the cause of a continuously delayed recovering. Parameters a, p, q and τ are named respectively the homeostatic control power, the excitation effect power, the inhibitor effect power and the inhibitor effect delay. Unlike the model presented in [10], the excitation effect is non-linear and the inhibitor effect appears in the differential equation of the $s(t)$ dynamics. This last feature permits to reduce from eight to seven the number of parameters to be calibrated, which represents a reduction in the model calibration complexity. In addition, the hypothesis that underlies the model is different to the presented in [10]: the inhibitor effect is the delayed organism's reaction to the effects produced by the stimulus in order to decrease the amount of the stimulus in the organism.

The calibration of (1) provides two different kinds of results, depending on the participant and on the kind of stimulus. On a hand, the model does not calibrate correctly for the scores of Participant 1 when the stimulus is placebo: the determination coefficient for the GFP response is $R^2 = 0.49$ and the residuals are not random. This case corresponds with a non-clear subjective sensation of the response. However, the model does calibrate correctly when the stimulus is 10 mg of MPH, with determination coefficient for the GFP response R^2=0.94 and random residuals. It does correspond with a clear subjective sensation of the response. The result is provided in Fig. 3. On the other hand, the model does calibrate correctly for the three kinds of stimulus in Participant 2. For placebo stimulus $R^2 = 0.98$, for the 5 mg of MPH stimulus R^2=0.97, for the SRT stimulus $R^2 = 0.85$, and for the three cases the residuals are random. They also correspond with clear subjective sensations of the response. The results are provided, respectively, in Fig. 4, Fig. 5 and Fig. 6. We show the model's parameters for the most important conditions for both participants in the Tables 1-4. We can see in case 1 that parameter M in table 1, which represents the equivalent of 10 mg of MPH in the placebo condition, is low (6.13), while in case 2, we observe that parameter M is very close to 10 mg, being 9.19 and 9.44 for placebo and SRT conditions, respectively. All this confirms what has been said above, and it is that in the SRT-trained participant a more similar effect to the drug is observed, whether it is a placebo with deception or without deception.

5 Discussion

In this study we compared the effect of a single dose of methylphenidate with placebo over 3 hours on a personality scale. The participants were volunteers who had already experienced the effects of MPH previously. The effect curve (inverted U) of the placebo was very similar to that of MPH. This supports the thesis of classical conditioning as a basic mechanism of the placebo

effect. Participant 1 thought he was taking 5 mg of MPH when he actually took a placebo. This can support the idea that novelty and uncertainty can be positive factors in placebo response, especially in placebo without deception, whose basic mechanism is the prediction and error processing. More dopamine is only release with the uncertainty [11]. The peak of the curve of the placebo effect was very similar for the two participants and although the shape of the curve was similar (U Inverted), the slope was much more pronounced in Participant 2, which makes the effect more similar to that produced by the MPH. This can be interpreted as the deceptive placebo in a person trained with SRT is very similar to the reproduction of the effects of the drug (placebo without deception). In addition, Participant 2 guessed the placebo since he was able to distinguish it from the effect of the drug, sometimes by the fact of being trained to discriminate the situations in which he takes the drug and in which he reproduces the drug. In summary, the experience with the drug increases the placebo effect, and the training in SRT causes the placebo to be easily detected but, even so, its effect is even more similar to that of the drug. The therapeutic application of these results is possible, using deceptive and placebos without deception as "dose extenders" based on classical conditioning. In a study with children with ADHD, pairing open-label placebo pills with amphetamines allowed children to be treated effectively with a lower dose of stimulant medication [12]. Besides, training patients with SRT can allow them to learn and use coping strategies to overcome anxiety and depression disorders and other kinds of diseases [13]. Finally, the personality mathematical model presented, which has a stimulus-response model, is an advance respect to the presented in [10]: it has one less parameter to be calibrated and links non-linearly the stimulus dynamics to the GFP dynamics. It can become in a future a good mathematical tool to predict the FGP responses to the placebo and SRT stimulus, after being calibrated the GFP dynamics as a consequence of MPH consumption, as well as to classify typologies of personality that help us to solve the personality disorders mentioned above.

Figures

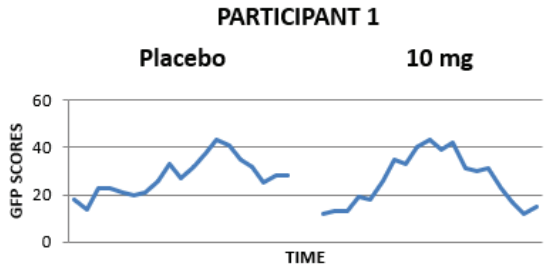

Figure 1: GFP dynamics of Placebo and 10 mg conditions for Participant 1.

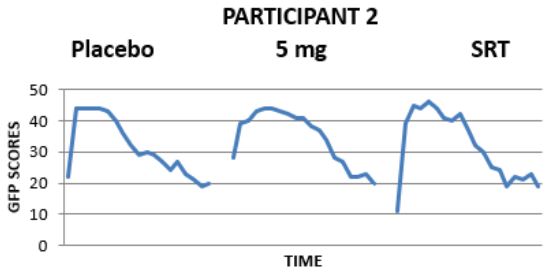

Figure 2: GFP dynamics of Placebo, 5 mg and SRT conditions for Participant 2.

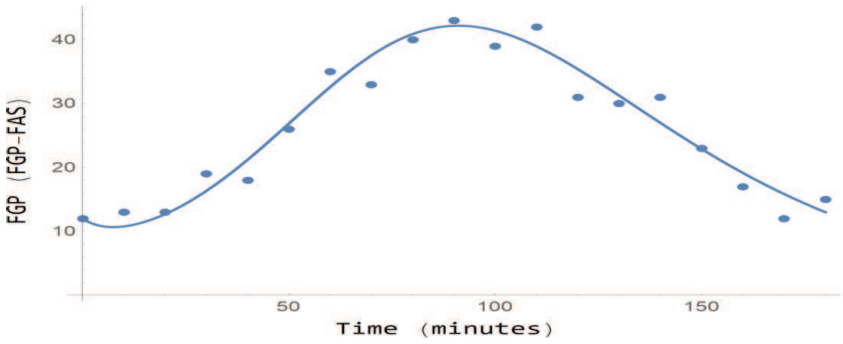

Figure 3: GFP dynamics for 10 mg of MPH (Participant 1). $R^2 = 0.94$.

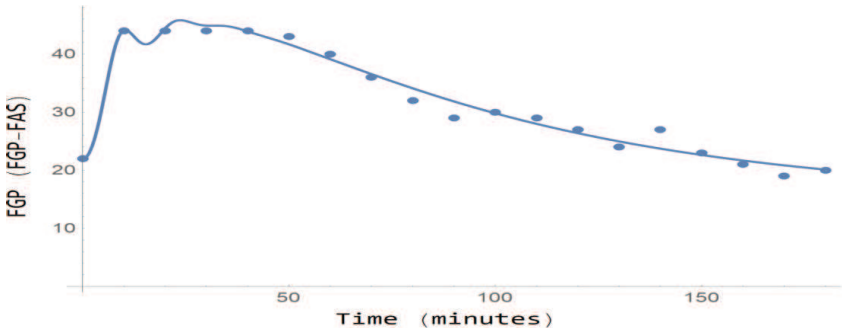

Figure 4: GFP dynamics for placebo (Participant 2). $R^2 = 0.98$.

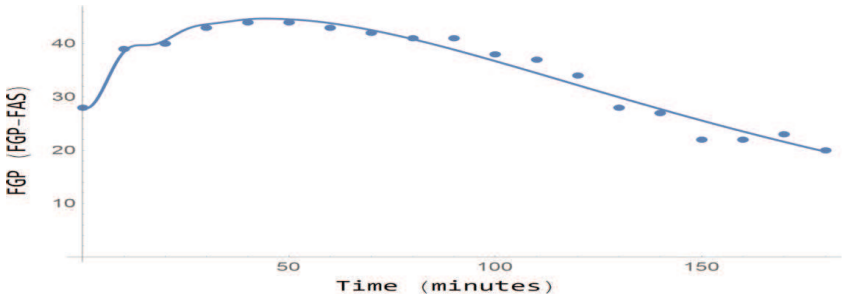

Figure 5: GFP dynamics for 5 mg of MPH (Participant 2). $R^2 = 0.97$.

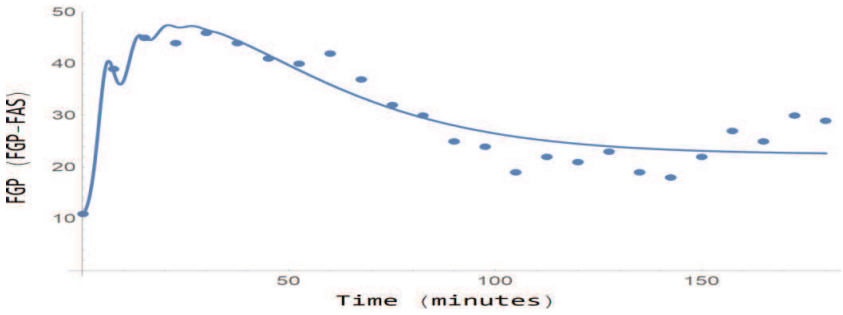

Figure 6: GFP dynamics for SRT (Participant 2). $R^2 = 0.85$.

Tables

Parameter symbol	Name	Optimalvalue
M	PLACEBO-MPH	6.13
τ	Inhibitor effect delay	12.0136952188179790
α	Assimilation rate	0.097804
β	Distribution rate	0.111893
a	Homeostatic control power	0.0437382
b	Tonic level	33.5433959960937500
p	Excitation effect power	0
q	Inhibitor effect power	0.00196436

Table 1: Optimal values of the model parameters, **Placebo Phase**, corresponding to the GFP dynamics (Y). Participant 1.

Parameter symbol	Name	Optimalvalue
M	Methylphenidate	10
τ	Inhibitor effect delay	230.8067913884371800
α	Assimilation rate	0.0240989
β	Distribution rate	0.0365474
a	Homeostatic control power	0.00703561
b	Tonic level	1.04588×10^{-7}
p	Excitation effect power	0.0113137
q	Inhibitor effect power	0.0000795275

Table 2: Optimal values of the model parameters, **10 mg Phase**, corresponding to the GFP dynamics (Y). Participant 1.

Parameter symbol	Name	Optimalvalue
M	PLACEBO-MPH	9.19
τ	Inhibitor effect delay	214.018949817644650
α	Assimilation rate	0.0356595
β	Distribution rate	0.000724157
a	Homeostatic control power	0.538046
b	Tonic level	40.788269042968750
p	Excitation effect power	0.0160338
q	Inhibitor effect power	0.000504011

Table 3: Optimal values of the model parameters, **PLACEBO PHASE**, corresponding to the GFP dynamics (Y). Participant 2.

Parameter symbol	Name	Optimalvalue
M	PLACEBO-MPH	9,44
τ	Inhibitor effect delay	125.9781022862648600
α	Assimilation rate	0.173822
β	Distribution rate	0.559143
a	Homeostatic control power	0.0136305
b	Tonic level	36.866760253906250
p	Excitation effect power	0.0966999
q	Inhibitor effect power	0.00110927

Table 4: Optimal values of the model parameters, **SRT PHASE**, corresponding to the GFP dynamics (Y). Participant 2.

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