METHYLPHENIDATE AND THE SELF-REGULATION THERAPY: A SYSTEMIC MATHEMATICAL MODEL

Salvador Amigó. Departament de Personalitat, Avaluació i Tractaments Psicològics. Universitat de València (Salvador.Amigo@uv.es)
Joan C. Micó. Institut de Matemàtica Multidisciplinar. UniversitatPolitècnica de València (jmico@mat.upv.es)
Antonio Caselles. Departament de Matemàtica Aplicada. Universitat de València (Antonio.Caselles@uv.es)

Abstract

The Self-Regulation Therapy (SRT) is a learning and suggestion process designed specially to "mentally" reproduce effects of drugs without taking drugs. To date, its efficacy to compare the higher scores obtained by scales of subjective effects either by the drug or SRT has been experimentally proven. However, only a visual inspection has been able to verify the similarity of the SRT and effects of drugs dynamics. This article presents a single-case 3-phase (ABC) experimental design to mathematically analyze, from the Systems Theory, if the temporal evolution of the effects of a stimulant drug, methylphenidate (MP), are reproducible by a psychological procedure (SRT). Finally, the relevance of the results for psychology, psychiatry and mathematics, and future proposals for improvement in designs and calculations, are discussed.

Keywords*: Self-regulation Therapy; Methylphenidate; response model; integro-differential equation; bridge model; second order partial differential equation.*

1. Introduction

The Self-Regulation Therapy (SRT) is a psychological procedure based on learning and suggestion that has been specially designed to facilitate reproducing effects of drugs, imitation and re-experimenting effects of drugs. For a review of the theoretical foundations and experimental results, see Amigó (2016). This article deals with reproducing the effects of a stimulating drug, methylphenidate (MP).

The SRT can be used to remember the effects of a drug taken in the past, or to re-experiment the effects of a recently taken drug when a detailed account of its effects is still remembered. In the latter case, the procedure consists in two sessions: 1) a drug-taking session by experiencing real effects and scoring them with subjective scales of the effects and with instruments to measure physiological variables; 2) reproducing effects of a drug "mentally" by next using the SRT (2 or 3 days later).

To compare the effects, former research has statistically compared the subjective and physiological scores obtained at the most intense point of the effects of a drug, or what is known as the drug's *high* (and rush). In this way, the similarity between the drug's high and that achieved with the SRT is verified. This is precisely what was achieved for MP and the SRT (Amigó, 1997, 2005, Amigó, Caselles, Micó & García, 2009).

Comparing the dynamic effects of a drug and the SRT is most interesting to verify whether the evolution of the subjective and objective scores corresponds. The main tool employed to date for this purpose has been a visual inspection, which verifies the similarity between the effect of MP and the SRT as far as the course of the effects curve is concerned, although the duration of the effect with the SRT is shorter than it is with the drug (Amigó, Caselles & Micó, 2013; Micó, Amigó & Caselles, 2012). Nonetheless, the mathematical analysis is more complex for two reasons; on the one hand, scores present serial dependence; on the other hand, and as previously mentioned, a visual inspection reveals differences in the type of effects curve. For instance, the duration of the effect of the SRT is shorter than it is with the drug and, moreover, the effect starts earlier, is more intense and also ends earlier with the SRT than with the drug. Thus determining a direct correspondence between the effects curve obtained with MP and the SRT is not the most suitable approach.

This article proposes dealing with this matter, that of comparing the effects curves of MP and the SRT, with a voluntary participant using a single-case experimental design.

Participant, design and procedure

The participant was a 46-year-old man who was a University of Valencia staff member. A single-case experimental ABC design was used. In phase A, the participant received no treatment. At the start of phase B, the participant took 20 mg of MP. In phase C, he underwent the SRT to reproduce the effects of MP, but did not take this drug. In phases A and B, the participant filled in a sheet of adjectives every 15 minutes over a 4-hour period. In phase C, the participant filled in the list for 2 hours as previous studies have indicated visibly shorter effects than that of the drug. These adjectives measure the General Factor of Personality, which represents the organism's general activation. It is a Five-Adjective Scale of the General Factor of Personality (GFP-FAS, Amigó, Mico & Caselles, 2009), and the five adjectives are: adventurous, daring, enthusiastic, merry and bored. For the mathematical analysis, the response model was applied as an integro-differential equation, whose usefulness has been shown to model the dynamic effect of a stimulant drug (Amigó, Caselles & Micó, 2008; Caselles, Micó & Amigó, 2010, 2011). The model is as follows:

$$\left.\begin{array}{c} \frac{dy(t)}{dt} = a(b - y(t)) + \frac{p}{b}s(t) - b \cdot q \cdot \int_0^t e^{\frac{x-t}{\tau}} \cdot s(x) \cdot y(x)\, dx \\ y(0) = y_0 \end{array}\right\} \quad (1)$$

In (1), $s(t)$ represents the stimulus, $y(t)$ represents the GFP-FAS, and b e y_0 are respectively their tonic level and initial value. The other parameters are a, p, q and τ , which are respectively called the power of the homeostatic effect, the power of the excitement effect, the power of the inhibitor effect and the delay in the inhibitor effect. The stimulus was calculated as:

$$s(t) = \begin{cases} \frac{\alpha \cdot M}{\beta - \alpha}(\exp(-\alpha \cdot t) - \exp(-\beta \cdot t)) : \ \alpha \neq \beta \\ \alpha \cdot M \cdot t \cdot \exp(-\alpha \cdot t) : \ \alpha = \beta \end{cases} \quad (2)$$

In (2), it is assumed that the organism is completely free of MP before it is administered. M is the quantity of MP taken, α is the assimilation rate and β is the distribution rate.

Results

Figure 1 depicts the GFP dynamics during the 4-hour period of Phase A without treatment. We observe mass data dispersion. Figure 2 shows the GFP dynamics caused by 20 mg of MP in Phase B, with an inverted U, which has been obtained in the studies cited in the previous section. The GFP dynamics also takes an inverted U, obtained after reproducing the effects of MP with the SRT in Phase C (see Figure 3). However, the Phase C duration lasts half the time of the other two phase durations (because the effect of the SRT is known to last less than that of MP). The GFP recovers in the end.

Tables 1 and 2 provide the value of the model parameters that correspond to Phases B (with MP) and C (with the SRT). We can see that some parameters considerably differ. Indeed in Phase C, both the excitement and inhibitor effects are greater than in Phase B, as is the assimilation rate, while the delay in the inhibitor effect is shorter. On the whole, we can conclude that the effect becomes more intense with the SRT than with MP itself, but the MP dose is 20 mg (M1) and the SRT "dose" is 7.67 (M2), which seems a contradiction. However, as already mentioned, the SRT effect duration is approximately half that of the MP.

Discussion

Now it is important to reflect on the apparent contradictions that we have just pointed out. The duration of the effect is shorter with the SRT than it is with MP. Hence we can conclude that the suggested SRT "dose" (7.67 mg) is lower than the MP one (20 mg) and, to a point, it is proportional to the duration of the effect.

So, why is it that when reading the parameters in Tables 1 and 2 we think that the SRT effect is more intense despite lasting less? Let's remember that the excitement and inhibitory effects, and the assimilation rate, are greater. The response is found in the shape of the curve. The curve produced by MP is flatter than that produced by the SRT, and the latter curve presents an initially more pronounced slope and also a quicker drop. Nonetheless in the two phases, the participant experiences a high at the same level with both MP and the SRT, with a score of 24 out of 25. So why then is the SRT "dose" considerably smaller than that of MP?

The response that best includes these apparently different and contradictory results is to consider the hypothesis that the SRT reflects the effect of the drug, but the drug is administered differently. We know that as opposed to being taken orally, snorting causes subjective effects more quickly, with a more intense "rush" in stimulants like d-amphetamine or methamphetamine (e.g., Hart et al., 2008; Lile et al., 2011). The hypothesis that stems from this article is that the SRT reproduces the effect of MP, but not when taken orally, rather when it is snorted or taken intravenously. Following intravenous dosing, uptake in the brain is very fast for methylphenidate (6–10 minutes) and the onset of the perceived "high" parallels the fast uptake of the drugs in the striatum, with the peak for the "high" reported at about the same time as the peak striatal concentration. But, however, the "high" returned to baseline even while the striatal levels of methylphenidate remained high (80% of peak). "Behavioral/reinforcing half life" of intravenous methylphenidate is much shorter than its pharmacokinetic half life (Volkow and Swanson, 2003; pp. 1912-1913). Thus we could consider that the SRT "dose" of 7.67 mg (M2) is the equivalent of MP being snorted or taken intravenously, which corresponds to an oral 20 mg dose (M2) in the M1/M2=2.6, proportion, as seen in Table 2.

The consequences would be most significant if this were indeed the case. With the mathematical response model that was used herein, and which we mentioned earlier, we could calculate the proportional doses of a given drug according to how it is administered, which would extend its application in the pharmacology domain and in the study of drugs, and also with therapeutic consequences. Thus if someone is capable of applying the SRT to him/herself to experiment the rush of a drug by snorting or by taking it intravenously, and without having to take the drug, or by remembering its effects when orally taken, it would be feasible to follow this procedure to reduce, or to even eliminate, real drug use. Evidence exists that the SRT can reduce drug craving (see Amigó, 1996, for a review).

Although what is currently a hypothesis needs to be empirically confirmed, and repeating this study with more participants is also necessary, it is true that we have established a reasonable criterion to mathematically compare the real effect of a drug and the conditioned effect which, in this case, is done by the SRT. Thus it is a matter of mathematically studying the invariance of real effects with "mental" or psychological ones. This also opens up a new perspective on the path that we have been following to study the mind-body problem (Micó, Caselles, Amigó, Cotolí & Sanz, 2013).

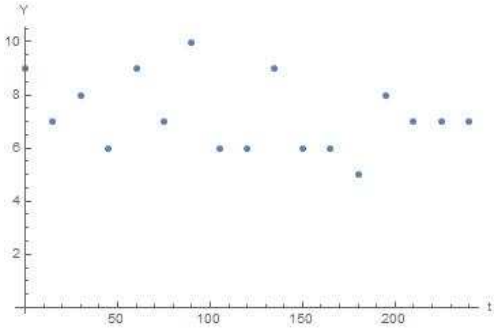

Figure 1: Dynamics of the *GFP*(Y) versus time (t) in minutes, for Phase A

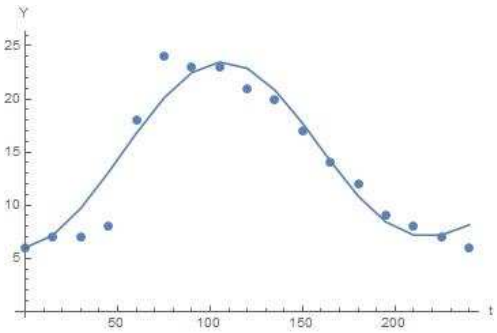

Figure 2: Dynamics of the *GFP* (Y), measured by the *GFP-FAS*, versus time (t) in minutes, for Phase B. The dots represent the experimental values and the curve the theoretical values. R^2=0.91.

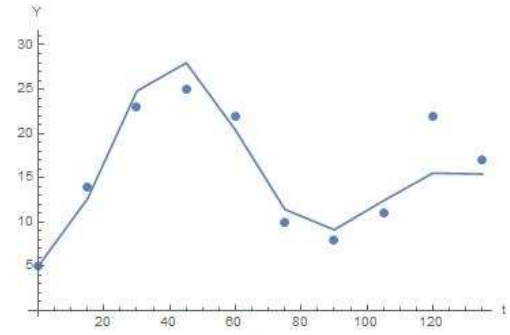

Figure 3: Dynamics of the *GFP* (Y), measured by the *GFP-FAS*, versus time (t) in minutes, for Phase C. The dots represent the experimental values and the curve the theoretical values. R^2=0.81.

Parameter symbol	Name	Optimal value
M1	Methylphenidate dose	20.0
τ	Inhibitor effect delay	102.1278972923755600
α	Assimilation rate	0.0032860666513443
β	Distribution rate	0.0008838047437323
a	Homeostatic control power	0.0049064028928751
b	Tonic level	10.9240722656250000
p	Excitation effect power	1.3321752324700356
q	Inhibitor effect power	0.0000126763916016
p/b	Excitation effect intensity	0.1219485920705610
q.b	Inhibitor effect intensity	0.0001384778179232

Table 1: optimal values of the model parameters 2, Phase B, corresponding to the *GFP* dynamics (Y).

Parameter symbol	Name	Optimal value
M2	Dose without Methylphenidate	7.6786547899246216
τ	Inhibitor effect delay	26.8286811240000200
α	Assimilation rate	0.0374856430099922

β	Distribution rate	0.0001013970502164
a	Homeostatic control power	0.0010036492012055
b	Tonic level	16.6801452636718750
p	Excitation effect power	5.1046919459528768
q	Inhibitor effect power	0.0000507841074228
p/b	Excitation effect intensity	0.3060340222018650
q.b	Inhibitor effect intensity	0.0008470862888982
M1/M2	Dose proportion	2.6046228860610500

Table 2: optimal values of the model parameters, Phase C, corresponding to the *GFP* dynamics (Y).

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