The Spanish Journal of Psychology
2012, Vol. 15, No. 2, 850-867
http://dx.doi.org/10.5209/rev_SJOP.2012.v15.n2.38896

ISSN 1138-7416

Changing the General Factor of Personality and the c-fos Gene Expression with Methylphenidate and Self-Regulation Therapy

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A deepening in the biological nature of the general factor of personality (*GFP*) is suggested: the activation level of the stress system is here represented by the gene expression of c-*fos*. The results of a single case experimental design are reported. A model of four coupled differential equations that explains the human personality dynamics as a consequence of a single stimulant drug intake has been fitted to psychological and biological experimental data. The stimulant-drug conditioning and its adaptation to the considered mathematical model is also studied for both kinds of measures. The dynamics of the c-*fos* expression presents a similar pattern to the dynamics of the psychological measures of personality assessed by the *GFP-FAS* (Five-Adjective Scale of the General Factor of Personality) as a consequence of a single dose of stimulant drug (methylphenidate). The model predicts similar dynamic patterns for both psychological and biological measures. This study proves that describing mathematically the dynamics of the effects of a stimulant drug as well as the effects of a conditioning method on psychological or subjective variables and on gene expression is possible. It verifies the existence of biological mechanisms underlying the dynamics of the General Factor of Personality (*GFP*).
Keywords: personality, general factor of personality, self-regulation therapy, methylphenidate, c-fos, dynamic model.

Este artículo estudia la naturaleza dinámica del Factor General de Personalidad (*FGP*) en respuesta a una dosis única de metilfenidato a partir de un diseño experimental de caso único con replicación. Para medir el *FGP*, se emplean tanto medidas psicológicas (Escala de Cinco Adjetivos del Factor General de Personalidad; *ECA-FGP*), como un marcador biológico (propuesto como substrato biológico del *FGP*) que es la concentración del gen c-*fos* en los linfocitos de la sangre. También se estudia el condicionamiento de los efectos subjetivo y biológico del metilfenidato con una técnica de sugestión y condicionamiento, denominada terapia de auto-regulación. Por último, se propone un modelo matemático de cuatro ecuaciones diferenciales acopladas que explican la dinámica del *FGP* como consecuencia de una ingestión de droga estimulante y del condicionamiento de la droga, ajustadas a los datos experimentales psicológicos y biológicos. Los resultados muestran un patrón dinámico similar para ambas medidas psicológicas y biológicas del *FGP* en respuesta tanto a una dosis de metilfenidato como al condicionamiento con terapia de auto-regulación. Así, se evidencia que es posible la formulación matemática de la dinámica del *FGP* y sus correlatos biológicos, como el gen regulador c-*fos*, y su condicionamiento mediante la terapia de auto-regulación.
Palabras clave: personalidad, factor general de personalidad, terapia de auto-regulación, metilfenidato, c-fos, modelo dinámico.

We thank very much Professor Pedro Carrasco and the "Servei Central de Suport a la Investigació Experimental" (SCSIE) of the Universidad de Valencia, Spain, for the help with blood analyses.

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The genetics of the general factor of personality

Recently, the studies about the General Factor of Personality (*GFP*) define a new, emergent and novel field inside personality research. It treats about "the single general factor hypothesis" and proposes a general factor of personality within the five-factor model, or other personality models, which occupies the apex of the hierarchy of personality factors (Erdle, Irwing, Rushton, & Park, 2010; Musek, 2007; Rushton, Borns, & Hull, 2008; Rushton et al., 2009; Rushton & Irwing, 2008; Rushton & Irwing, 2009a,b,c,d; Schermer & Vernon, 2010; Veselka, Schermer, Petrides, Cherkas, et al., 2009; Veselka, Schermer, Petrides, & Vernon, 2009). Moreover, a psychometric approach to assess the *GFP* from Life History Theory has been proposed, obtaining the K-Factor, by Bogaert and Rusthon, (1989) and Figueredo et al. (2006) and, the first questionnaire constructed expressly to measure *GFP*: the General Factor of Personality Questionnaire (*GFPQ*) has been presented by Amigó, Caselles, and Micó, (2010). Also, the first adjective scale of the *GFP* named Five-Adjective Scale of the General Factor of Personality (*GFP-FAS*) has been presented by Amigó, Micó, and Caselles (2009).

Some evidence about the heritability of the general factor of personality has been found. Studies with identical twins show that *GFP* has an early age of onset with 50% of its variance attributable to non-additive (dominance) genetic influence and the other 50 % attributable to non-shared environmental influence (Figueredo & Rushton, 2009; Rushton et al., 2008; Veselka, Schermer, Petrides, & Vernon, 2009). Moreover, Figueredo et al. (2006) proposed an integrated theoretical and neuropsychological model of the Super-K factor. They predict a common set of additive and pleiotropic regulatory genes (K-Factor Genes) which underlies all four phenotypic composite factors: frontal function, personal/social function, amygdale function and hippocampus function. But they don't propose any specific regulatory genes or dynamical mechanisms for the genetic regulation of *GFP*. Such proposition and a mathematical explicative model is the principal objective of this study.

Methylphenidate, activation and c-fos expression

Methylphenidate is a stimulant drug that binds and inhibits the dopamine transporter (Gatley, Pan, Chen, Chaturvedi, & Ding, 1996; Schweri et al., 1985) and produces dopamine overflow in the striatum (Butcher, Liptrot, & Arbuthnott, 1991; Gerasimov et al., 2000; Hurd & Ungerstedt, 1989; Kuczenski & Segal, 1997; Volkow et al., 2001). As other psycho stimulants do, the acute administration of methylphenidate produces changes in gene regulation, increasing the expression of the transcription factor (immediate-early gene) c-*fos* in a dose-dependent manner. Increased *Fos* protein levels have been detected in different animal species such as cat (Lin, Te, Huang, Chi, & Hsu, 1997), mouse (Penner et al., 2002) and rat (Chase, Brown, Carrey, & Wilkinson, 2003). Also, an increased c-*fos* and *zif-268-mRNA* levels after 2 - 20 *mg/kg* (i.p.) injection has been detected in adolescent rats (Brandon & Steiner, 2003). Besides, an increased c-*fos mRNA* level is found also in adult rats after 0.5 - 10 *mg/kg* (i.p.) injection (Yano & Steiner, 2005). With 5 mg/kg, c-*fos mRNA* levels peaked at 40 minutes and returned to the base-line 3 hours after injection. Similar effects are found for other stimulant drugs (Harlan & García, 1998; Torres & Horowitz, 1999).

c-*fos* is a member of a family of immediate early genes (*IEGs*). c-*fos* gene is implicated in a wide variety of fundamental cellular processes, including mitosis, differentiation, senescence, carcinogenesis, and neuronal activity (Morgan & Curran, 1991). In addition, c-*fos* serves as a marker of metabolic activity in individual neurons (Akins, Liu, & Hsu, 1996; Kogure & Kato, 1993). Thus, this gene contributes to multiple functions and represents a physiological activation mechanism inside cells. The expression of c-*fos* after focal cerebral ischemia has been extensively studied (for a review, see Akins et al., 1996). A rapid but transient induction of *mRNA* c-*fos* after focal and global cerebral ischemia has been shown (Akins et al., 1996; Kogure & Kato, 1993). Moreover, the induction of c-*fos* gene products possibly enables the organism to promote cell survival after ischemic insult (Lin et al., 1997). Also, c-*fos* has been used as a neural marker of pain (Harris, 1998). Besides, stimulant drugs increase *mRNA* c-*fos* rapidly and its level returns to the base-line after 2 or 3 hours (Berke, Paletzki, Aronson, Hyman, & Gerfen, 1998). Testing c-*fos* expression level has been used for classification of psychoactive drugs (Sumner et al., 2004).

The scientific literature about the topic shows that the relationship between personality and c-*fos* expression is possible. Take into account that c-*fos* expression is considerably increased in brain's regions involved in the regulation of arousal states, such as the locus coeruleus (noradrenergic neurons) and the medial preoptic area (non-*GABA*ergic neurons) (Pompeiano, Cirelli, Arrighi, & Tononi, 1997). In addition, neuronal immediate-early gene expression is regulated by synaptic activity and plays an important role in the neuroplastic mechanisms such as spatial learning and memory consolidation task (Bertaina-Anglade, Tramu, & Destrade, 2000; Guzowski, Setlow, Wagner, & McGaugh, 2001). Moreover, an increased level of c-*fos mRNA* following exploration of a novel environment has been found (Hess, Lynch & Gall, 1995; Montag-Sallaz, Welzl, Jul, Montag & Schachner, 1999) as well as changes in c-*fos* expression in human lymphocytes in response to stress (Platt, He, Tang, Slater, & Goldstein, 1995). Exploration of a novel environment and the patterns of response to stress are principal characteristics of the Unique Trait or *GFP* (Amigó, 2005). Because of all that, c-*fos* expression can be considered as one of the possible indicators of the *GFP*.

According to the "peripheral marker hypothesis", the gene expression in peripheral blood lymphocytes (*PBL*) reflects its expression in the brain. *mRNA* dopamine receptors have been found in the human *PBL* (Ostadali et al., 2004) and *mRNA* c-*fos* has been found in human *PBL* (Ogard, Bratholm, Kristensen, Almdal, & Christensen, 2000). In addition, catecholamine is a critical molecular mediator between immune and nervous systems. It transmits information from *CNS* through sympathetic nerve fibers innervating lymphoid organs (Levite, 2006).

Drug conditioning and self-regulation therapy

Since Pavlov's experiment (1927) about drug-effects conditioning, drug-associated conditioning responses have been well established (Lynch, Stein, & Fertziger, 1976; O'Brien, Childress, McLellan, & Ehrman, 1992; Stewart, de Wit, & Eikelboom, 1984). What is more, there are evidences about conditioned gene expression elicited by drug-associated environmental cues. Also, marked up-regulation of the immediate early gene product expression, *Fos*, has been found during exposure to the morphine-paired environment, (Schoeder, Holahan, Landy, & Kelley, 2000) or cocaine-paired environment (Brown, Robertson, & Fibiger, 1992; Neisewander et al., 2000).

The self-regulation therapy (Amigó, 1992) was created to increase the therapeutic efficacy of the conditioning mechanism. This procedure uses conditioning techniques to reproduce all kinds of sensorial effect. This therapy has been effective in order to reproduce (conditioning) stimulant drug effects such as ephedrine effect (Amigó, 1994) or methylphenidate effect (Amigó, 1997).

The general systems theory and the unique personality trait theory

General Systems Theory faces several challenges in the context of science development. One of them is to provide new formulations to better understand complexity. A way to understand complex systems is to model them as differential equations systems. In this paper a model of four coupled first order differential equations is used to explain human personality dynamics as a consequence of a single stimulant drug intake. The model predicts the same dynamic patterns for both psychological and biological measures of personality. Thus, the model reveals itself as an instrument to unify mathematically the concept of personality dynamics and its different psychological and biological aspects. The adaptation of both sets of measures to a same mathematical pattern can contribute in a future time to forecast personality-types and to help diagnosis and therapy in psychology and in psychiatry.

The suggested formalism is based on the Unique Personality Trait Theory (*UPTT*) (Amigó, 2005). The *UPTT* proposes a hierarchical model where the highest level corresponds to the unique trait or general factor of personality (*GFP*), extended from an impulsivity and aggressively pole (approach tendency) to an anxiety and introversion pole (avoidance tendency). In addition, this theory asserts that personality, represented by the *GFP*, can have both compatible dynamic and biological natures.

The hypothesis of the biological nature of personality asserts that the human activation level of the stress system is the responsible of the different responses to a stimulus. Lower activation levels correspond with the impulsivity and aggressively pole (approach tendency), while higher activation levels correspond with the anxiety and introversion pole (avoidance tendency).

The hypothesis of the dynamic nature of personality asserts that the activation level response to a stimulus is given by a certain time pattern that can be described mathematically (Amigó, Caselles, & Micó, 2008a; Caselles, Micó, & Amigó, 2010) and explains personality dynamics as a consequence of the effect of a stimulant drug. In addition, the study of drug conditioning is dealt as a consequence of the consumption of a stimulant drug.

The experimental paradigm used in the performed experiment is a *single case design*, such as it is described by Barlow and Hersen, (1984). Two persons participate in the experiment. A participant consumes two different doses of methylphenidate. The other participant consumes a dose of methylphenidate, whose effects will be conditioned. The psychological response (*GFP-FAS*) and the biological response (c-*fos* gene expression) are then evaluated. The experimental design is presented below. Some questions about methylphenidate, c-*fos* and the conditioning technique are discussed in the context of the goals of the study, in the next section.

Goals of this study

The first goal of this paper is to deepen in the biological nature of personality: the activation level of the stress system is here represented by the gene expression of c-*fos*. In addition, the dynamics of the c-*fos* expression presents a similar pattern to the dynamics of the psychological measures of personality, assessed by the Five-Adjective Scale of the General Factor of Personality (*GFP-FAS*) (Amigó, Micó et al., 2009). This Scale is constituted by five adjectives selected from the Sensation Seeking Scale (*SSS*) of the *MAACL* (Zuckerman & Lubin, 1965). Several combinations of adjectives of this scale have revealed to be highly related with the *GFP* (Amigó, Micó, & Caselles, 2008). In addition, they are a good measure of the *GFP* in state-format (Amigó, Micó et al., 2009). Showing the similar patterns contributes to strengthen the concept of unique trait or *GFP* presented by Amigó, (2005) and Amigó et al., (2008a), as well as to unify the same concept both from the biological and the psychological perspectives in an only conceptual system.

The second goal of this paper is to present an experimental verification of a model that reproduces the effect of methylphenidate. The gene expression measured by the c-*fos* levels in blood and, the psychological measures assessed by the *GFP-FAS* scores, performed in two experimental subjects in response to methylphenidate challenge, are confirmed to fit the model. This model is a generalization obtained from the one presented by Amigó et al. (2008a). Moreover, some ideas about the present article are taken from the paper of Amigó, Caselles, and Micó (2008b), where the psychological effects of caffeine, measured as well by the *GFP-FAS*, are studied, and a mathematical dynamic model of gene expression produced by caffeine is suggested. As a consequence, the dynamic nature of personality has been indicated by the time patterns obtained. The empirical verification of this mathematical model has been reinforced recently with an experiment concerning the dynamics of the *GFP* as a result of a single dose of caffeine (Caselles, Micó, & Amigó, 2011).

A third goal of the present paper is to study the stimulant drug conditioning and its adaptation to the mathematical model for both kinds of measures. There is empirical evidence about the conditioning of the dynamics of the *GFP* as a result of methylphenidate intake by means of self-regulation therapy, over both subjective effect and increase of glutamate in blood (Amigó, Caselles et al., 2009). The adaptation of both biological and psychological measures to the same mathematical explanation for its evolution can contribute to create a procedure to forecast personality-types as a consequence of certain stimuli and a formal tool to help diagnosis and therapy in psychology and in psychiatry.

In Section 2 the experimental design is described. In Section 3 the experimental results are discussed qualitatively from the UPTT perspective. Section 4 is devoted to summarize the mathematical model that is going to be verified. In the Section 5 this model is verified from the experimental results. In Section 6 the paper conclusions are stated.

Method

Participants

Two male participants with ages of 45 and 46 years old participated in the experiment. They are two voluntaries of the university teaching staff.

Instruments

– General Factor of Personality Questionnaire (GFPQ) (Amigó et al., 2010).

– Five-Adjective Scale of the General Factor of Personality (GFP-FAS, Amigó, Micó et al., 2009). The 5 adjectives are: adventurous, daring, enthusiastic, merry and bored.

– Biological analysis. Firstly, the blood samples were obtained and lymphocytes were isolated by density centrifugation on Lymphoprep. Finally, an automated mass spectrometry platform (Sequenom, MassARRAY Quantitative Gene Expression) was used for quantification of the c-*fos* concentration in lymphocytes. β-*actin* was used as internal standard *RNA*.

Two versions of the *GFP-FAS* were used: trait-format version and state-format version ("Are you like this at this moment?" or "do you feel so at this moment?"). Both participants filled out the state-format version form each fifteen minutes to obtain a situational measure of the *GFP*.

As it has been stated above and explained in other side (Amigó, Micó et al., 2009), the *GFP-FAS* is considered in this study as a good approximation to the *GFP* in state-format.

Experimental design and procedure

Firstly, both participants filled out the *GFPQ* and the *GFP-FAS* (trait-format).

An ABC single case experimental design with replication was used. In all of these phases the participants compliment the *GFP-FAS* each fifteen minutes (17 registers each phase) and peripheral blood samples were obtained each one hour (5 samples each phase).

Phase A is the base-line, without treatment. In phase B the participants received a dose of 20 *mg* of methylphenidate immediately after filling out the first *GFP-FAS*. At the same time, the first blood sample was obtained. In the following, the participants complimented 16 *GFP-FAS,* one each fifteen minutes and, a blood sample was obtained once per hour along 4 hours.

In phase C, the *GFP-FAS* registers and the blood samples are obtained as in phase B, but other experimental conditions are different for both participants. Participant 1 takes 40 *mg* of methylphenidate immediately after complimenting the first *GFP-FAS*. Next, the first blood sample is obtained. In the following, like in phases A and B, a blood sample is obtained from both participants each hour along 4 hours, after filling out the corresponding *GFP-FAS*. Participant 1 fills out the *GFP-FAS* every 15 minutes during the 4 hours (16 *GFP-FAS*). Participant 2 also fills out the *GFP-FAS* every 15 minutes during the 4 hours but, for this participant, phase C is divided into two parts: base-line (C1) and self-regulation therapy (C2). After the first hour and 45 minutes, participant 2 applies himself the self-regulation therapy to try to reproduce the drug effects obtained in phase B. Note that, in the mathematical model presented in this paper, the value of M (dose) corresponds to the amount of methylphenidate in phases B and C of participant 1 and in phase B of Participant 2. However, in the self-regulation therapy, the value of M is given by the *therapy-predisposition variable,* whose scale is [0, 10]. The *therapy-predisposition variable* takes the value $M = 8.0$ in the self-regulation therapy for Participant 2 in Phase C.

The sequence of the experiment is:

• First day (the participants go to the medical laboratory). Phase A: base-line.

• Second day (a week later). Phase B: the participants take 20 *mg* of methylphenidate.

• Third day (a week later). Phase C: Participant 1 takes 40 *mg* of methylphenidate, and Participant 2 reproduces the stimulant effects with the self-regulation therapy (C2) after a phase of base-line (C1).

Results

This study is based on a single case experimental design with replication. This design allows making an exhaustive and intensive study from the perspective of unique case. And this perspective is necessary when a new or still little-usual research method such as the detection of regulating genes in blood like answer to a dose of a stimulating drug is. In addition, this study tries to develop a dynamic mathematical model from the theory of systems to explain and to predict the results. For that reason, this section is especially exhaustive and displays a good amount of tables and figures. These tables and figures show qualitative and descriptive results, and the differences between the data obtained from blood samples and those simulated with a dynamic model, and can firmly orient the future research using group designs.

Qualitative discussion of the experimental results

The percentile of the scores of both participants on the *GFPQ* and the *GFP-FAS* Trait-Format are shown in Table 1. The percentiles have been obtained from large samples (Amigó, Micó et al., 2009; Amigó et al., 2010).

Nevertheless, in the two questionnaires, participant 1 scored higher than participant 2. The difference is better observed in the *GFPQ*. In this work, *GFP-FAS* and *GFPQ* scores are representative of the psychological expression of the activation level of the human stress system. The Unique Personality Trait Theory predicts that the phasic activation following a stimulant intake will be higher in participant 1 than in participant 2.

Figure 1 shows the *GFP-FAS* scores for participant 1 in each one of the three phases of the experiment. In both Phases B (20 *mg*) and C (40 *mg*) an inverted U pattern is observed. Such pattern is not observed in Phase A (base-line). The curve corresponding to Phase B reaches a higher peak than the peak reached by the curve corresponding to Phase C. This difference indicates a greater subjective response in the psychological expression of the activation level.

Figure 2 shows the c-*fos* measures for the three phases of participant 1. A very high difference is observed between the inverted U curves of Phases B (20 *mg*) and C (40 *mg*) and the U shape of Phase A (base-line). Observe also that, qualitatively, the pattern obtained in Figure 1 and Figure 2 is similar. This outcome represents equivalence between the psychological and the biological expressions of personality. However, in Figure 2, a greater response of the c-*fos* measure is observed in Phase C respect to Phase B, oppositely to what Figure 1 shows. Here, a discrepancy between the psychological and the biological measures is observed. In Phase C the participant increases his c-*fos* level while the self-informed activation is lower. An explanation of this difference can be that the biologic response, when the dose is doubled, is generally greater than the subjective response. This is a question to be investigated.

Figure 3 shows the *GFP-FAS* scores of Participant 2 in each one of the three experimental phases. In Phases B (20 *mg*) and C (conditioned response) a response pattern (inverted U-shape) very different than the base-line pattern is observed. In Phase C the conditioning technique is applied after the first hour and 45 minutes from the beginning of the experiment (Phase C2). The effect takes an hour. A further final increase is observed, although, the subjective experience was pleasant and quiet rather than activating. In this hour a peak in *GFP-FAS* scores greater than the one corresponding to Phase B is observed, as well as a decrease of the activation level deeper than the one corresponding to Phase B.

Table 1
The percentile of the scores of the participants in the experiment. GPFQ = General Factor of Personality Questionnaire; GFP-FAS = Five-Adjectives Scale of the General Factor of Personality

	GFP-FAS	GFPQ
Participant 1	95	85
Participant 2	80	40

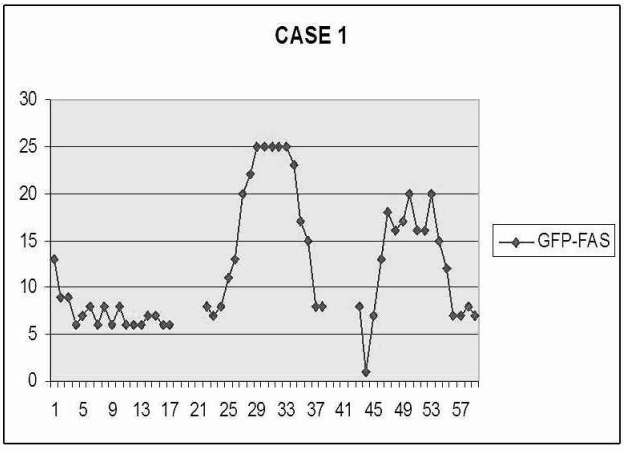

Figure 1. GFP-FAS scores in the experimental phases A, B and C for participant 1.

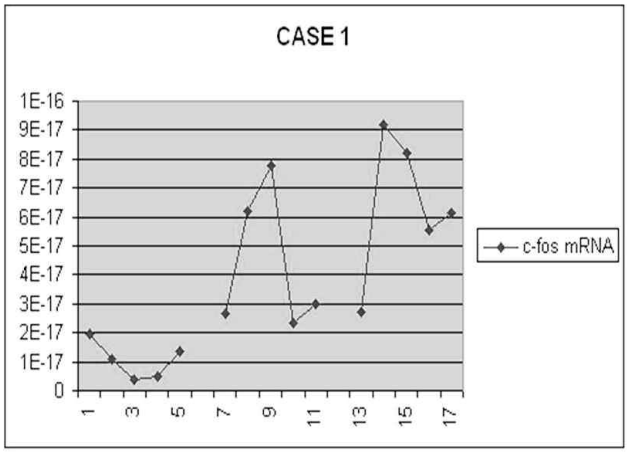

Figure 2. c-*fos mRNA* expression in phases A, B and C for participant 1.

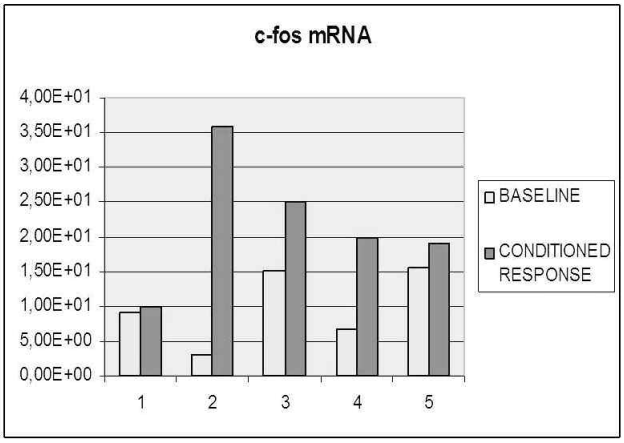

Figure 5. c-*fos mRNA* for the base-line and the conditioned response for participant 2.

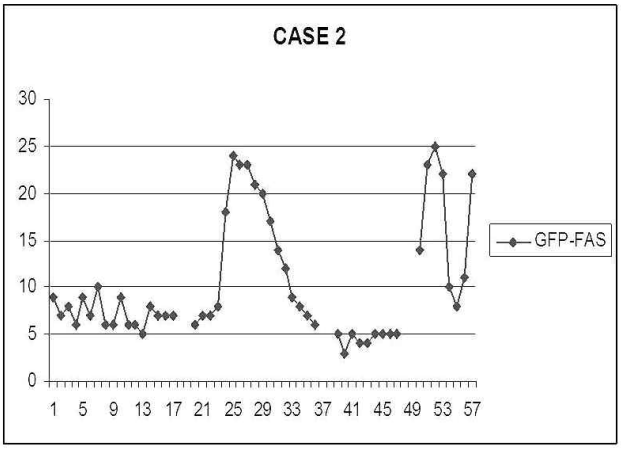

Figure 3. *GFP-FAS* scores in phases A, B and C for participant 2.

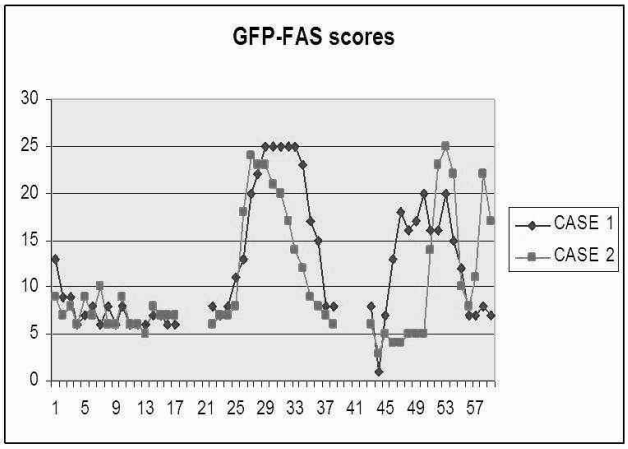

Figure 6. *GFP-FAS* scores in phases A, B and C for participants 1 and 2.

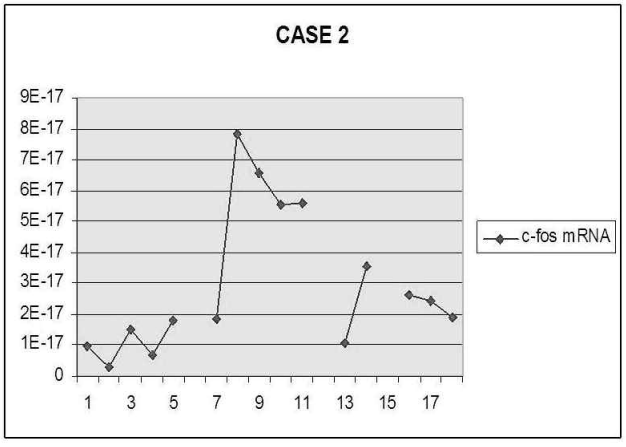

Figure 4. c-*fos mRNA* expression in phases A, B and C for participant 2.

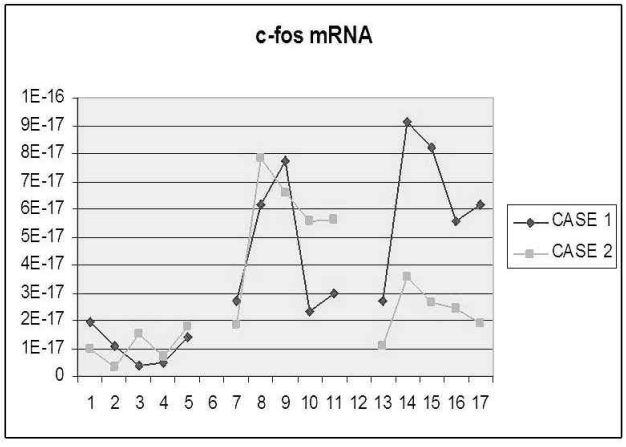

Figure 7. c-*fos mRNA* scores in phases A, B and C for participants 1 and 2.

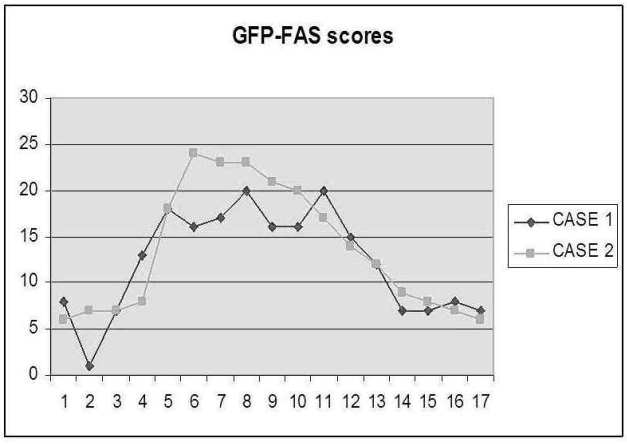

Figure 8. *GFP-FAS* scores for participant 1 (phase C, 40 *mg*) and participant 2 (phase B, 20 *mg*).

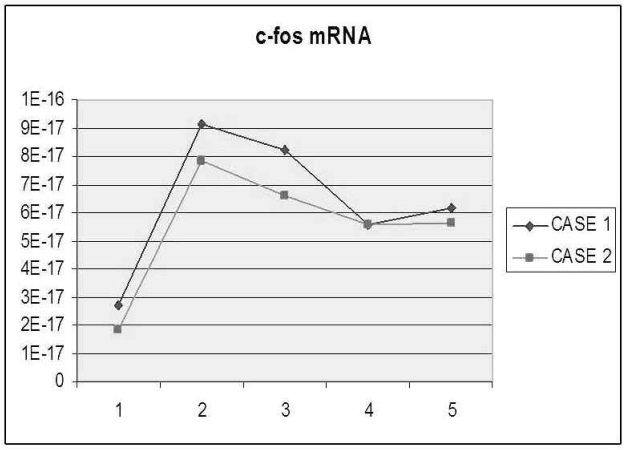

Figure 9. c-*fos mRNA* for participant 1 (phase C, 40 *mg*) and participant 2 (phase B, 20 *mg*).

Figure 4 shows the c-*fos* measures in the three phases for participant 2. A drastic change in the response pattern in Phase B (U-inverted shape) respect to the base-line is observed. In Phase C, a decrease pattern in *mRNA* c-*fos* is as well observed from the third hour, i.e., when the conditioning technique was applied (Phase C2). This pattern is similar to the one produced by the drug, but with a much lower magnitude.

Observing jointly the *GFP-FAS* scores and the *mRNA* c-*fos* measures for Phases B and C of participant 2, a similar pattern between the subjective response and the c-*fos* expression is detected in Phase B. However, the c-*fos* expression is much lesser than the subjective response in Phase C. This difference confirms that the biological conditioning is weak, but the conditioning of the subjective activation is high.

Figure 5 shows, by means of a bar diagram, the base-line of the c-*fos* expression (Phase A) and the conditioning therapy-effect on the c-*fos* expression (Phase C) for participant 2. Observe that from the third hour, when the conditioning therapy is applied, the results show a level in Phase C higher than in Phase A. This difference suggests that a conditioning effect on the c-*fos* expression has been produced as a consequence of the previous administration of methylphenidate. This effect is weak and will have to be confirmed in future studies. In addition, the highest difference is produced during the second hour, when the conditioning therapy has not yet been applied. A possible explanation of the c-*fos* increase is the expectation of the participant previous to the conditioning therapy.

Such as it can be observed in Figure 1 for participant 1, a difference between the *GFP-FAS* scores (subjective) and the c-*fos* expression (biological) exists. Note that the *mRNA* c-*fos* level is higher in Phase C (40 *mg*) than in Phase B (20 *mg*), and the subjective response is lower. A way to deeper analyze this outcome is to compare the responses of both participants. Figure 6 shows that the subjective response of participant 1 is higher, but delayed with respect to the one corresponding to participant 2 in Phase B. However, the pattern of the c-fos expression in Figure 7 shows a delayed but shorter-in-time response for participant 2 when compared with participant 1 in Phase B. In the following figures and for more clarity in comparisons, phases C1 and C2 of participant 2 are joined as an only phase C.

In addition, Figure 8 shows two similar patterns: the one corresponding to the *GFP-FAS* scores of participant 1 in Phase C (40 *mg*) and the one corresponding to participant 2 in Phase B (20 *mg*).

Moreover, Figure 9 shows a c-*fos* expression pattern in Phase C of participant 1 similar to the one corresponding to Phase B of participant 2. However, the peak of the curve is slightly higher in participant 1. In Figures 6-9, a similar response pattern is observed between Phase C of participant 1 and Phase B of participant 2, for both subjective (*GFP-FAS*) and c-*fos* expression.

Descriptive and differential statistics

In tables 2 and 3, the U of Mann-Whitney between the different experimental conditions is presented for both participants. For participant 1, the score in *GFP-FAS* in relation to its base-line increases, as with 20 *mg* as with 40 *mg* of methylphenidate but, comparing the scores between phases B and C, we see as 20 *mg* of methylphenidate increase significantly more the score in *GFP-FAS* than 40 *mg* (possible effect of habituation). For participant 2, the score in *GFP-FAS* increases significantly with 20 *mg* of methylphenidate (B) and with self-regulation therapy (C2) in comparison with its respective base-lines (A and C1).

The percentage of low scores (0-1) and high scores (4-5) of each one of the five adjectives for both participants and all the experimental conditions are shown in tables 4

Table 2
Mann-Whitney U to differences between experimental conditions. Case 1. A: Base-line; B: Methylphenidate 20 mg; C: Methylphenidate 40 mg.

CASE 1			
	U	Average range	*p*
A	17	9.56	.001
B		23.44	
A	45.5	11.34	.002
C		21.66	
B	75	19.81	.045
C		13.19	

Table 3
Mann-Whitney U to differences between experimental conditions. Case 2. A: Base-line; B: Methylphenidate 20 mg; C1: Base-line; C2: Self-regulation Therapy

CASE 1			
	U	Average range	*p*
A	45	11.31	.002
B		21.69	
C1	30	4	.001
C2		12	

and 5. We can observe in participant 1 that, no adjective scores high in phase A while, in phase B, all adjective-scores increase with the same proportion (16.7% between 4 and 5) and in phase C, all they lower of similar form, "merry" staying a bit higher.

In participant 2, only "bored" reaches a low (2.1%) percentage of answers between 4 and 5. The dose of 20 *mg* of methylphenidate (B) increases the percentage of answers between 4 and 5 for "daring" and "enthusiastic" and, between 0 and 1 for "bored". But in C2 (self-regulation therapy), the percentage of scores between 4 and 5 is reduced, in relation to B, except for "merry", that increases from 8.4% to 10.4%. Therefore, we have observed different patterns of answer for each one of the adjectives and experimental conditions in each one of the participants. As far as self-regulation therapy, in comparison with the effect of the 20 *mg* of methylphenidate, it reduces the high scores (0 to 5) but increases the percentage of high scores in "merry".

The mathematical model

Amigó et al., (2008a) demonstrate that the dynamic effect produced by a stimulant drug on the *activation level* of an individual is leaded by a coupled set of three differential equations: two ordinary differential equations that describe the dynamics of the drug stimulus and a discrete-delay differential equation that describes the dynamics of the *activation level*. The *activation level* characterizes quantitatively the *GPF*, which can be either psychological (measured by the *GFP-FAS* scores) or biological (measured by the c-*fos* expression). The dynamic model provided by these coupled set of three differential equations is congruent

Table 4
Low (0-1) and high (4-5) scores to five adjectives and experimental conditions. Case 1

ADJECTIVES	SCORE	A	B	C
Adventurous	0-1	31.3	6.3	12.5
	4-5	0	16.7	4.2
Daring	0-1	27.1	10.4	10.4
	4-5	0	16.7	4.2
Enthusiastic	0-1	18.8	6.3	10.4
	4-5	0	16.7	6.3
Merry	0-1	29.2	8.3	12.5
	4-5	0	16.7	8.3
Bored	0-1	2.1	21.5	27.1
	4-5	0	0	2.1

Table 5
Low (0-1) and high (4-5) scores to five adjectives and experimental conditions. Case 2

ADJECTIVES	SCORE	A	B	C1	C2
Adventurous	0-1	8.3	2.1	14.6	0
	4-5	0	8.3	0	8.4
Daring	0-1	8.3	4.2	14.6	0
	4-5	0	14.6	0	8.4
Enthusiastic	0-1	31.2	18.7	14.6	4.2
	4-5	0	12.6	0	8.4
Merry	0-1	31.2	14.6	14.6	8.4
	4-5	0	8.4	0	10.4
Bored	0-1	0	23	0	14.6
	4-5	2.1	0	2.1	0

with the model by Grossberg (2000), which predicts a different phasic reaction in response to the previous arousal level according to an inverted-U function. This is also the conclusion of the *Opponent-Process Theory* by Solomon and Corbit (1974) to explain the acute effect of drugs. To examine any detail about the process to obtain the model, consult the work of Amigó et al., (2008a).

This paper presents a model of four (instead of three) coupled differential equations obtained by transforming the model of Amigó et al., (2008a) into a continuous-delay (instead of discrete-delay) differential equations system. The need of such transformation is explained below. A summary of the model's mathematical skeleton is presented in the following, as well as the interpretation of any equation and the way to convert the model of Amigó et al., (2008a).

The discrete-delay differential equation for the *activation level* variable presented in the paper of Amigó et al., (2008a) is the following:

$$\left.\begin{aligned}\frac{dy(t)}{dt} &= \begin{cases} a\big(b-y(t)\big)+\dfrac{p}{b}\,s(t): & 0\le t\le \tau \\ a\big(b-y(t)\big)+\dfrac{p}{b}\,s(t)-b\cdot q\cdot s(t-\tau)\cdot y(t-\tau): & t>\tau \end{cases} \\ y(0) &= y_0 \end{aligned}\right\} \quad (1)$$

Where:

• $y(t)$, b and y_0 are respectively the *activation level* variable, its tonic level and its initial value.

• $a(b-y(t))$ represents the homeostatic control which tends to fast recover the tonic activation level after a deviation, being a the "power" of this control.

• $p\cdot s(t)/b$ represents the *excitation effect* of the stimulus $s(t)$ which tends to increase the activation level, being p the "power" of this stimulus.

• τ is the *inhibitor effect delay* (the delay the inhibitor effect needs to begin working).

• $q\cdot b\cdot s(t-\tau)\cdot y(t-\tau)$ represents the *inhibitor effect*, which tends to slowly decrease the activation level, being q the "power" of this effect.

• $s(t)$ is the *stimulus-variable* that can represent the amount of drug in blood. If $c(t)$ is the non-assimilated drug by blood, $s(t)$ and $c(t)$ are computed by the following two coupled differential equations:

$$\left.\begin{aligned}\frac{dc(t)}{dt} &= -\alpha\cdot c(t) \\ c(0) &= M\end{aligned}\right\} \quad (2)$$

$$\left.\begin{aligned}\frac{ds(t)}{dt} &= \alpha\cdot c(t)-\beta\cdot s(t) \\ c(0) &= s_0\end{aligned}\right\} \quad (3)$$

Where:

• M is the amount of the drug intake, and α is the drug absorption rate.

• s_0 is the amount of drug present in blood before the present intake, and β is the drug distribution rate.

The parameters of the model (α, β, a, b, p, q, τ) depend on the individual biology and the type of stimulus (drug).

The functional dependence on time of $s(t)$, as a consequence of integrating (2) and (3), is:

$$s(t)=\begin{cases}\dfrac{\alpha\cdot M}{\beta-\alpha}\big(\exp(-\alpha\cdot t)-\exp(-\beta\cdot t)\big): & \beta\neq\alpha \\ \alpha\cdot M\cdot t\cdot\exp(-\alpha\cdot t): & \beta=\alpha\end{cases} \quad (4)$$

The differential equation (1) has an analytical solution (see Amigó et al., 2008a) that depends on definite integrals and can be programmed for a computer. The forecasted dynamics coincides with what the opponent-process theory proposed by Solomon and Corbit (1974) predicted to explain the acute effect of drugs, and with the model proposed by Grossberg (2000).

Observe that the inhibitor effect provides an "all or nothing" delayed dynamic regulation. This dynamics is typical of a microscopic description but not of a macroscopic one. In order to introduce an inhibitor effect with a continuous delay, typical of a macroscopic description, we consider an inhibitor effect that arises from a minimum weight (zero in the initial time), increasing continuously up to reach a maximum weight in the computation time. The quantification of this hypothesis consists of considering a mathematical structure as the following one: $b \cdot q \int_0^t \exp\left((x-t)/\tau\right) \cdot s(x) \cdot y(x) \cdot dx$. This kind of inhibitor effect can be interpreted as a continuous sum of the product $s(x) \cdot y(x)$ between the initial time, $t = 0$ and the computation time t, with a weight given by $\exp\left((x-t)/\tau\right)$. This function is increasing in the computation interval [0, t]. Moreover, it takes its minimum at its initial time (that is, when x = 0) and it takes its maximum (equal to the unit) at the computation time t (that is, when $x = t$) and, it tends to zero as $t \to +\infty$. For this mathematical structure, τ represents an adjusting time, depending on each individual.

Considering this new inhibitor effect, Equation (1) can be rewritten as:

$$\left.\begin{aligned} \frac{dy(t)}{dt} &= a\left(b - y(t)\right) + \frac{p}{b}s(t) - b \cdot q \int_0^t \exp\left((x-t)/\tau\right) \cdot s(x) \cdot y(x) \cdot dx \\ y(0) &= y_0 \end{aligned}\right\} \quad (5)$$

Equation (5) together with equations (2) and (3) define a *continuous-delay model*. However, the fact of being (5) an integrodifferential equation makes difficult to handle the model. In order to solve the problem a new variable is defined:

$$z(t) = \int_0^t \exp\left((x-t)/\tau\right) \cdot s(x) \cdot y(x) \cdot dx \quad (6)$$

Observe that $z(0) = 0$. Deriving (6) with respect to time, equation (7) is obtained:

$$\frac{dz}{dt} = \frac{d}{dt}\left[\exp\left(-t/\tau\right) \cdot \int_0^t \exp\left(x/\tau\right) \cdot s(x) \cdot y(x) \cdot dx\right] = -z(t)/\tau + s(t) \cdot y(t) \quad (7)$$

Substituting (6) in (5) and introducing (7) as a new equation the following system is obtained:

$$\left.\begin{aligned} \frac{dy(t)}{dt} &= a\left(b - y(t)\right) + \frac{p}{b}s(t) - b \cdot q \cdot z(t) \\ y(0) &= y_0 \end{aligned}\right\} \quad (8)$$

$$\left.\begin{aligned} \frac{dz(t)}{dt} &= -z(t)/\tau + s(t) \cdot y(t) \\ z(0) &= 0 \end{aligned}\right\} \quad (9)$$

The system defined by the two coupled equations (8) and (9) together with equations (2) and (3) is the *continuous-delay model* of the evolution of the *activation level* as a consequence of a single intake of a stimulant drug. This model has been tested by Micó, Amigó, & Caselles, (2008) with the evolution of the *GPF-FAS* scores obtained as a consequence of an intake of caffeine and it is here used to describe the dynamics of the subjective activation state and the c-*fos* expression of an individual, as a consequence of a stimulant drug intake (methylphenidate).

Fitting the mathematical model

The aim of this section is to show how the mathematical model given by equations (2), (3), (8) and (9), adapts to the dynamic patterns of the *GPF-FAS* scores and of the c-*fos* expression.

The model is going to be tested in the experimental phases B for both participants and in phase C for participant 1. Phase B corresponds to an intake of $M = 20$ *mg* of methylphenidate for both participants and, phase C of participant 1 corresponds to an intake of $M = 40$ *mg* of methylphenidate. In phase C of participant 2, methylphenidate is substituted by the conditioning therapy. Being the dynamic pattern of the effect of this therapy similar to the effect of the drug, the mathematical model is also checked under the hypothesis that the stimulus pattern is governed by equations (2) and (3) but with an unknown amount M of drug.

For *GPF-FAS* scores, the range of the data is [0, 25], while the data of the c-*fos* expression vary inside an unknown a priori scale that seems to be inside the interval [0, 100] (presented multiplied by 10^{-17}).

The analytical solution of the model has been programmed in *Mathematica* 7.0, and the fitting of the model to the data has been computed by the minima square method. The evaluation of the degree of fitting has been performed by the computation of the determination coefficient R^2. Following this method, the optimal values of the model's parameters arise. These values depend on the participant and on the kind of stimulant drug. They depend as well on whether the activation level *y(t)* has a psychological nature (*GPF-FAS*) or a biological one (c-*fos*

expression). In Tables 6 to 9 the optimal values obtained are represented for both participants and for both phases.

Figures 10 to 17 present the evolution curves obtained from the fitted differential equations joined with the experimental results (*GPF-FAS* scores or c-*fos* expression) classified per participants. Such figures permit to observe easily the good fit between the curves and the experimental results and to compare the dynamics of *GPF-FAS* and c-*fos* between participants.

For participant 1 in phase B (20 *mg* of methylphenidate), Figure 10 shows the actual *GPF-FAS* scores and the corresponding curve given by the model, with $R^2 = .97$. The fitting can be considered excellent. The same conclusion can be deduced from Figure 11, being now the c-*fos* expression fitted with $R^2 = .99$. However, the c-*fos* expression presents a final increase that differences this pattern from the *GPF-FAS* pattern. Observe in Tables 6 and 7 that the absorption rate (α) and the distribution rate (β) are the same for both *GPF-FAS* and c-*fos* expression dynamics, that is, the dynamics of the drug in blood can be considered as independent of the dynamics of the stress in brain.

Figure 12 shows the *GPF-FAS* scores and the corresponding model curve, with $R^2 = .81$, for phase C (40 *mg* of methylphenidate) of participant 1. The real data have more dispersion, but the residuals are random. Thus, the fitting can be considered acceptable. The corresponding c-*fos* expression in Figure 13 has a fitting degree of $R^2 = .99$, i.e., the real data present a slight dispersion. In this case, the c-*fos* expression presents a final slight increase that differences this pattern from the *GPF-FAS* pattern, similarly to phase B. Observe again in Tables 6 and 7 that the absorption rate (α) and distribution rate (β) are the same for both *GPF-FAS* and c-*fos* expression dynamics. Their values coincide also with the respective values of phase B. It confirms that the dynamics of the drug in blood can be considered as independent of the dynamics of stress in brain. On the other hand, observe that, in the psychological

Table 6
Values of the parameters of the model for GFP-FAS measures in Participant 1

PARTICIPANT 1: *GFP-FAS measures*		
	PHASE B	PHASE C
M	20.0	40.0
y0	8.0	8.0
α	0.000069	0.000069
β	0.006114	0.006114
a	0.010598	0.030901
b	1.957947	1.047782
p	12.235929	5.785946
q	0.001514	0.003568
τ	490.853858	240.414747

Table 7
Values of the parameters of the model for c-fos expression in Participant 1

PARTICIPANT 1: *c-fos* expression		
	PHASE B	PHASE C
M	20.0	40.0
y0	26.87	26.95
α	0.000069	0.000069
β	0.006114	0.006114
a	0.007437	0.005667
b	3.691873	6.570634
p	113.273231	160.916231
q	0.002348	0.001374
τ	126.564076	48.265008

Table 8
Values of the parameters of the model for GFP-FAS measures in Participant 2

PARTICIPANT 2: *GFP-FAS* measures		
	PHASE B	PHASE C
M	20.0	8.0
y0	6.0	5.0
α	0.000730	0.000468
β	0.013518	0.000572
a	0.0003689	0.000212
b	8.646789	14.504409
p	6.2751	22.2305
q	0.000096	0.000287
τ	79.776	36.300103

Table 9
Values of the parameters of the model for c-fos expression in Participant 2

PARTICIPANT 2: *c-fos* expression		
	PHASE B	PHASE C
M	20.0	8.0
y0	19.9	36.0
α	0.000730	0.000468
β	0.013518	0.000572
a	0.015704	0.000165
b	20.742641	13.644298
p	144.586185	20.729941
q	0.000113	0.000533
τ	46.082587	11.049751

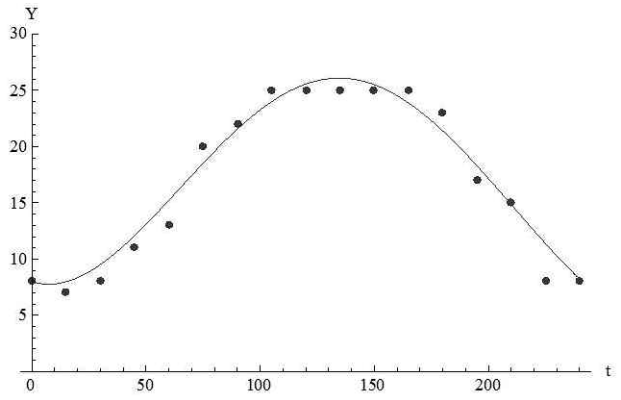

Figure 10. *GPF-FAS* scores (points) and model curve (line) in Phase B for Participant 1. $R^2 = 0.97$.

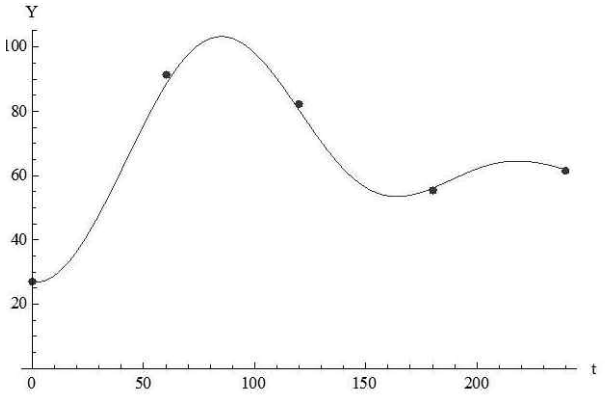

Figure 13. c-*fos* expression (points) and model curve (line) in Phase C for Participant 1. $R^2 = 0.99$.

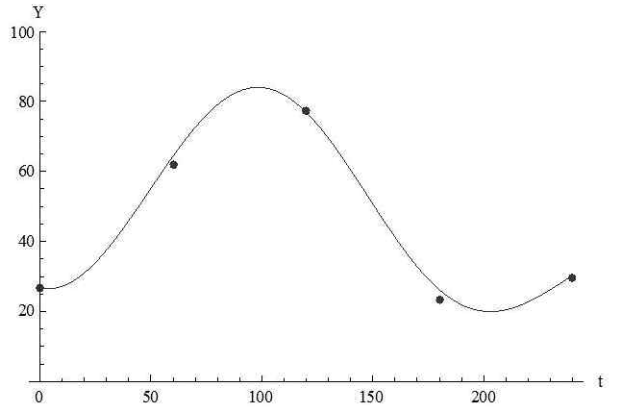

Figure 11. c-*fos* expression (points) and model curve (line) in Phase B for Participant 1. $R^2 = 0.99$.

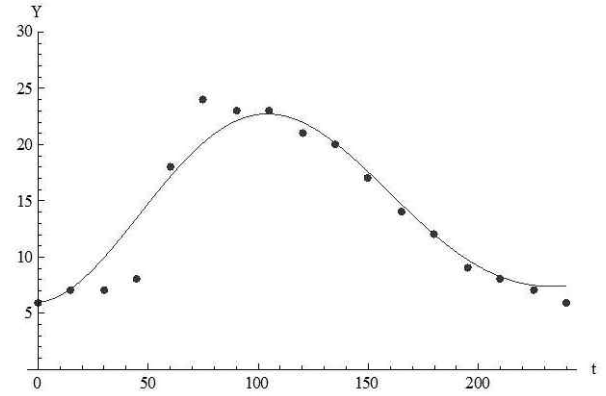

Figure 14. *GPF-FAS* scores (points) and model curve (line) in Phase B for Participant 2. $R^2 = 0.93$.

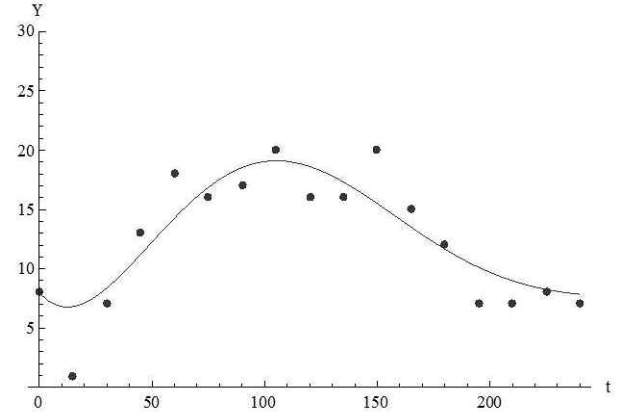

Figure 12. *GPF-FAS* scores (points) and model curve (line) in Phase C for Participant 1. $R^2 = 0.81$.

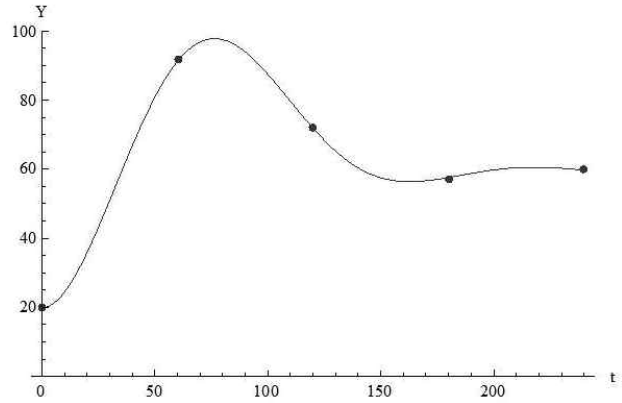

Figure 15. c-*fos* expression (points) and model curve (line) in Phase B for Participant 2. $R^2 = 0.99$.

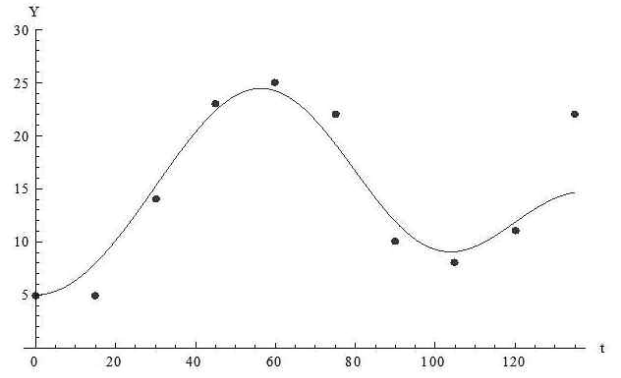

Figure 16. *GPF-FAS* scores (points) and model curve (line) in Phase C for Participant 2. $R^2 = 0.85$.

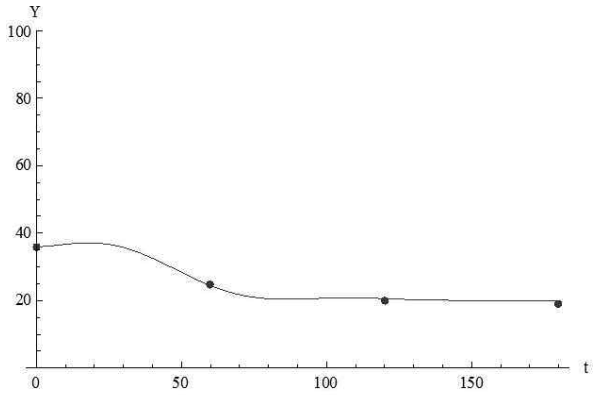

Figure 17. c-*fos* expression (points) and model curve (line) in Phase C for Participant 2. $R^2 = 0.99$.

measures of participant 1, the greatest values are about 5 points lesser in phase C than in phase B, while in the biological measures of participant 1 there is an increase of 5 points in phase C respect to phase B. That is, despite the drug intake is double in phase C than in phase B, a habituation phenomenon in psychological measures has occurred, and contrarily, a sensitizing phenomenon has occurred in biological measures.

For participant 2 in phase B (20 *mg* of methylphenidate), Figure 14 shows the *GPF-FAS* scores and the corresponding model curve, with $R^2 = .93$, revealing a slight dispersion. However, the fitting can be considered as good due to the residuals are random. Figure 15, shows the fitted curve of the c-*fos* expression and the experimental data, with $R^2 = .99$, i.e., there is an excellent fitting degree. A slight recovery, similar to the final increase of the c-*fos* curves of participant 1, must be emphasized. In addition, note again in Tables 8 and 9 for participant 2 that the absorption rate (α) and distribution rate (β) are the same for both *GPF-FAS* and c-*fos* expression dynamics, that is, the dynamics of the drug in blood shows here again to be independent of the dynamics of stress in brain.

For participant 2 in phase C (conditioning therapy), the mathematical dynamics of the stimulus is unknown but produced by the conditioning therapy. The stated hypothesis is that this dynamics can be described by Equations (2) and (3), i.e., by the same equations than for a stimulant drug, such as methylphenidate. Observe that the absorption rate (α) and the distribution rate (β) must be different than in phase B of participant 2 because no drug dynamics in blood exists, thus, both optimal parameters' values and the corresponding optimal parameters' values of Equations (8) and (9) have all been found through the minima square method. Tables 8 and 9 show these values. Figure 16 shows the *GPF-FAS* scores obtained as a consequence of the conditioning therapy, and the corresponding model's curve, with $R^2 = .85$. The fitting can be considered as good, because the residuals are random, although the final tendency of the curve does not describe completely all the actual recovering. Therefore, the cause of the abrupt recovering of the experimental measures could be due to other influences not considered in the model. Figure 17, shows the fitted curve of the c-*fos* expression and the corresponding experimental data, with $R^2 = .99$, i.e., an excellent agreement between experimental data and theory is obtained. Observe that the hypothesis stating that the conditioning therapy has the same dynamic-effects pattern than the methylphenidate administration and that the corresponding amount of drug *M* can be substituted by a subjective *therapy-predisposition-variable* are confirmed. Thus, the dynamics of both the psychological and the biological dynamic patterns can be described by the same model.

General discussion and conclusions

In this study it has been proved that it is possible to describe mathematically the dynamics of the effects of a stimulant drug and the effects of a conditioning method of such effects on psychological or subjective variables and on the gene expression. That verifies the existence of biological mechanisms underlying the dynamics of the General Factor of Personality (*GFP*) such as the Unique Personality Trait Theory predicts (Amigó, 2005; Amigó et al., 2008a). The Five Adjective Scale of the General Factor of Personality (*GPF-FAS*) suggested by Amigó, Micó et al. (2009) in state-format was used to measure the subjective effects that a stimulant drug (methylphenidate) produces. The participants in the experiment filled the corresponding questionnaire every 15 minutes during 4 hours. In order to measure the c-*fos* expression, its concentration was analyzed in blood lymphocytes from samples obtained each one hour. The self-regulation therapy (Amigó, 1992; 1997) was used as a technique for conditioning the effect of the drug.

The experiment was a single-case experiment with two voluntary participants and three phases of 4 hours duration each one: phase A (base line), phase B (20 *mg* of methylphenidate) and phase C (40 *mg* of methylphenidate for participant 1 and the conditioning technique for participant 2). Subjective measurements (*GPF-FAS*) and biological measurements (c-*fos* expression) were performed in all phases.

The obtained results show that 20 *mg* of methylphenidate (phase B) produce an intense psychological activation effect in both participants with respect to the base line (phase A). This effect has an inverted U shape, what means that 20 *mg* of methylphenidate (phase B) change the psychological activation at short term (4 hours) increasing it and later decreasing it. Moreover, both participants modify their c-*fos* expression in the same manner with respect to the base line.

Accepting that the psychological activation measured by the *GPF-FAS* scale is a good approximation to a measurement of the *GFP* (Amigó et al., 2009b), it can be concluded that 20 *mg* of methylphenidate modify personality at short term (4 hours) while its genetic background is modified. This result represents a confirmation of the integration of the dynamics of the subjective and genetic aspects of personality as a response to a stimulant drug intake.

Thus, the change pattern of the subjective and genetic activation is the same after a 20 *mg* methylphenidate intake (phase B) but, when a second 40 *mg* intake was done (participant 1 in phase C) the correspondence between the subjective and genetic measures was not the same than in phase B. That is, while the genetic activation increased respect to phase B, the psychological activation decreased. A possible explanation of this fact may be that the increase of the c-*fos* expression in phase C triggers a strong physiological reaction inhibiting the activation.

The self-regulation therapy (as a technique of drug conditioning) was applied at the beginning of the third hour of the phase C of participant 2. So, such phase C is divided into two sub-phases: base-line or sub-phase 1 (C1), during the first two hours and, conditioning technique or sub-phase 2 (C2) during the last two hours. With respect to the psychological activation, sub-phase 1 presents a pattern identical to the general base-line pattern (phase A) and, sub-phase 2 presents an increase similar, even greater, than the one corresponding to phase B, while it decreases quickly and afterwards increases a little bit. That may be due to the fact that participant 2 manifested that felt very activated and energetic at the beginning and with an agreeable sensation of peace and wellbeing at the end. That is, the activation was not reduced but transformed from energy to quite wellbeing. On the other hand, sub-phase 1 presents a strong increase of c-*fos* level with respect to phase A (base line) that may be due to the expectation of receiving the conditioning technique (participant 2 knew it); and sub-phase 2 presents an increase of the c-*fos* level with respect to phase A but much lesser than the one produced in phase B. Summarizing, the effect of the conditioning technique on the c-*fos* expression is light and must be considered with caution. Nevertheless, the conditioning of the increment of glutamate in blood has been obtained with the self-regulation therapy (Amigó, Caselles et al., 2009). This fact suggests that to investigate about other neurotransmitters or genes as biological substrates of the *GPF* and which can be conditioned by the self-regulation therapy can be interesting.

Observe that in all presented figures and for both participants the same type of relation between the psychological and genetic activations exists: they present the same increasing trend during the first two hours but, the psychological activation falls slowly during the next two hours while the genetic activation falls much faster towards a level lower that the initial one and recovers slowly the initial level. That may be interpreted saying that the c-*fos* increase starts different physiological activation systems that maintain the activation during a long time in spite of the fast degradation of the regulator gen.

Observe also that there are some differences between the change patterns of both participants. The *UPTT* predicts that the phasic response to a stimulant drug will be greater in persons with a greater *GFP*. Consequently, participant 1, with a higher percentile than participant 2 (85 and 40 respectively), should have to present a higher phasic response. This fact is found in phase B while the corresponding results in phase C suggest a possible habituation in participant 1. Thus, in phase B, participant 2 increases his psychological and genetic activation faster than participant 1 in phase C. Furthermore, the psychological and genetic activation pattern is the same in both participants when comparing phase C of participant 1 with phase B of participant 2, that is, the activation produced by 20 *mg* of methylphenidate in participant 2 is almost the same than the one produced by 40 *mg* of methylphenidate in participant 1. In other words, the activation of participant 1 with 20 *mg* of methylphenidate is greater than the one of participant 2 with the same dose but, the activation of participant 1 with 40 *mg* of methylphenidate is similar than the one of participant 2 with 20 *mg* of methylphenidate. That is, the psychological and genetic activation produced by methylphenidate is regulated by the dose, by the past intakes and by the type of individual.

Summarizing, this study, that presents a single case experimental design with two participants, shows that it is possible to describe mathematically the change pattern of the activation (as psychological one as genetic one) produced by a given dose of a stimulant drug such as methylphenidate. It is also possible to reproduce the activation (mainly the psychological one) produced by methylphenidate with self-regulation therapy. This fact opens good expectations about therapeutic applications of the here obtained results. A precedent can be found in a clinical study where self-regulation therapy was applied to

reproduce the effect of methylphenidate for reducing anxiety and depression (Amigó, 1997). Personality is a system that integrates all systems of the human being, as psychological as biological ones. Starting from the hypothesis of the existence of a unique and dynamical personality trait or General Factor of Personality (Amigó, 2005; Amigó et al., 2008a) that corresponds to the general activation of the organism, it has been demonstrated that this activation can be measured as well with adjective scales as with the level of expression of c-*fos*. The existence of a correspondence between the change patterns of psychological activation and genetic activation as a response to methylphenidate has been pointed out (although psychological activation carries on for a longer time). Furthermore, such patterns depend on variables such as: the subject, the dose and, the consumption's history.

With respect to limitations of this study and to future research, in this paper, the influence of the subject, the dose and, the consumption's history over the response to methylphenidate have been studied for single cases but, the study for groups in order to generalize the results remains for future research. In addition to increment the number of experimental subjects, it is necessary to design intra and inter-individuals experiments to test some of the hypothesis and assumptions, as biological ones as mathematical ones, which this exhaustive (it is an experimental design with replication and not a simple case study) single case study has provided. Also, it will be interesting for future research to consider other regulatory related genes (such as DRD2 and DRD3 for instance) to check the combined effects between activator and inhibitor genes on physiological activation and on psychological activation. Another interesting research line is to test the suggested mathematical model with the effects of other stimulant drugs and with sedative drugs to check if it is able to explain and predict its action mechanisms.

This study shows that personality, and concretely the *GFP*, measured through the psychological and genetic activation, changes as a response to a certain dose of a stimulant drug and, that this change can be reproduced by conditioning techniques. Consequently, it represents the beginning of a research line to describe and predict the personality changes and to analyze with detail the short-term genetic-expression evolution, applying the "peripheral marker hypothesis" as an underlying personality factor.

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Received February 28, 2011
Revision received May 25, 2011
Accepted July 14, 2011