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THE SELF-REGULATION THERAPY TO REPRODUCE DRUG EFFECTS: A SUGGESTION TECHNIQUE TO CHANGE PERSONALITY AND THE *DRD3* GENE EXPRESSION

Self-regulation therapy to reproduce drug effects (FOR SHORT)

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Abstract

This study proposes a strategy, based on the Self-regulation Therapy, to change personality and its biological substrate, the *DRD3* gene expression. It has been demonstrated that acute doses of stimulating drugs, like methylphenidate, are able to change personality and the expression of certain genes in the short term. On the other hand, the Self-regulation Therapy has been proved to reproduce the effects of drugs. Thus, it is feasible to hope that the Self-regulation Therapy is equally effective to change personality and the gene expression as methylphenidate. This is a preliminary study with a single case experimental design with replication in which two subjects participate. The results and potential implications for research and psychotherapy are discussed.

Keywords: Self-regulation Therapy; personality; methylphenidate; *DRD3* gene.

Acknowledgement

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Introduction

Since Pavlov's experiment on conditioning drug effects (1927), drug-associated conditioning responses have been well-established (Lynch, Stein & Fertziger, 1976; O'Brien, Childress, McLellan & Ehrman, 1992; Stewart, deWit & Eikelboom, 1984).

If we take the drug as being the US (unconditioned stimulus) and the reproduction of its effects the CR (conditioned response), when repeatedly matching the US and a CS (conditioned stimulus, neutral), the latter will be able to elicit the CR in the absence of the drug.

As regards abuse drugs, there is experimental evidence in humans for conditioning responses similarly to heroin (Blachley, 1971; Levine, 1974; O´Brien, 1975; O´Brien, Ehrman & Ternes, 1986; Solé, 1983). These studies show the already classic "fantasy of the needle" phenomenon (Levine, 1974) which is characterized by the appearance of sensations of euphoria and well-being in response to the self-administration of a pharmacologically inert substance, such as saline solution. Subjects can feel subjective sensations (well-being, "getting high") and physiological changes (constriction of pupils) in response to an injection of saline solution (O´Brien, 1975; O´Brien, Nace, Mintz, Meyers & Ream, 1980; O´Brien et al., 1986). The similar conditioned effects to those of drugs will become greater if subjects inject saline solution into the habitual places of consumption where they hope "to get high" (O´Brien, Childress, McLellan & Ehrman, 1993).

On the other hand, conditioning the effects of cocaine has been verified in animals (Barr et al., 1983; Post, Lockfeld, Squillage & Contel, 1981) and humans (Muntaner et al., 1989). In humans, the power of verbal instructions to elicit the effects of a previous cocaine intake experience has been demonstrated. Not only can a certain stimulus elicit the effects of drugs, but the context and the atmosphere (room, people, drug injection ritual) can also act as elements of a complex conditional stimulus which, when repeatedly connected with a cocaine injection, will elicit similar conditioned placebo responses to those produced by the drug (O'Brian et al., 1986).

In addition to classic conditioning, attempts have been made in which subjects experience the sensations of the drug by means of suggestion. Pavlov previously stated that: "suggestion is the simpler and typical conditioned reflex of the human being". Thus, it has been ascertained that users and non users of drugs experience the effects of a wide variety of drugs, like cannabis, barbiturates, ecstasy, amphetamines or LSD, by means of suggestion (Bauman, 1971; Fogel & Hoffer, 1962; Granone, 1973; Hastings, 2006).

Besides, there is evidence for a conditioned gene expression elicited by drug-associated environmental cues. A marked up-regulation of the expression of the immediate early gene product *Fos* has been found during exposure to a morphine-paired environment (Schroeder, Holahan, Landy & Kelley, 2000) or to a cocaine-paired environment (Brown, Robertson & Fibiger, 1992; Neisewander et al., 2000). Furthermore, the same mechanism has been observed to up-regulate the *arc* during exposure to a nicotine-paired environment (Schiltz, Kelley & Landry, 2005).

In order to increase the therapeutic efficacy of the conditioning mechanism and suggestion, the Self-regulation Therapy was created (Amigó, 1992). This procedure is a therapeutic suggestion technique deriving from the cognitive-behavioral approach to hypnosis (Spanos & Chaves, 1989). It uses direct suggestions without any formal hypnosis induction procedure, but introduces suggestions through normal conversation with the subject fully awake and conscious. The Self-regulation Therapy has proved effective for smoking reduction (Bayot, Capafons & Cardeña, 1997; Capafons &

Amigó, 1995) and for reproducing (conditioning) drug effects, ranging from heroin (Amigó, 1998) to stimulants such as ephedrine (Amigó, 1994) or methylphenidate (Amigó, 1997). The Self-regulation Therapy has been described elsewhere (for instance, Amigó, 1994; 1998). Next we present a brief description of this therapy.

The Self-regulation Therapy is comprised of three phases. In the first phase, several sensory recall exercises are used to teach subjects how to voluntarily reproduce various physical sensations (salivation, leg paralysis, arm heaviness and hand rigidity) which are initially provoked by real stimuli. Subjects are asked to associate these sensations with images, words or other cues that will help them to later reproduce the sensations without the physical stimuli.

In the second phase, subjects reproduce these sensations several times without the physical stimuli for the purpose of making the response quicker and clearer in each trial. At the end of the second phase, the use of images and other cues is faded so that a direct suggestion suffices to produce a sensation with the feeling of automaticity.

In the last phase, also called the "generalization phase", demand of any kind generates the suggested effects. At the beginning of the phase, subjects are told that as they have performed exercises previously, their minds are highly activated and receptive, so they can respond to the therapist's verbal suggestions without having to be trained for each new session. At this point, patients are provided with therapeutic suggestions or drug reproduction suggestions. In subsequent sessions, the first and second phases are shortened, or even omitted altogether.

Acute administration of psycho-stimulants, such as cocaine or methylphenidate, brings about changes in the gene expression (Berke, Paletzki, Aronson, Hyman & Gerfen, 1998; Torres & Rivier, 1994; Yano & Steiner, 2005). The *D3* dopamine receptor is one of the three of the *D2* subtype, these being *D2, D3* and *D4*. The *D1* dopamine receptor subtype exists, as does *D5*. All these *mRNA* dopamine receptors have been found in human peripheral blood lymphocytes (Ostadali et al., 2004; Ricci et al., 1999; Takahashi, Nagai, Ueno, Saeki & Yanagihara, 1992).

The *D3* dopamine receptor shows a high affinity for dopamine (Strange, 1993), is preferentially localized in the mesocortical-limbic dopamine system and projects to the ventral striatum (Levant, 1998; Suzuki, Hurd, Sokoloff, Schwartz & Sedvall, 1998). Thus, *DRD3* is considered to play a major role in cognition and emotion (Meador-Wooddruff, Mansour, Saul & Watson, 1994), in neuropsychiatric diseases (Levant, 1997) and in personality (Czermak et al., 2004).

Furthermore, there is evidence that *DRD3* plays a role in addiction mechanisms, such as drug-seeking and drug-taking behavior (Caine & Koob, 1993; Pilla et al., 1999). These authors reported that *D3*-selective agonists provoke reductions in cocaine reward and seeking. However, similar effects have been reported with a potent, highly selective *D3* antagonist (Vorel et al., 2002). Hence, the results are variable and contradictory. Yet it is possible that the putative *D3* agonists used in previous studies do not possess full *D3* agonist properties (Levant, 1997). It is also possible that they are partially agonist or mixed *D3* agonists/antagonists, and that they are predominant antagonist properties. On the other hand, *D3*-preferring antagonist nafadotride produces *biphasic effects* on locomotive activity in rats by stimulating locomotion at lower doses and inhibiting locomotion at higher doses (Sautel et al., 1995). The nafadotride doses which increase locomotive activity produce *D2* receptors occupancy; whereas those that inhibit locomotion generate significant *D3* occupancy. On the other hand, *D3*-preferring agonist *7-OH-DPAT* produces not only inhibitory effects at lower doses, which are attributed to *DRD3*, but also stimulatory effects at higher doses, which are attributed to *DRD*2 (Daly & Walington, 1993). There is also evidence that the blockage of *DRD3*

reduces *c-fo*s (Merchant, Figur & Evans, 1996). In our study, it is possible that the dopamine level is not high enough during the first hour, and that the dopamine level is higher during the second or third hour.

It is also feasible that a dynamic study into the variation of *DRD3 mRNA* can prove useful in our understanding of its mechanism of action. At present however, the direct assessment of human brain changes in *DRD3 mRNA* is not possible. The "peripheral marker hypothesis" asserts that the expression of the dopamine receptors in peripheral blood lymphocytes (*PBL*) reflects their expression in the brain. Kwak, Koo, Choi and Sunwoo (2001) measured the changes of the *DRD3 mRNA* expression in lymphocytes of schizophrenic patients after they took antipsychotics. After taking medication, *DRD3 mRNA* peaked at the 2nd week to later decrease, but the level was above baseline one at 8th week.

The findings of Kwak et al. (2001) reveal the reactivity of *DRD3 mRNA* to drugs. Nevertheless, no study into the reactivity of the *DRD3 mRNA* expression in human lymphocytes deriving from an acute administration of a stimulant drug has been found.

According to the "peripheral marker hypothesis", the expression of the dopamine receptors in peripheral blood lymphocytes (*PBL*) reflects their expression in the brain. There is accumulative evidence for an altered neurotransmitter receptor expression in the *PBL* of patients with neuropsychiatric disorders. For example in relation to the *D3* dopamine receptor, a reduced *mRNA* expression of the *DRD3* in *PBL* was found in patients with Parkinson's disease which correlated with clinical severity (Nagai et al., 1996). Moreover, a reduced *PBL* expression of *DRD3* in patients with Alzheimer's disease has been reported (Barbanti et al., 2000a). Nevertheless, an increased *PBL* expression of *DRD3, DRD4* (Barbanti et al., 2000b) and *DRD5* (Barbanti et al., 1996) was found in migraine patients. An elevated dopamine receptor *D3 mRNA* in the *PBL* of patients with schizophrenia has also been reported (Illani et al., 2001), which also correlates with clinical severity and reacted sensitively to the administration of antipsychotics (Kwak et al., 2001).

The dopaminergic system has been implicated in personality traits in healthy individuals (Comings et al., 2000). There is a negative correlation between the *DRD3 mRNA* expression in *PBL* and the persistence trait (Czermak et al., 2004). Nevertheless, the temporary dynamics of gene expression and personality has not yet been studied. It is possible that *DRD3* is related to inhibiting mechanisms of personality. Accili et al. (1996) encountered increased locomotive activity and rearing behavior and hyperactivity in one strain of *D3* "knock-out" mice in an exploratory test. Some evidence suggests that *DRD3* activation inhibits the mesocorticolimbic *DA* function (Gilbert, Millar & Cooper, 1995; Lejeune & Millan, 1995) and that *DRD3* inhibition actives the mesocorticolimbic *DA* system (Nissbrant, Ekman, Eriksson & Heilig, 1995). Czermak et al. (2004) explained how the *DRD3* expression level accounts for the dopamine release pattern. Thus, a reduced pre-synaptic self-receptor function enhances tonic dopamine release. Furthermore, the *D3* receptor inhibits dopamine release (Tang, Todd & O'Malley, 1994). On the other hand, a low postsynaptic expression reduces phasic dopaminergic neurotransmission in the prefrontal cortex.

A dynamic mathematical model has been proposed to explain short-term personality changes caused by an acute administration of psycho-stimulants such as cocaine (Amigó, Caselles & Micó, 2008a; Caselles, Micó & Amigó, 2011) using a personality adjectives scale. Besides, a dynamical model of personality and gene expression changes produced by caffeine has been proposed (Amigó, Caselles & Micó, 2008b). In addition, the Self-regulation Therapy has reproduced the dynamics of the

effect of methylphenidate on the pattern of change in the glutamate concentration in blood and of the general factor of personality scores (Amigó, Caselles, Micó & García, 2009).

In this study, we analyze the personality and gene expression changes (*DRD3 mRNA* gene) deriving from an acute administration of methylphenidate and a psychological suggestion technique to reproduce drug effects. Two voluntary subjects participated in this study. A single case experimental design with replication to control the considered variables is proposed. Both subjects took a dose of methylphenidate and the pattern of change in the gene expression of *DRD3* and in personality was recorded. The *mRNA* expression of *DRD3* was measured in peripheral blood lymphocytes. Personality was measured by the Big Five Personality Adjectives List (*BFPAL*) (Brody & Ehrlichman, 1998). Schutte, Malouff, Segrera, Wolf and Rodgers (2003) devised the Big Five States Inventory by starting with the hierarchical model of personality. Traits are conceptualized as a higher level with enduring characteristics, while states are a lower level with less enduring characteristics (p. 592). These authors did a confirmatory factor analysis (CFA) to show an acceptable degree of fit between the responses in the transitory states measurements and the Big Five dimensions. We also measured the Big Five in a state-format version, but with another adjective list, the *BFPAL*. One of the subjects applied the Self-regulation Therapy to reproduce the short-term change patterns in personality and gene expression which methylphenidate produced.

Indeed, we herein propose that the Self-regulation Therapy changes personality measured by *BFPAL*, as it does with methylphenidate, and that it also modifies the *DRD3 mRNA* levels dynamically.

Materials and Methods

A single case experimental design.

a) Subjects.

Two male subjects, aged 45 and 46 years, participated in the experiment as two University staff volunteers.

b) Instruments.

- The Big Five Personality Adjectives List (*BFPAL*) (Brody and Ehrlichman, 1998). This list is made up of 25 adjectives. A state-format version ("Are you like this at the moment?" was used. Both subjects completed the state-format version every 15 minutes to obtain a situational measure of the *BFPAL*.
- Biological analysis. First, blood samples were taken and lymphocytes were isolated by density centrifugation in Lymphoprep. Second, an automated mass spectrometry platform (Sequenom, MassARRAY Quantitative Gene Expression) was used for the quantification of the *DRD3 mRNA* concentration in lymphocytes. β-actin was used as an internal *RNA* standard.

c) Procedure and experimental design.

One experiment was done per subject. The experimental design for Subject 1 was *ABC* and *ABAD* for Subject 2. Both experiments were a partial replication of each other, where two experimental conditions agreed: *A* and *B*. For Subject 2, an experiment with replication was considered to be intra-subject since *AB* was replicated by *AD*, although conditions *B* and *D* were not exactly the same ones. As seen, and when the experimental design is complex, we go on to present it in detail:

- Subject 1 filled in the *BFPAL* form every 15 minutes (17 records per phase) in all these phases and blood samples were taken once per hour (five samples per phase).
  - Phase *A* is the baseline, without treatment.

- In phase *B*, the subject took a 20 mg dose of methylphenidate immediately after completing the first *BFPAL* form. At the same time, the first blood sample was taken. Next, the subject completed 16 *BFPAL* forms, one every 15 minutes, and a blood sample was taken once per hour during 4 hours.
- In phase *C*, the subject took 40 mg of methylphenidate immediately after completing the first *BFPAL* form. Next, the first blood sample was taken. As in phase *A*, the subjects filled in 16 *BFPAL* forms, one every 15 minutes. A blood sample was taken each hour during 4 hours after filling in the corresponding *BFPAL* form.

The sequence of the experiment for Subject 1 was:

- Day 1: the experimental subjects went to the medical laboratory. Phase *A*: baseline.
- Day 2: the subjects took 20 mg of methylphenidate. Phase *B*.
- Day 3: Subject 1 took 40 mg of methylphenidate. Phase *C*.

➢ Subject 2 followed the same procedure as Subject 1 in Phases *A* and *B*. On day 3, there were two experimental conditions: 1) baseline (*A*) for one hour and 45 minutes, and 2) after the second hour, the subject applied the Self-regulation Therapy to reproduce the drug effects obtained in Phase *B* (*D*). The *BFPAL* register and the blood samples were obtained following the same protocol as in the previous phases.

Thus for Subject 2, there were a control condition (the first 7 points) and an experimental condition (the Self-regulation Therapy, 9 points). We can state that the experimental design for Subject 2 was *ABAD*: A (baseline 1), *B* (20 mg methylphenidate), *A* (baseline 2), and *D* (the Self-regulation Therapy).

Besides following the sequence of the experiment described in the previous section, Subject 2 participated in three Self-regulation Therapy training sessions: one session with a 20 mg administration of methylphenidate and three sessions in which the effects of the drug were reproduced with the Self-regulation Therapy.

The sequence of the experiment for Subject 2 was:

1) Phase A, baseline. The *BFPAL* scores were recorded and blood samples were taken.
2) Phase B, 2 weeks later. Intake of 20 mg of methylphenidate; the *BFPAL* scores were recorded and blood samples were taken.
3) Phase R1, 2 days later. The effects of the drug were reproduced with the Self-regulation Therapy and the *BFPAL* scores were recorded.
4) Phase B2, 1 week later. Intake of 20 mg of methylphenidate and the *BFPAL* scores were recorded.
5) Phase R2, 2 days later. The effects of the drug were reproduced with the Self-regulation Therapy and the *BFPAL* scores were recorded.
6) Phase D, 1 week later. In which the effects of the drug were reproduced with the Self-regulation Therapy, the *BFPAL* scores were recorded and blood samples were taken.

Thus, we can see that the sequence of the experiment for Subject 2 coincides with that of Subject 1 in Phases *A* and *B*. Also for Subject 2, three training sessions took

place between Phases *B* and *D*, of which two were to reproduce the drug effects with the Self-regulation Therapy (*R1* and *R2*) and one session involved the intake of 20 mg of methylphenidate (*B2*).

In sessions *B2*, *R1* and *R2*, blood extractions were not taken, but the subjective activation was recorded using the *BFPAL*. Sessions *R1* and *R2* were replication sessions involving the reproduction of the subjective effects of the drug with the Self-regulation Therapy and, simultaneously, they served as training sessions.

During Phase *D*, the Self-regulation Therapy was applied 1 hour and 45 minutes after beginning the session. This time prior to applying the Self-regulation Therapy constitutes an intra-session baseline.

Both subjects took 20 mg of methylphenidate in Phase *B*. A literature review of the effect of different oral doses of methylphenidate (Kollins, MacDonald & Rush, 2001) shows that, depending on the experimental context, doses from 10-40 mg can cause clear subjective effects. Yet in the research into the acute effects of oral methylphenidate doses, the standard amount of 20 mg has been used on many occasions (Volkow, Wang, Fowler, Telang et al., 2004; Volkow, Wang, Telang, Fowler et al., 2008). On the other hand, some studies have considered that the therapeutic methylphenidate dose should be between 0.3 mg/kg and 0.6 mg/kg (Volkow, Wang, Fowler, Gatley & Logan, 1998).

If we take this into account, the methylphenidate dose in Phase *B* was infra-therapeutic in both cases. Thus for Subject 1, whose weight was 86 kg, the therapeutic dose oscillated between 25.8 mg and 51.6 mg, whereas for Subject 2, who weighed 75 kg, the therapeutic dose ranged between 22.5 mg and 45 mg. However, Subject 1 took 40 mg in Phase *C*, which is indeed a therapeutic dose.

In order to verify the effectiveness of the Self-regulation Therapy to reproduce the effect of the drug, we designed a complex single case experiment in which several controls have been set out for this very purpose. Thus, it is possible to compare the Self-regulation Therapy training sessions (*R1* and *R2*) with their respective 20 mg methylphenidate intake sessions (*B* and *B2*).

This reveals the complexity and goodness of the single case experimental design with replication which we have used. Next, we present some relevant results of the many results that can be obtained.

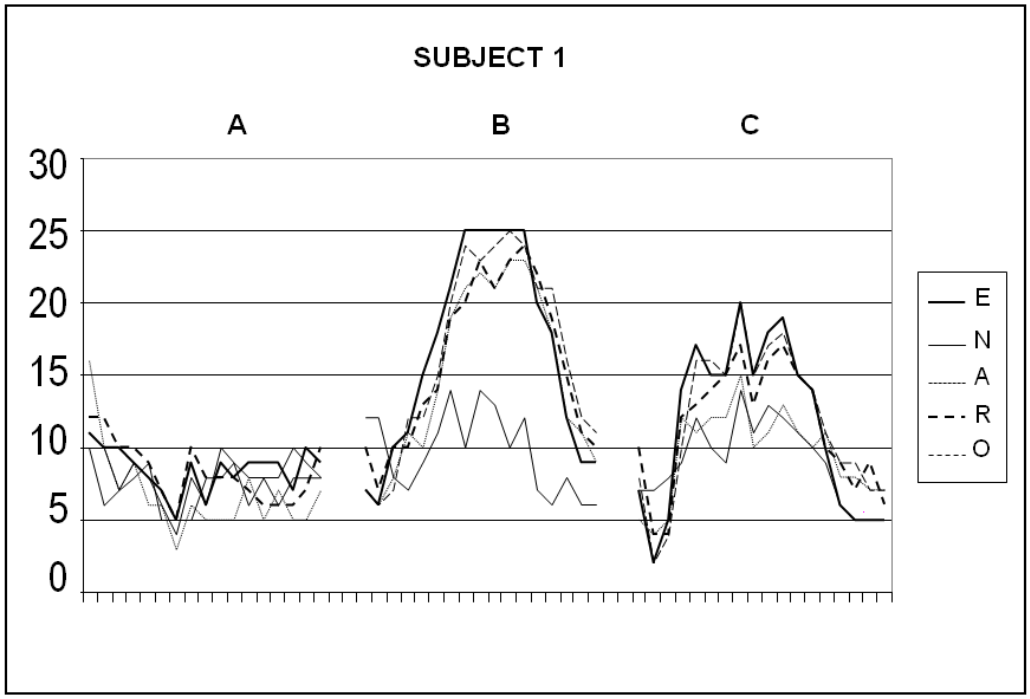

Figure 1. *BFPAL* registers (points) for subject 1 for phases A, B and C.
E: Extraversion; N: Neuroticism; A: Agreeableness, R: Responsibility; O: Openness.

Results

Figure 1 presents the graph of Subject 1's *BFPAL* score records for the three phases (separated by a space): *A* (baseline), *B* (20 mg methylphenidate) and *C* (40 mg methylphenidate). A very clear difference between the baseline record and the record with the two methylphenidate intake conditions was observed. In the first case (baseline), no pattern was observed in the Big Five factors scores. In Phase *B* (20 mg), an inverted U shape was observed for the scores of all the factors, although it was less intense for Neuroticism. In Phase *C* (40 mg), the effect was particularly lower than with 20 mg, but the pattern was the same, an inverted U shape, for the Big Five factors scores (Extraversion, Neuroticism, Agreeableness, Responsibility and Opening).

These results indicate that the Big Five factors tend to change simultaneously and that 40 mg produces, in this subject, a slighter subjective effect than the effect of 20 mg, which indicates a possible effect of habituation or transmarginal inhibition.

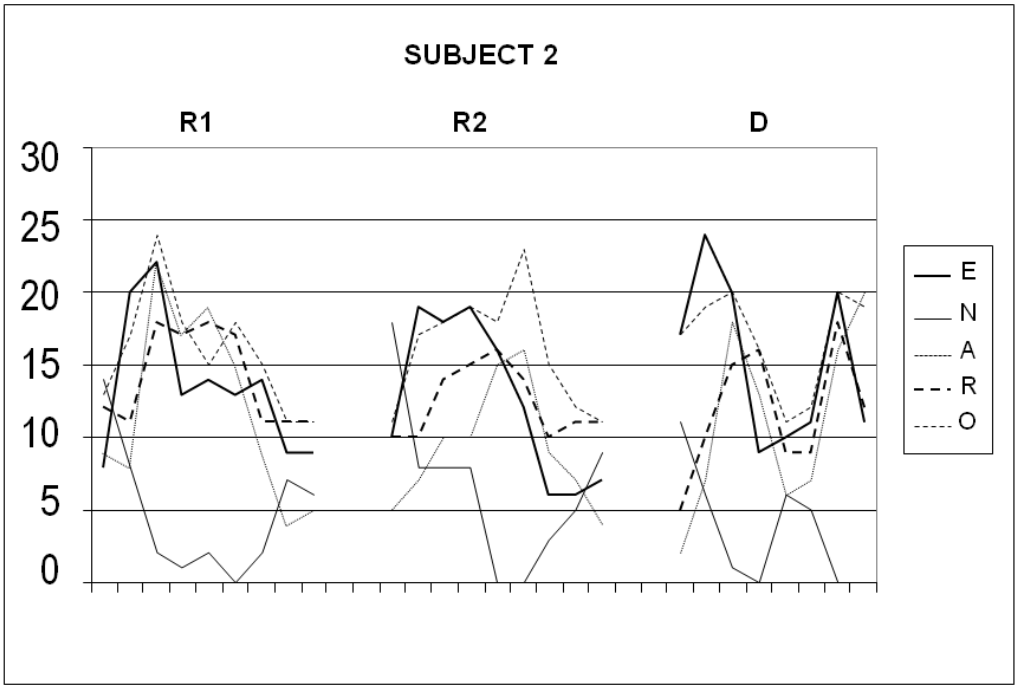

Figure 2. *BFPAL* registers (points) for subject 2 for phases R1, R2 and D.
E: Extraversion; N: Neuroticism; A: Agreeableness; R: Responsibility; O: Openness.

Figure 2 offers the graph of Subject 2's *BFPAL* score records for the three Self-regulation Therapy sessions: *R1, R2* and *D*. A very similar pattern of change in the three sessions was observed: an inverted U for the Extraversion, Agreeableness, Responsibility and Opening factors, and a normal U for Neuroticism. In Phase *D*, a new activation took place when reaching the baseline since the subject once again thought about the effects of methylphenidate. It is necessary to indicate that the Kruskal-Wallis test did not show any differences between the records of the three Self-regulation Therapy sessions, indicating that they are the equivalent to each other. For this reason from among the three Self-regulation Therapy training sessions reproducing the methylphenidate effects (*R1, R2* and *D*), for presentation purposes, we chose the data of the first session (*R1*) for the remaining analyses because of the clearer pattern of change shown, and because it seemed advisable for us to present the pattern of change of the first and closer session after the first 20 mg intake.

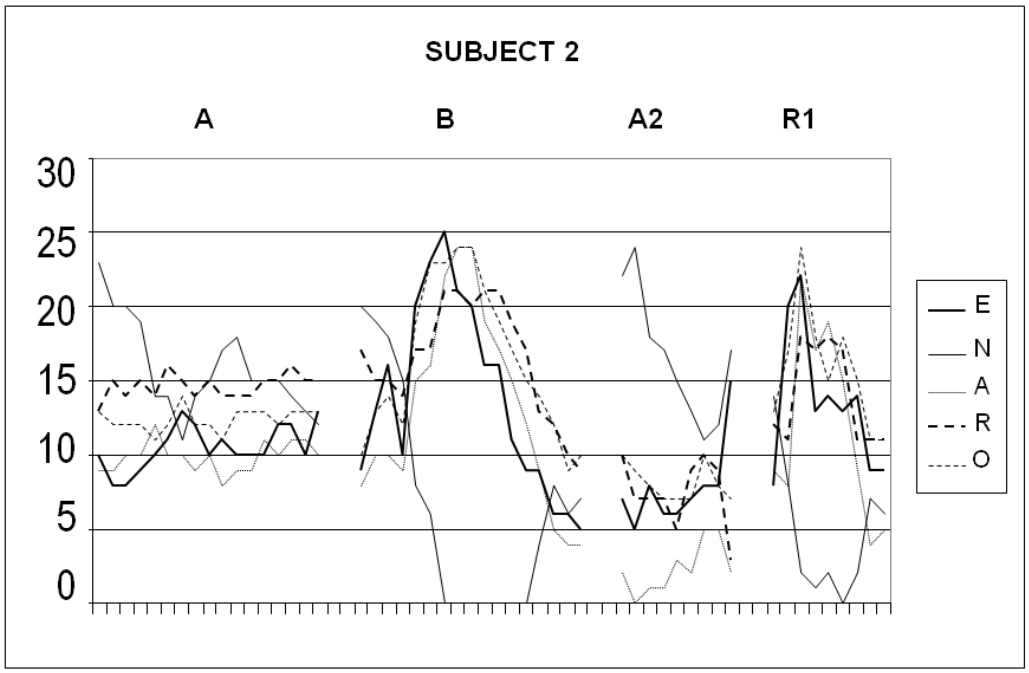

Figure 3. *BFPAL* registers (points) for subject 2 for phases A, B, A2 and R1.
E: Extraversion, N: Neuroticism; A: Agreeableness, R: Responsibility, O: Openness.

Figure 3 provides the graph of Subject 2's *BFPAL* scores records for the four experimental conditions: *A* (baseline), *B* (20 mg), *A* (new baseline) and *R1* (first reproduction of the methylphenidate effects with the Self-regulation Therapy).

If we compare conditions *A* and *B*, the result is similar to that of Subject 1; that is, the Big Five personality factors do not display a clear pattern of change for condition *A*, unlike the clear pattern of change observed in condition *B* (20 mg) with an inverted U shape for four of the factors and a normal U shape for Neuroticism. This last factor was not noted in Subject 1, which indicates that different patterns of change can be obtained. In any case, all the patterns of change observed were very clear.

In the third condition (the second baseline of *A2*), the new baseline displayed some differences if compared with the first baseline, mainly a reduction in Neuroticism and an increase in Agreeableness. The levels for at least four of the five factors were lower than in the first baseline. Our interpretation is that on this day (the second baseline) the subject showed less activation. This finding also contrasts with the Phase R1 result, where the pattern of change for the Big Five was practically identical to that produced for 20 mg of methylphenidate. In other words, although the subject showed less activation that day, he was able to reproduce the effects of methylphenidate with the same pattern of change. The only difference noted was that the effect brought about by the Self-regulation Therapy lasted less than the effect caused by 20 mg of methylphenidate, but the intensity of the effect was similar and the pattern of change (an inverted U for four factors and a normal U for Neuroticism) was identical.

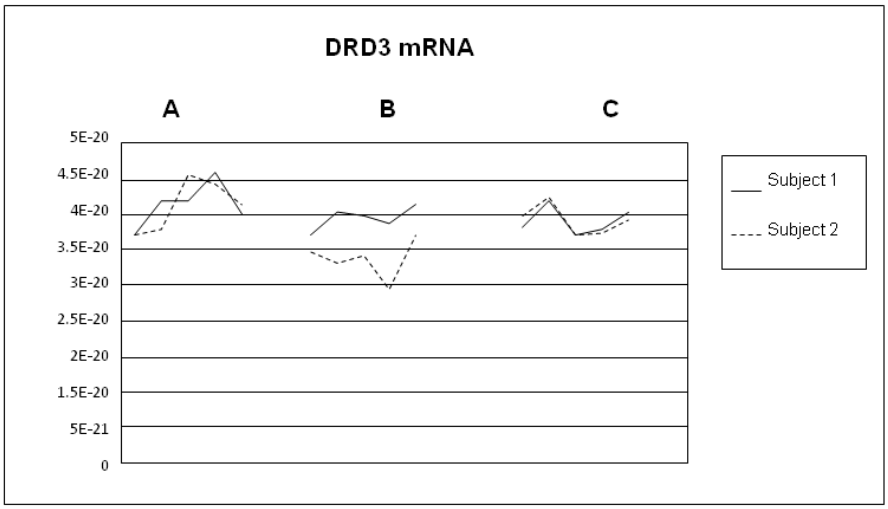

Figure 4. *DRD3* expression for Subjects 1 and 2 in phases A, B and C.

Figure 4 depicts the *DRD3* measures for the three phases in both subjects. By way of example, we joined Subject 2's Phases *A2* and *D* to form a single phase which we called Phase *C*. In both cases, we observed a different response pattern between Phase *A* (baseline) and Phases *B* and *C*. Thus, while the *DRD3* expression showed an inverted U shape in Phase *A*, the opposite occurred in Phases *B* and C, which showed a normal U shape. In comparison to Subject 2, a delay in the gene expression in Phase *B* was noted for Subject 1; that is, it increased during the first hour to lower in the two following hours and to once again increase at the end. In Subject 2, a more marked reduction was noted.

Furthermore for Subject 2, we observed that the Self-regulation Therapy proved effective to lower the gene expression. We see how the gene expression in Phase *C* increased after the first hour, which also happened in Phase *A* (baseline). However, 20 minutes after applying the Self-regulation Therapy, that is, already in the second hour, the gene expression clearly lowered and progressively recovered until the baseline at the end of the session, which took a similar form, be it less pronounced than in Phase *B*. When comparing both subjects, we saw that the gene expression curves overlapped in Phase *C*. In other words, the *DRD3* expression pattern that the Self-regulation Therapy produced was similar to that generated by 20 mg of methylphenidate for the same subject.

Table 1. The Kruskal-Wallis test to Subject 1.

Big Five	Condition	Average Rank	X	σ	χ^2
E	A	14.81	8	1.63	15.53***
	B	34.25	17.12	6.87	
	C	24.44	12.19	5.79	
N	A	16.25	7.13	1.4	8.48*
	B	28.56	9.56	2.85	
	C	28.69	9.44	2.73	
A	A	11.59	6.19	1.75	24.1***
	B	35.66	15.56	5.98	
	C	26.25	10	2.92	
R	A	13.34	8.06	1.94	18.79***
	B	34.66	16.31	5.67	
	C	25.50	11.81	4.23	
O	A	13.94	8.38	1.45	16.85***
	B	34.09	17.06	6.45	
	C	25.47	12.38	5.14	

E: Extraversion, N: Neuroticism; A: Agreeableness,
R: Responsability, O: Opennes; A: Base-line, B: drug 20 mg, C: drug 40 mg;
* $p < .05$; *** $p < .001$

Table 2. The Kruskal-Wallis test to Subject 2.

Big Five	Condition	Average Rank	X	σ	χ^2
E	A1	23.81	10.56	1.54	14.77**
	B	29.47	14.13	6.42	
	A2	7	6.86	1.21	
	R1	30.50	13.56	4.82	
N	A1	34.66	15.38	2.7	22.71***
	B	15.88	5.69	6.62	
	A2	34.07	15.43	3.86	
	R1	14.33	4.67	4.5	
A	A1	25.69	9.94	0.1	17.07**
	B	30.78	13.44	6.66	
	A2	5.14	2.29	2.13	
	R1	26.28	12	6.42	
R	A1	26.06	14.75	0.68	18.22***
	B	31.56	16.19	4.38	
	A2	4.93	7.71	1.07	
	D	24.39	14	3.35	
O	A1	21.25	12.38	0.8	23.44***
	B	32-69	16.85	5.12	
	A2	4.29	8	1.15	
	R1	31.44	15.78	4.08	

E: Extraversion, N: Neuroticism; A: Agreeableness,
R: Responsibility, O: Openness; A1: Base-line 1, B: drug 20 mg, A2: Base-line 2,
R1: Self-regulation therapy; ** $p < .01$; *** $p < .001$

In addition to the graphical representation, we did several statistical analyses from the single case experimental design perspective (Barlow and Versen, 1984). In Tables 1 and 2, the Kruskal-Wallis test results for both subjects and the Big Five factors appear; where each experimental condition is taken as a sample. The rank average data, as well as the averages and standard deviations of each experimental condition, have been added. Significant differences for the different conditions and both subjects' personality factors have been found, and this is the reason why we analyzed the differences between conditions in pairs.

Table 3. Two sample Kolmogorov-Smirnov test to subject 1.

Big Five	Condition	Z
E	A-B	2.12***
	A-C	2.12***
	B-C	1.06
N	A-B	1.14*
	A-C	1.14*
	B-C	0.35
A	A-B	2.12***
	A-C	2.12***
	B-C	1.41*
R	A-B	1.94**
	A-C	1.94**
	B-C	1.41*
O	A-B	2.47***
	A-C	2.47***
	B-C	0.09

E: Extraversion, N: Neuroticism; A: Agreeableness,
R: Responsibility, O: Openness; A: Base-line, B: drug 20 mg, C: drug 40 mg;
* $p < .05$; ** $p < .01$; *** $p < .001$

Table 4. Two sample Kolmogorov-Smirnov test to subject 2.

Big Five	Condition	Z
E	A1-B	1.41*
	A2-R1	1.76**
	A1-A2	1.93**
	B-R1	0.66
N	A1-B	2.29***
	A2-R1	1.76**
	A1-A2	0.53
	B-R1	0.78
A	A1-B	1.41*
	A2-R1	1.54*
	A1-A2	2.2***
	B-R1	0.58
R	A1-B	1.59*
	A2-R1	1.98**
	A1-A2	2.2***
	B-R1	0.9
O	A1-B	1.76**
	A2-R1	1.98**
	A1-A2	2.2***
	B-R1	0.78

E: Extraversion, N: Neuroticism; A: Agreeableness,
R: Responsibility, O: Openness; A1: Base-line 1, B: drug 20 mg, A2: Base-line 2,
R1: Self-regulation therapy; * $p < .05$; ** $p < .01$; *** $p < .001$

The results of the two sample Kolmogorov-Smirnov tests done with both subjects are presented in Tables 3 and 4. Thus for Subject 1 in relation to the baseline (*A*), the Big Five factors scores significantly increased for methylphenidate for both condition *B* (20 mg) and condition *C* (40 mg), although Neuroticism increased to a lesser extent, as observed in Figure 1. However, the Agreeableness and Responsibility scores significantly lowered for the 40 mg condition since no significant differences were found for the remaining factors. If we observe the averages and standard deviations in Table 1, we see how the averages and standard deviations of the scores for the other personality factors are lower, except Neuroticism. This is in agreement with what we can see in Figure 1, where a 40 mg methylphenidate dose produced the same pattern of change for the Big Five factors, but with lower scores.

Table 4 provides the results for Subject 2. First of all, the Big Five factors scores significantly increased when this subject took 20 mg of methylphenidate (*B*) if compared with the first baseline (*A1*). Moreover, the same pattern between the scores obtained with the Self-regulation Therapy (*R1*) and the second baseline is observed (*A2*). On the other hand, and save Neuroticism, the Big Five factors scores were significantly lower in *A2* if compared with *A1*. This is coherent with that presented in Figure 2 as this subject showed less activation in *A2* than in *A1*. Finally, no significant differences between conditions *B* (20 mg) and *R1* (Self-regulation Therapy) were been obtained, which can be interpreted as them being two equivalent conditions.

Discussion

The results obtained in this study support the hypothesis that the Self-regulation Therapy (Amigó, 1992; 1997) reproduces as many patterns of change for the Big Five personality factors as the biological ones after one methylphenidate dose. A very similar results pattern with *EEG* and cerebral imaging (*SPECT*) has been observed with the Self-regulation Therapy and the methylphenidate (Amigó, 2005). In addition, a similar pattern of change of personality and glutamate concentration in blood has been obtained with both methylphenidate intake and the Self-regulation Therapy (Amigó, Caselles, Micó & García, 2009). In particular, and as far as the biological effect is concerned, this study has verified that the Self-regulation Therapy reproduces the same pattern of change (an inverted U) of the *DRD3* expression as produced by the stimulating drug.

A single case experiment with two voluntary subjects has been conducted. For Subject 1, the experiment consisted in three phases, each lasting 4 hours: Phase *A* (baseline), Phase *B* (20 mg of methylphenidate) and Phase *C* (40 mg of methylphenidate). For Subject 2, the experiment consisted in 4 phases: Phase *A1* (baseline 1), Phase *B* (20 mg of methylphenidate), Phase *A2* (baseline 2) and Phase *D* (Self-regulation Therapy). In all the phases, as many measures from the Big Five personality factors were taken as biological measures (the *DRD3* expression). In addition, Subject 2 underwent three training sessions: one session with a 20 mg methylphenidate intake (*B2*) and two Self-regulation Therapy training sessions (*R1* and *R2*). After training, this subject re-applied the Self-regulation Therapy in Phase *D*.

A general factor of activation or personality has been set out which underlies the Big Five factors of personality (Musek, 2007). This indicates that a change in the Big Five factors can be interpreted as a change in the general level of activation. Along the same lines, some research works consider that the general factor of personality can be interpreted (Amigó, 2005; Amigó et al., 2008a, Amigó, Caselles & Micó, 2010). These authors propose the Unique Personality Trait Theory (*UPTT*) as a biological mechanism to explain the interrelation and pattern of change among the Big Five factors, which is based on a balance between tonic general activation, at rest, and phasic activation in response to external stimuli such as drugs.

Thus, the results provided herein also demonstrate that 20 mg of methylphenidate (Phase *B*) produce an intense psychological activation effect on both subjects in comparison with the baseline (Phase *A*). This activation effect takes an inverse U shape, meaning that 20 mg of methylphenidate change psychological activation in the short term (4 hours) by firstly increasing to descend later (inverted U shape). In addition, both subjects modify the *DRD3* expression in the same manner if compared to the baseline. Therefore, the same dynamic activation pattern produced by 20 mg of methylphenidate is observed: an inverted U shape for the psychological variable (scores in the *BFPAL*) and a normal U shape for the biological one (the *DRD3* expression). If we consider that the psychological activation measured by the *BFPAL* scores is a state-format version of the Big Five factors or of the general factor of personality (Amigó, Micó & Caselles, 2009), we can conclude that 20 mg of methylphenidate can modify not only personality in the short term (4 hours), measured on scales of adjectives, but also its genetic substratum simultaneously in the same way. This result thus confirms the integrated dynamics of the subjective and genetic aspects of personality as a response to a stimulating drug.

On the other hand, certain evidence for the two-phase effects produced by methylphenidate has been obtained on subjective activation by means of the *DRD3* expression. Hence, an increase in the *DRD3* expression at one hour after the intake of 20 mg and of 40 mg of methylphenidate is observed mainly in Subject 1, which lowers

over the next two hours and then returns to the baseline during the last hour. This pattern of change corresponds to the pattern of change of subjective activation; therefore, the subjective activation peak agrees with the minimum activation peak of the *DRD3* expression. Thus, the higher the methylphenidate concentration in blood (the second half of Phase *B*) or the greater the methylphenidate dose (Phase *C*), the lower the *DRD3* expression in relation to the baseline in Subject 1 (Phase *A*). Subject 2 presents a pattern of change in the *DRD3* expression in Phase *B*, which is inverse to that of Subject 1 during the first two hours. Then a similar, more marked pattern of reduction with a subsequent increase in the gene expression is noted during the next two hours. This can be interpreted as methylphenidate producing an effect of increased activation in Subject 2 by progressively reducing the *DRD3* expression where the two-phase effect is barely perceivable. We can therefore conclude that, for equal doses (20 mg of methylphenidate), Subject 1 presents more marked two-phase effects in the *DRD3* expression than Subject 2.

Methylphenidate increases *DRD3 mRNA* after the first hour, which subsequently lowers progressively at the end of the second and third hours to then return to the baseline at the end of the fourth hour. Following the two-phase reactivity hypothesis of *DRD3*, we propose that an initial increase in the low activation condition takes place, which is accompanied by a progressive increase in the positive mood. As activation increases (a greater dopamine flow in the brain), *DRD3 mRNA* lowers and, consequently, the positive mood diminishes.

We also obtained other interesting results. For instance, 40 mg of methylphenidate led to a less marked change in personality in Subject 1 (lesser general activation) than 20 mg. It is possible that 40 mg of methylphenidate elicit transmarginal inhibition. It has been proved that high doses of stimulants produce transmarginal or protector inhibition to elude excessive activation (Eysenck, 1967; Gilbert & Hagen, 1985; Smith, Wilson & Davidson, 1983), producing a lower positive effect and increasing negative effects. There is a mathematical model available that predicts this mechanism for stimulants based on dose and consumption frequency (Caselles, Micó & Amigó, 2011).

In addition, very similar patterns of change were obtained for both subjects, but with different levels of activation, both of which have been recorded by the *BFPAL* scores and by the *DRD3 mRNA* measurements. This fact shows another relevant aspect in personality studies: individual differences. As Figures 1 and 3 illustrate, Subject 1 was less activated at his baseline than Subject 2 (lower *BFPAL* scores). Following the *UPTT*, subjects with a lower basal activation level would be more extraverted and would display a higher response to stimuli like drugs. Thus, transmarginal inhibition would appear earlier in these individuals, as our results corroborate. Finally, a mathematical model exists that simulates subjects' different activation responses as a function of their personality (Amigó, Caselles & Micó, 2008a; Caselles, Micó & Amigó, 2010).

This study has clear limitations when it comes to interpreting the biological results and personality since it is a study which includes only two subjects. It is necessary to extend this study with more regulating genes and a larger number of subjects to be able to compare the combined effects of different genes in different subjects. However, the single case experimental design with replication presented herein is rigorous and allows to put forward the first causal proposals among various variables: subjective activation versus biological activation; exciting effects of the *DRD3* gene expression versus inhibiting effects; subjective and biological effects of a

stimulating drug versus biological and the subjective Self-regulation Therapy effects which attempts to reproduce the effects of the drug.

This it is the first study to state that a subject is able to voluntarily reproduce the genetic effects of methylphenidate simultaneously with personality factors. Thus, it is possible to voluntarily change, at least temporarily, global personality simultaneously with its genetic substratum (the *DRD3* expression). Furthermore, the potential therapeutic effect of voluntary reproduction from methylphenidate effects has already been verified (Amigó, 1997, 2005). This opens up important research and application fields, while the possibility of voluntarily changing the expression of a regulating gene opens up new and unsuspected possibilities.

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