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SELF-REGULATION THERAPY TO REPRODUCE DRUG EFFECTS: A Suggestion Technique to Change Personality and the DRD3 Gene Expression

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Abstract: This study proposes a strategy, based on 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, self-regulation therapy has been proven to reproduce the effects of drugs. Thus, it is feasible to hope that self-regulation therapy is equally effective as methylphenidate in changing personality and the gene expression. This is a preliminary study with a single-case experimental design with replication in which 2 subjects participated. The results and potential implications for research and psychotherapy are discussed.

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, 1992a; Stewart, De Wit, & Eikelboom, 1984).

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

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As regards abuse drugs, there is experimental evidence in humans for conditioning responses similar 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-injection 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 et al., 1986; O’Brien, Nace, Mintz, Meyers, & Ream, 1980). 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, 1992b).

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 that, when repeatedly connected with a cocaine injection, will elicit similar conditioned placebo responses to those produced by the drug itself (O’Brien, Ehrman, & Ternes, 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 nonusers 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). Further, 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, 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. 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). Self-Regulation Therapy has been described elsewhere (for instance, Amigó, 1994, 1998). Next, we present a brief description of this therapy.

Self-Regulation Therapy comprises 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) that 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, 1994). The D3 dopamine receptor is one of the three D2 subtypes, 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, Ūeno, 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-Woodruff, Mansour, Saul, & Watson, 1994), in neuropsychiatric diseases (Levant, 1997), and in personality (Czermak et al., 2004).

Further, there is evidence that DRD3 plays a role in addiction mechanisms, such as drug-seeking and drug-taking behavior (Caine & Koob,
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 have 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 that 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 DRD2 (Daly & Waddington, 1993). There is also evidence that the blockage of DRD3 reduces c-fos (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 second week to later decrease, but the level was above baseline at the eighth 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 that 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,
Nevertheless, an increased PBL expression of DRD3, DRD4 (Barbanti, Fabbrini, Ricci, Pascali, et al., 2000), 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 have 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 mesocorticollimbic DA function (Gilbert, Millar, & Cooper, 1995; Lejeune & Millan, 1995) and that DRD3 inhibition activates the mesocorticollimbic DA system (Nissbrandt, Ekman, Eriksson, & Heilig, 1995). Czermak et al. (2004) explained how the DRD3 expression level accounts for the dopamine release pattern. Thus, a reduced presynaptic 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 dynamic model of personality and gene expression changes produced by caffeine has been proposed (Amigó, Caselles, & Micó, 2008b). In addition, 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 (Schutte et al., 2003, 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 Self-Regulation Therapy to reproduce the short-term change patterns in personality and gene expression that methylphenidate produced.

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

**Method**

**Participants**

A single case experimental design with 2 male subjects, aged 45 and 46 years, participated in the experiment as university staff volunteers.

**Instruments**

*The Big Five Personality Adjectives List.* The BFPAL is a list 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. $\beta$-actin was used as an internal RNA standard.

**Procedure and Experimental Design**

One experiment was done per subject. The experimental design for Subject 1 was $ABC$ and for Subject 2 was $ABAD$. 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 intrasubject 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.** This is the baseline, without treatment.

**Phase B.** Here, 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.

**Phase C.** In this phase, 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 subject 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.

**Subject 1.** The sequence of the experiment for Subject 1 was:

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

**Subject 2.** 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 1 hour and 45 minutes;
2. After the second hour, the subject applied 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 was a control condition (the first 7 points) and an experimental condition (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 (self-regulation therapy).

In addition to 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 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 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 self-regulation therapy and the BFPAL scores were recorded.
6. Phase D—1 week later: The effects of the drug were reproduced with 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 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 self-regulation therapy and, simultaneously, they served as training sessions.

During Phase D, self-regulation therapy was applied 1 hour and 45 minutes after beginning the session. This time prior to applying self-regulation therapy constitutes an intrasession 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 to 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 et al., 2004, 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 et al., 1998).

If we take this into account, the methylphenidate dose in Phase B was infratherapeutic 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 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 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 that we have used. Next, we present some relevant results of the many results that can be obtained.

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 BFPAL 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 BFPAL 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 offers the graph of Subject 2’s BFPAL score records for the three self-regulation therapy sessions: R1, R2, and D. Figure 2, first mention 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

![Graph of Subject 1's BFPAL score records](image-url)

*Figure 1. BFPAL registers (points) for Subject 1 for phases A, B, and C. E: Extraversion; N: Neuroticism; A: Agreeableness, R: Responsibility; O: Openness.*
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 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 provides the graph of Subject 2’s BFPAL scores for the four experimental conditions: A (baseline), B (20 mg), A2 (new baseline), and R1 (first reproduction of the methylphenidate effects with 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
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.

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 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 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 that 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.

Further, for Subject 2, we observed that 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 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 self-regulation therapy produced was similar to that generated by 20 mg of methylphenidate for the same subject.

In addition to the graphic representation, we did several statistical analyses from the single-case experimental design perspective (Barlow & Hersen, 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.

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
Table 1
The Kruskal-Wallis Test for Subject 1

<table>
<thead>
<tr>
<th>Big Five</th>
<th>Condition</th>
<th>Average Rank</th>
<th>X</th>
<th>σ</th>
<th>χ²</th>
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<tr>
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<td>8</td>
<td>1.63</td>
<td>15.53***</td>
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<td></td>
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<td>C</td>
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</tr>
<tr>
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<td>A</td>
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<td>7.13</td>
<td>1.4</td>
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</table>

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

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 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 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 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 self-regulation therapy (Amigó et al., 2009). In particular, and as far as the biological effect is concerned, this study has verified that 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 of 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 of four 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...
Table 3
Two Sample Kolmogorov-Smirnov Tests for Subject 1

<table>
<thead>
<tr>
<th>Big Five</th>
<th>Condition</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>A-B</td>
<td>2.12***</td>
</tr>
<tr>
<td></td>
<td>A-C</td>
<td>2.12***</td>
</tr>
<tr>
<td></td>
<td>B-C</td>
<td>1.06</td>
</tr>
<tr>
<td>N</td>
<td>A-B</td>
<td>1.14*</td>
</tr>
<tr>
<td></td>
<td>A-C</td>
<td>1.14*</td>
</tr>
<tr>
<td></td>
<td>B-C</td>
<td>0.35</td>
</tr>
<tr>
<td>A</td>
<td>A-B</td>
<td>2.12***</td>
</tr>
<tr>
<td></td>
<td>A-C</td>
<td>2.12***</td>
</tr>
<tr>
<td></td>
<td>B-C</td>
<td>1.41*</td>
</tr>
<tr>
<td>R</td>
<td>A-B</td>
<td>1.94**</td>
</tr>
<tr>
<td></td>
<td>A-C</td>
<td>1.94**</td>
</tr>
<tr>
<td></td>
<td>B-C</td>
<td>1.41*</td>
</tr>
<tr>
<td>O</td>
<td>A-B</td>
<td>2.47***</td>
</tr>
<tr>
<td></td>
<td>A-C</td>
<td>2.47***</td>
</tr>
<tr>
<td></td>
<td>B-C</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Note. 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.

therapy training sessions (R1 and R2). After training, this subject reapplied self-regulation therapy in Phase D.

A general factor of activation or personality has been set out that 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 first increasing only to descend later (inverted-U shape). In addition, both subjects modify the \( \text{DRD3} \) expression in the same manner if compared to the baseline. Therefore, the same dynamic
Table 4
Two Sample Kolmogorov-Smirnov Tests to Subject 2

<table>
<thead>
<tr>
<th>Big Five</th>
<th>Condition</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>A1-B</td>
<td>1.41*</td>
</tr>
<tr>
<td></td>
<td>A2-R1</td>
<td>1.76**</td>
</tr>
<tr>
<td></td>
<td>A1-A2</td>
<td>1.93**</td>
</tr>
<tr>
<td></td>
<td>B-R1</td>
<td>0.66</td>
</tr>
<tr>
<td>N</td>
<td>A1-B</td>
<td>2.29***</td>
</tr>
<tr>
<td></td>
<td>A2-R1</td>
<td>1.76**</td>
</tr>
<tr>
<td></td>
<td>A1-A2</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>B-R1</td>
<td>0.78</td>
</tr>
<tr>
<td>A</td>
<td>A1-B</td>
<td>1.41*</td>
</tr>
<tr>
<td></td>
<td>A2-R1</td>
<td>1.54*</td>
</tr>
<tr>
<td></td>
<td>A1-A2</td>
<td>2.20***</td>
</tr>
<tr>
<td></td>
<td>B-R1</td>
<td>0.58</td>
</tr>
<tr>
<td>R</td>
<td>A1-B</td>
<td>1.59*</td>
</tr>
<tr>
<td></td>
<td>A2-R1</td>
<td>1.98**</td>
</tr>
<tr>
<td></td>
<td>A1-A2</td>
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<tr>
<td></td>
<td>B-R1</td>
<td>0.90</td>
</tr>
<tr>
<td>O</td>
<td>A1-B</td>
<td>1.76**</td>
</tr>
<tr>
<td></td>
<td>A2-R1</td>
<td>1.98**</td>
</tr>
<tr>
<td></td>
<td>A1-A2</td>
<td>2.20***</td>
</tr>
<tr>
<td></td>
<td>B-R1</td>
<td>0.78</td>
</tr>
</tbody>
</table>


* p < .05. ** p < .01. *** p < .001.

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 1 hour after the intake of 20 mg and of 40 mg of methylphenidate is observed mainly in Subject 1, which lowers over the next 2 hours and then returns to 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 the 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 the inverse to that of Subject 1 during the first 2 hours. Then a similar, more marked pattern of reduction with a subsequent increase in the gene expression is noted during the next 2 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 1st 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 et al., 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 that includes only 2 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 us 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 that attempt to reproduce the effects of the drug.

This 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.

References


**Eigenregulierende Therapie zur Reproduktion von Drogeneffekten: Eine suggestive Technik, um die Persönlichkeit und die DRD3 Genexpression zu verändern**

**Salvador Amigó, Antonio Caselles und Joan C. Micó**

**Abstrakt:** Diese Studie stellt eine auf Selbstregulationstherapie basierende Strategie auf, um die Persönlichkeit und ihr biologisches Substrat, die DRD3 Genexpression zu verändern. Es wurde gezeigt, daß akute Dosen stimulierender Drogen, wie Methylphenidat, in der Lage sind, die Persönlichkeit und die Expression bestimmter Gene in kurzer Zeit zu verändern. Andererseits ist belegt, daß Selbstregulationstherapie die Effekte von Drogen reproduzieren kann. Somit ist es plausibel zu hoffen, daß Selbstregulationstherapie in Bezug auf eine Persönlichkeitsveränderung und Veränderung der Genexpression genauso effektiv ist wie Methylphenidat.
Dies ist eine vorläufige Studie im experimentellem single-case Design mit Parallelversuch, an dem 2 Personen teilnahmen. Die Ergebnisse und potenzielle Implikationen für die Forschung und Psychotherapie werden diskutiert.

Stephanie Reigel, MD

Une thérapie autorégulatrice pour reproduire les effets d’un médicament: une technique par la suggestion visant une altération de la personnalité et de l’expression génétique DRD3

Salvador Amigó, Antonio Caselles et Joan C. Micó

Résumé: Cette étude propose une stratégie, fondée sur une thérapie autorégulatrice, visant à altérer la personnalité et son support biologique, l’expression génétique DRD3. Il a été démontré que des doses aiguës de médicaments stimulants, comme le méthylphénidate, peuvent altérer la personnalité et, à court terme, l’expression de certains gènes. Or, il a été prouvé que la thérapie autorégulatrice peut reproduire les effets des médicaments. Ainsi, on peut espérer que la thérapie autorégulatrice soit aussi efficace que le méthylphénidate dans l’altération de la personnalité et de l’expression génétique. Il s’agit d’une étude préliminaire fondée sur un concept expérimental comprenant un cas unique, avec répétition, à laquelle deux sujets ont participé. L’article aborde les résultats de cette expérience et ses implications potentielles pour la recherche et la psychothérapie.

Johanne Reynault
C. Tr. (STIBC)

Terapia de autorregulación para reproducir los efectos de medicamentos: Una técnica de sugerencia para cambiar la personalidad y la expresión del gene DRD3

Salvador Amigó, Antonio Caselles, y Joan C. Micó

Resumen: Este estudio propone una estrategia, basada en la terapia de autorregulación, para cambiar la personalidad y su sustrato biológico, la expresión del gen DRD3. Se ha comprobado que altas dosis de medicamentos estimulantes, como el metilfenidato, son capaces de cambiar la personalidad y la expresión de ciertos genes en el corto plazo. Por otro lado, se ha probado que la terapia de autorregulación reproduce los efectos de estos medicamentos. Por lo tanto, es factible esperar que la terapia de autorregulación sea igualmente eficaz que el metilfenidato para cambiar la personalidad y la expresión de genes. Este es un estudio preliminar con un diseño experimental de un solo caso con replicación en donde participaron dos sujetos. Se discuten los resultados y sus implicaciones potenciales para la investigación y la psicoterapia.

Omar Sánchez-Armáss Cappello, PhD
Autonomous University of San Luis Potosi, Mexico