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Review Article

Sugar Pills To Experience Cocaine and Other Drug Effects: The Self-Regulation Therapy As a Placebo Without Deception

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Abstract

This article presents the Self-Regulation Therapy (SRT), a psychological procedure designed specially to reproduce effect of drugs. The historical background and grounds of the SRT are presented, based on classical conditioning mechanisms, suggestion and placebo without deception. The SRT is briefly described as a psychological training procedure for patients to be able to master and control reproducing drug effects. This makes the SRT a genuine placebo without deception procedure that patients control. Evidence is presented for the biological bases of the SRT, as are proposals to fully develop the therapeutic potentials of this procedure in fields like Psychology, Psychiatry and Neurology.

Keywords: *Self-Regulation Therapy; Placebo; Placebo without deception; Hypnosis; Sugar pills; Expectancies*

Introduction

The Self-Regulation Therapy (SRT) [1,2] is a psychological procedure based on suggestion from the cognitive-behavioral perspective of hypnosis [3].

The SRT was specially designed to reproduce drug effects, but has also been employed for other different therapeutic objectives: treat smoking, obesity, fear of flying, etc. [4].

Even though the SRT uses similar suggestions to those employed in hypnosis, the patient-therapist relationship that it establishes is much different to that observed with hypnosis. Whereas patients in conventional hypnosis follow the hypnotizer's instructions with apparent passivity, and with their eyes closed and in a static position (lying down or sitting), those who undergo the SRT actively participate throughout the procedure, can make suggestions and amendments, keep their eyes open, move freely, and can maintain a perfectly normal conversation at all times. This difference between the SRT and hypnosis means that the former can be applied to more people as it does away with the fear that many people have of hypnosis which, in turn, makes it a much more versatile and flexible procedure. An example of such is the transcription of a therapeutic session applied to a case of smoking, which was the first publication on the SRT [5]. Later the procedure is briefly described herein.

Based on many studies, which include case studies, single-case experimental designs, group experimental designs, the efficiency of a single SRT session to reproduce effects of a wide variety of drugs has been confirmed, which range from ephedrine [6], to methylphenidate [7], cocaine, ecstasy and heroin [8,9].

The potential therapeutic benefit of reproducing drug effects with the SRT is evident and the fields it can be applied to are very wide. Later we will reflect on the potential therapeutic applications of the SRT, but for the time being we state that it is possible to reproduce favourable drug effects, and to reduce or eliminate negative ones. This procedure can be used in psychiatry, psychology, neurology and drug addiction, hence the importance of presenting the grounds of this procedure and reflecting on its applications.

Background of the Self-Regulation Therapy

The background of the SRT, insofar as it is a procedure to reproduce drug effects, represents three fundamental historic milestones of the 20th century in this field:

1) Classical conditioning of drugs

2) Hypnosis to reproduce drug effects

3) Placebo (especially placebo without deception)

Classical conditioning of drugs

Ivan Pavlov was the first person to describe drug conditioning. Lesson 3 of his book entitled *Conditioned Reflexes* [10] describes how a CS (conditioned stimulus), previously associated with an apomorfine injection (US, unconditioned stimulus), produced similar effects to those of a drug in dogs in his laboratory (CR, conditioned response), when they watched him prepare injections: salivation, vomiting, etc. It is well worth transcribing this major discovery:

"Dr. Krylov, of the Tashkent Bacteriological Laboratory, has made some interesting observations on this matter in the course of certain serological investigations, when he repeatedly injected morphine into dogs hypodermically. It is well-known that the first effect of a hypodermic injection of morphine is nausea with profuse saliva secretion, followed by vomiting, and then by profound sleep. Dr. Krylov, however, observed that after 5 or 6 days of regularly repeating injections, the preliminaries of the injection were in themselves sufficient to produce all these symptoms: nausea, saliva secretion, vomiting and sleep. In such circumstances, the symptoms are now the effect of not the morphine acting through the blood stream directly on the vomiting center, but of all the external stimuli that had previously preceded the morphine injection" .

As for the impact of conditioning drug effects on the scientific community, it has helped explain certain mechanisms of drug addictions [11], such as drug tolerance and withdrawal symptoms (conditioning homeostatic compensatory effects and, therefore, negative drug effects) [12], to help explain the presence of a drug as an incentive to take it (conditioning positive drug effects) [13], to develop craving treatment procedures (by counter conditioning) [14], and to explain the effect of a placebo with pills that contain no active ingredients [15]. In the next section we present the grounds of the placebo effect.

Hypnosis to reproduce drug effects

In the 1960s and 70s, the first studies with hypnosis were carried out to reproduce drug effects [16-18]. Later other studies were conducted [19]. They were nearly all case studies or experimental studies with very few participants. Indeed this line of work has hardly been examined and has received much less attention.

Surprisingly positive drug conditioning has not received due attention by the scientific community as far as its potential therapeutic benefits are concerned. As we have stated, studies into hypnosis and positive drug effects are quite scarce, lack rigor and barely refer to classical conditioning.

Placebo without deception

Further historical background for SRT grounds is the study by Park and Covi [20]. For the first time it used the term "placebo without deception" or "non blind placebo". These authors employed sugar pills with patients who knew the composition of these pills and their harmless nature.

These authors presented the "sugar pill" to their patients as follows:

"Many different kinds of tranquilizers and similar pills have been used for conditions such as yours, and many have helped. Plenty of people with your condition have also been helped by what are sometimes called "sugar pills," and we feel that a so-called sugar pill may help you too. Do you know what a sugar pill is? A sugar pill is a pill with no medicine in it at all. I think this pill will help you as it has helped so many others. Are you willing to try this pill?"

Even so, the placebo proved beneficial to their patients. It has only been until quite recently that publications on the "placebo without deception" have appeared. Nor would it appear that Park and Covi's pioneering idea from the 20th century has been put to best use. We will return to the placebo without deception effect in the next section.

None of the following has received due attention in the 20th century: drug conditioning, placebo without deception, suggestion to reproduce effects of drugs. The objective of the SRT is to bridge this inexplicable gap, which emerges as a specially designed procedure to reproduce positive drug effects, and the therapeutic use that this entails.

Before we move on to describe the procedure in some detail, it is worth dealing with the common background of placebo and hypnosis in the next section as this will help us to better understand the underlying mechanisms of the SRT.

Background of the placebo and hypnosis

For a very long time, the background of placebo and hypnosis remained a mystery, but the mechanisms underlying both phenomena were gradually revealed. Although many factors are considered to influence the placebo effect, e.g., emotional states, vicarious learning, personality, etc. [21], two mechanisms are stressed in the scientific literature: 1) classical conditioning; 2) expectancies [22,23].

Although the scientific community has conventionally considered both mechanisms to be opposites, and even irreconcilable, as they can independently explain the placebo effect, the number of studies which have demonstrated that both these mechanisms can be interrelated, and can even be included in more complex processes, has grown [23].

Irving Kirsch's Response Expectancy Theory to explain placebo and hypnosis

One of the most interesting theories to include the basic mechanisms that explain the placebo effect is Irving Kirsch's Response Expectancy Theory [24,25] where, "response expectancies are expectancies for the occurrence of non volitional responses, such as pain, alertness, fear, sadness, and joy" (1999, p. 102). This author does not scorn the importance of classical conditioning or other mechanisms that influence the placebo effect, but considers that response expectancies basically modulate the classic conditioning effect.

The self-confirmatory nature of response expectancies make them the most important substrate that underlies both placebo and suggestion, and the latter is considered the fundamental component of hypnosis, and much more so than hypnotic induction itself. Although Kirsch establishes a close relation between placebo and suggestion, he tends to favour the use of suggestion as opposed to placebo because: "unlike placebos, hypnosis does not require deception in order to be effective" (1999; p. 108). However, other studies suggest that conditioning was more powerful than verbal expectancy in creating a placebo response [26]. Finally, multiple factors contribute to the placebo effect, including suggestibility, expectancy and conditioning [27].

Reconceptualizing the placebo effect and experimental designs with placebo

Apart from him favoring hypnosis, Kirsch studied the placebo effect in more detail by considering both biases of experimental designs with a placebo group and by reconceptualizing the placebo effect itself. In the majority of studies into drug effects, a group that takes the drug is compared with a placebo group, and these studies do not include another non treatment group. As they do not add a non treatment control group, and only compare the treatment group with a placebo group (randomized controlled trial-RCT), very low values are obtained for the placebo effect. So they consider the placebo to be a completely detached phenomenon from treatment [25]. In experimental designs whose main objectives is to study the placebo effect itself, the results are much clearer and favor the importance of this effect [28,29].

When we add non treatment groups, we obtain the placebo's contribution to treatment. We could consider the placebo to form a substantial part of any treatment. As Kirsh stated: "active medical treatments have placebo components" (2013; p.2). Indeed, an ever-increasing number of researchers conceive the placebo effect as another component of treatment, rather than a residual effect that must be isolated in experimental designs. Thus the placebo effect participates in what is known as "contextual healing" [30], which includes the global treatment context in which the "Doctor-Patient Relationship" stands out. In a study conducted with irritable bowel syndrome

(IBS) patients, the placebo effect was separated into two components: the placebo ritual alone and the placebo ritual+ supportive patient-practicioner relationship. The placebo effect was stronger when the placebo ritual came with a good "Doctor-Patient Relationship" [31].

The placebo effect being inherent to treatments undertaken in clinical practice is also supported by scientific evidence from the open-hidden paradigm. In this case, no placebo is administered as such, but open drug administration is compared in a good personalized medical care context, while a hidden medicine is administered; that is, without the psycho-social context component (e.g., a machine administers the drug). Various studies have demonstrated that the therapeutic context increases drug efficiency [23]. These authors consider that the psycho-social context "represents the placebo component, based on expectancies".

Experimental evidence of placebo without deception

If we continue with this placebo effect reconceptualization, we can stress the studies that have proposed using a placebo without deception. The scientific literature gives this kind of placebo different names: "placebo without deception", "open placebo", "placebo without non conceal", "placebo without blind", "non-blind placebo", etc. Perhaps the most well accepted name today is "placebo without deception", which is why we use it in the present work. Such studies are still few and far between, but represent a promising future research line. Recent evidence demonstrates the efficacy of the placebo without deception effect to reduce anxiety and depression [32], pain from cancer [33], in children with attention deficit hyperactivity disorder (ADHD) [34] and in IBS patients [35]. This last cited study is most interesting because it includes a control non treatment group and the verbatim of presenting a placebo without deception:

"The provider clearly explained that the placebo pill was an inactive (i.e., "inert") substance like a sugar pill, that it contained no medication, and then explained in an approximately 15-minute *a priori* script the following "four discussion points:" 1) the placebo effect is powerful; 2) the body can automatically respond to taking placebo pills like Pavlov's dogs who salivated when they heard a bell; 3) a positive attitude helps, but is not necessary; 4) taking pills faithfully is critical" (p.2).

These authors concluded:

"Our study suggests that patients are willing to take open-label placebos and that such a treatment may have salubrious effects. Further research is warranted in IBS and perhaps other illnesses to confirm that placebo treatments can be beneficial when provided openly and to determine the best methods for administering such treatments" (2010, p.7).

Self-Regulation Therapy as an integrative procedure of placebo and hypnotic suggestion

As Kaptchuk, *et al.* [35] acknowledged, it will be necessary to determine suitable methods to administer such treatments based on placebo without deception. At this point it is worth reconsidering Irving Kirsch's proposal, which closely connects the placebo effect and hypnosis by considering the expectancy of the results to be a fundamental mechanism that underlies both phenomena, which, in turn, include classical conditioning.

It is worth citing Pavlov here who, in lesson 23 (*The experimental results obtained with animals in their application to man*) in his book *Conditioned Reflexes* [10], considers the words (language) that constitute the Second System of Signs as "conditioned stimuli that are just as real as any other stimuli", and who defines the suggestion as "the most simple form of a typical conditioned reflex in a man" (1927, p. 407). Although no study from Pavlov has described the use of suggestion to reproduce drug effects, it opens up a way to use hypnosis (which he was particularly interested in) to be able to use it with this objective in mind.

However, as we previously mentioned, hypnosis for this very objective has been scarcely used and is poorly rigorous from a scientific viewpoint. The relevant point here, I insist, is that suggestion, placebo, classical conditioning and expectancies are closely related phenomena with mutual influences that share similar basic mechanisms.

The SRT appears as a procedure that includes all these points in such a way that it:

1) Combines and reinforces all the placebo elements or, in other words, of suggestion

2) Trains patients in strategies and skills that they can use *voluntarily* (this is not even proposed in the placebo without deception model)

This does not mean that the SRT can be applied to all therapeutic contexts, nor is it able to cover all kinds of strategies to enhance effects of treatments. It would occasionally be preferable if the doctor prescribed placebos with due precaution, or prescribed placebos without deception, according to the protocol that some previously cited authors have presented. Evidently placebos without deception are a novel and paradoxical strategy in the conventional medical context. Yet essentially, the way a placebo is taken and its use by patients follow the traditional medical format. Although strategies have been proposed to reproduce drug effects to treat cardiovascular disorders with the SRT, no experimental studies into them have been conducted in the classic medical context [36].

In order to prepare patients to learn to voluntarily and creatively use a "placebo without deception", the SRT can be a particularly valid procedure for psychological, medical and neurological treatments.

Self-Regulation Therapy and cocaine

Classical conditioning of the drugs effects has been proven [11-14,37]. Conditioning the effects of cocaine on animals [38,39], and humans [40] has been verified.

There are some examples of the powerful role of expectation in drug responses. Volkow et al. investigated the effect of placebos in both cocaine abusers and non-drug-abusing. They found that when the cocaine abusers expected to receive drug (methylphenidate), the effects were about 50% greater than when the participants did not expect the drug, increasing self-reports of "high" and "feel drug" [41]. In subjects who had minimal experience with stimulant drugs, the changes in brain glucose metabolism occurred in regions involved in emotional reactivity and reward, such as the ventral gyrus and NAc [42]. On the other hand, another study suggests that both verbal instructions, as well as conditioning in the laboratory, could contribute to the observed placebo responses to cocaine infusions [43]. Besides, expectations modulate the responses to the d-amphetamine [44] and delta 9-tetrahydrocannabinol [45].

The SRT, which combines classical conditioning with expectations and verbal instructions, can be a very useful technique to reproduce the effects of cocaine. It has been proven for both cocaine regular drug users [8, 46], as for cocaine abusers [47]. The SRT also facilitates the reproduction of the effects of other drugs, as it has been shown in this article.

A brief description of how it works can help understand its grounds, mechanisms and potential therapeutic uses.

Description of the Self-Regulation Therapy, pills and sugar powder

The first SRT session comprises three phases. In the first phase patients are explained the sensory recall mechanism. All kinds of fragrances, flavors, songs, feelings and experiences have been linked to certain emotions. A song can take us back to a loving relationship, to emotions and sensations we had in the past. The SRT consists in teaching someone to voluntarily use and master the brain mechanism of sensory recall, which significantly enhances our handling of emotions and behaviors. It is necessary to follow the therapist's instructions, trust in the psychological technique and in one's own capacities and know for sure that the technique will help us meet out therapeutic goals, etc.; in other words, handle expectancies.

Sensory recall is a type of classical conditioning, and explanations and encouragement when the session begins efficiently increase patients' expectations and motivations. From this point and until the session ends, the therapist works to keep patients' expectancies, motivation and collaborative attitude high.

Then some sensory recall exercises are put into practice, one of which is provided as an example. Patients are asked to stretch out their right arms with the palm of their hand facing upward. A book is placed on the palm of their hand, and they are asked to observe and remember all the feelings they notice, like weight, tension in the forearm, and lowering their arm since they must not fight against the natural tendency to lower it. They must also associate a word or picture with the series of feelings that they note so they can reproduce the same feelings later without using the book. After removing the book and having rested their arm, the therapist informs them that they have accomplished conditioning in their brain, and that they will be able to retrieve the same feelings that the book caused if they are confident in the technique and in their ability to "let themselves be led" by imagination. Once again, we can see from the very beginning how the SRT combines classic conditioning with handling expectancies.

Once again, patients stretch out their arm and with the help of some words or pictures associated with the book, and they feel the weight and the lowering movement again. Next the therapist reinforces the success achieved and proposes new exercises (mouth watering, legs cannot move). This ends the first phase.

The second phase is known as the "training phase", when the therapist teaches patients to do the same sensory recall exercises done in the first phase, but more swiftly. The exercises are repeated increasingly more quickly and patients are encouraged to acquire a feeling of certainty and skill when doing them.

In phase three, called "the generalization phase", patients are encouraged to experience past feelings and emotions which they did not practice in the first phase. Patients feel sure they are able to undergo any experience that results from the skill and ability acquired in the training phase. Drug effects are one of the past experiences that patients can recall and reproduce.

During the next sessions, patients do not need to redo all the exercises done during the first session. After practicing a few sensory recall exercises in a shorter SRT version, there is enough time during the sessions to be spent on the therapeutic application of the SRT or to reproduce drug effects.

Once patients feel they are able to experience drug effects again during several sessions, this new skill is therapeutically employed. In this way, they learn to once again experience the positive emotions that drugs provide; e.g.: stronger self-esteem or feeling better motivated to do tasks, etc.

But, how do drug effects begin to be experienced by suggestion? Different psychological strategies are proposed to patients and participants in experimental studies. They can recall a genuine recent experience they had with a drug, or use the pictures or thoughts they relate with drug use, which help them remember and, thus, reproduce its effects. They can also employ physical stimuli that remind them of real drug use. In some studies that have reproduced cocaine effects in both drug addicts and cocaine users in the general population, the participants used sugar powder to simulate snorting, or even sugar pills, cough pastilles or other harmless substances that come in pills, which they had previously associated with drug use. Sugar pills have also been used in studies with methylphenidate. In all these studies, the participants were well aware that the sugar pills were harmless and had no active ingredients, and that taking them during an SRT session formed part of a psychological strategy to reproduce drug effects [46].

A detailed description of the SRT, and the therapeutic procedures that derive from reproducing drug effects, can be found in[2].

Biological bases of the Self-Regulation Therapy

One of the criticisms of the SRT is that it is an experimental artifact based particularly on enhanced expectancy in relation to the drug effects expected during the reproduction session worked with the technique.

But this does not seem to be the case. In a qualitative study on reproduced drug effects during the first SRT session, it was observed that both the number of reproduced effects and their specificity led us to think that it was a "real" reproduction of effects rather than an exclusive product of patients' expectancy who, in this way, would attempt to favorably respond to the therapist's wishes. Many sensations experienced by all the subjects were counted (15-20 sensations), and were most specific depending on each case (pins and needles felt in hands, tickly throat, empty stomach, etc.) [48].

Another piece of evidence that the experience of drugs using the SRT is "true" to the effects of drugs themselves is to study its biological bases. It has been verified that reproducing effects of methylphenidate with the SRT increases the heart rate [7] and the level of glutamate in blood, just as it does with drugs [49]. Moreover, the same pattern of change in regulator genes c-fos and DRD3 has been found for two conditions: the SRT and methylphenidate [50,51].

Studies that have used brain imaging appear to indicate that the same biological response patterns are repeated for the SRT and methylphenidate conditions. This has been verified in a study with SPECT, which showed a similar response pattern [52].

A brain SPECT scan was done in the Department of Nuclear Medicine of the Brain Imaging Unit of the National Institute of Psychiatry, "Dr. Ramón de la FuenteMuñíz", in a tricke-detector Gamma camera, model Multi-SPECT (Siemens), with six healthy subjects, led by Dr. García Reina. Three sub cortical regions were found in which the change in brain flow was identical for both the SRT and methylphenidate conditions, compared to the respective baselines. Therefore, it can be concluded that the reproduction procedure activates the same areas as the drug. A significant effect was noted on the right thalamus and on the brain stem in both the right protuberance and the left midbrain.

A similar response pattern has also been observed between the SRT and methylphenidate in a study done with an EEG [53]:

Figure 1 shows the brain electrical activity sources of a 27-year-old voluntary subject. In all three experimental conditions (basal, methylphenidate, reproduction), the views of the axial, coronal and sagittal planes appear, where the most significant Z-scores are found, which correspond to frequencies 1.17 Hz., 10.92 Hz. and 11.30 Hz., respectively. Yellow corresponds to the highest Z-scores. For the baseline condition, the sources of greater frequency are found in the left posterior parietal area. It is noteworthy that the *methylphenidate* and *reproduction* conditions display sources with similar frequencies and locations: bilateral and predominantly right.

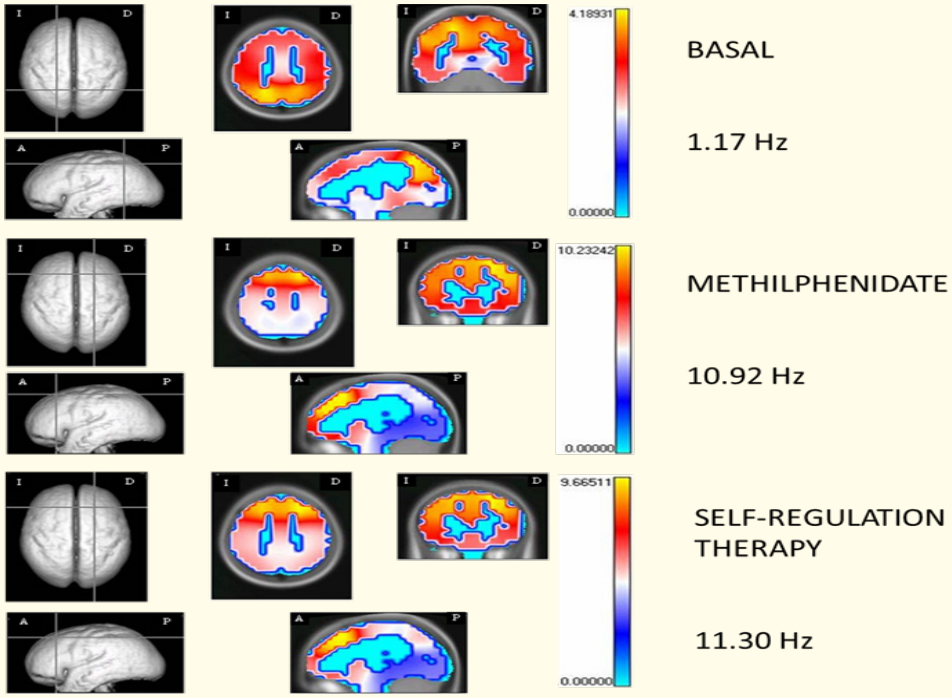

Figure 1*: Brain electrical activity sources for the basal, methylphenidate and reproduction conditions with the SRT.*

Although the studies into the biological bases of the SRT are still preliminary, they all seem to indicate that the SRT is capable of reproducing and imitating real drug effects which, as we will see in the next and last section, may have important consequences.

Discussion

Potential applications of the Self-Regulation Therapy

This article has reviewed the clinical and scientific evidencie that supports the potential of the SRT as a valid procedure to reproduce drug effects. The SRT' spotential applications include the following:

Treating emotional disorders in psychology and psychiatry

If it is possible to reproduce positive drug effects, and to reduce or even eliminate negative drug effects, so its potential use in psychotherapy is evident. This has been verified in a case study [7] and in a single-case experimental study[6]conducted with patients who were on psychological and psychiatric treatment. The levels of depression and anxiety considerably lowered with the reproduction of effects of stimulant drugs like ephedrine and methylphenidate.

Treating drug addiction

The potential use of the SRT in drug addiction has been evidenced with several studies, in which heroin and cocaine addicts were able to considerably lower their level of craving after one drug effect reproduction session. It was as if with the reproduction of the effects of heroin and cocaine that drug addicts felt "satisfied" and no longer needed to use the drug [9,47].

Drug abuse prevention programs in the general population

Several studies have confirmed that most frequent drug users do not agree with the total withdrawal that the majority of drug use prevention programs announce. Instead they prefer using drug use control strategies [54].In line with this, the SRT can be used as an efficient procedure to substitute part of drug use for exercises that reproduce drug effects. A recent study about the capacity of drug users in the general non drug-addicted population observed that they were able to reliably reproduce effects of drugs like cocaine and methamphetamine [46].

It offers a new approach with placebo, especially placebo without deception

Reproducing drug effects with the SRT can often be an alternative to today's use of placebos in medicine, psychology, psychiatry and neurology. Use of placebos is still a matter of debate as the ethical and scientific limitations of their application have not yet been overcome. Not even more recent studies into placebos without deception have been able to provide a genuine alternative as the administration and control procedure is similar to the placebo procedure. Thanks to it directly and clearly presenting patients with what the procedure implies, and given its participation perspective and voluntary use of learnt strategies, the SRT can be a valuable alternative to traditional placebo use.

Analogue Designs in Neurology

If the brain response pattern during drug effects reproduction with the SRT is similar to that produced by the drug, this opens up a way to design analogue studies, where it will be possible to extensively study the effects of certain drugs without the patient or participant in an experimental study having to repeatedly take drugs, which avoids the negative side effects that many drugs have, especially when taken regularly. An example can demonstrate how the SRT could be used in analogue studies, as part of different paradigms and research models, such as that which relates schizophrenia with psychosis trough cocaine, and in the context of the potential therapeutic effects of various substances, including caffeine. Patricia Broderick has worked intensely on the so-called model of cocaine-related schizophrenic disorders [55, 56]. A well-studied correlation is that between psychosis induced by cocaine and that psychosis endogenously present in the schizophrenic patient. Therefore, a relationship between schizophrenic and cocaine psychoses exists. Both disorders are remarkably similar in their neurobiological mechanisms of action that involves primarily dopaminergic dysfunction.

The SRT could prove most useful for studying the relationship between schizophrenia and psychosis through cocaine. In an experiment about reproducing the effect of cocaine with the SRT, in which cocaine addicts on treatment participated, similar effects to psychosis through cocaine were observed, such as feeling threatened, paranoid ideas, auditory hallucinations, etc. [47].

Cocaine increases dopamine (DA) levels in the reward areas of the brain. Conditioned dopamine release in humans has also been proven in a positron emission tomography racoplide study, in which the cues associated with amphetamine increased dopamine transmission [57]. The SRT could also be used to study the biochemical effects of cocaine and other stimulant drugs as it has been demonstrated that the SRT facilitates the reproduction of biological drug effects, which has been presented in an earlier section of this article.

Another relevant contribution made by Broderick is her suggestion that caffeine could play a jey therapeutic role to counteract effects of cocaine [58,59]. The SRT has been used to reproduce caffeine effects [60]. So the SRT could be employed in experiments with non addict or treated addict participants to study the biological phenomena of drug effects or its potential short- and long-term uses, without using drugs or only a very small quantity to avoid and reduce side effects. The general population could greatly participate in these experiments.

These are the five main potential applications of the SRT. Some have already been experimentally confirmed, as previously indicated. It is also necessary to point out the current limitations with studies done with the SRT to date. Thus it is necessary to increase the number of experimental group studies, especially clinical trials, to more certainly confirm some promising, but provisional, results of applying the SRT.

It is also necessary to conduct further brain imaging and genetic studies to consolidate the conviction that the SRT reliably reproduces real drug effects. It is also necessary to perform studies with the SRT using substances that produce much less evident effects than stimulating drugs, which have been used more in studies with the SRT. Some proposals have been made about this, such as applying the reproduction of the effects of nitroglycerine on cardiology [36], but they need to be experimentally confirmed.

Despite these limitations, the SRT has acquired ample clinical experience and a sound experimental basis. It is necessary to continue investigating and obtaining more clinical evidence, but as indicated herein, it is quite clear that the SRT used to reproduce drug effects is doubtlessly a proposal to bear in mind in twenty-first-century Medicine, Psychology, Psychiatry and Neurology.

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