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The placebo effect on psychomotor performance and working memory capacity: randomized single blind cross-over trial

Ammar W. Ashor

Department of Pharmacology, College of Medicine, Al-Mustansiriya University, PO Box 14132, Baghdad, IRAQ

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Corresponding Author:

Ammar W. Ashor, PhD
Tel : +964 7901261613.
E-mail : ammar_w_78@yahoo.com

ABSTRACT

Background: Imaging studies show that placebo enhance release of dopamine in the mesolimbic and mesocortical tracts. Dopamine in these areas are involved in attention and working memory function. **Purpose:** We wanted to investigating the effect of placebo on psychomotor function and working memory capacity. **Method:** 31 medical students participated in this single blind, crossover trial. Choice reaction time, critical flicker fusion threshold, *n*-back working memory tasks measured before and after one hour of the students receiving placebo in three different occasions as stimulant, unknown, and inert substance. **Results:** Placebo, as stimulant, significantly enhanced choice reaction time and working memory function ($P < 0.05$) while showed no significant effect on critical flicker fusion threshold ($P > 0.05$). Placebo as unknown significantly deteriorates working memory capacity ($P < 0.05$). Placebo as inert substance shows no significant changes regarding choice reaction time, critical flicker fusion threshold, and working memory task. **Conclusion:** Placebo, as stimulant enhanced attention and improved working memory capacity, while as unknown may deteriorate working memory function.

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Introduction

Placebo effect is defined as the physiological or psychological response to an inert substance or procedure.[1] Several neurological disorders that associated with dopamine neurotransmitter dysfunction are found to be susceptible to placebo effect, these disorders include dystonia, tremors, tics/Tourette's syndrome, tardive akathesia, tardive dyskinesia, restless leg syndrome, obsessive-compulsive disorder and panic disorder.[2]

It is essential that a person's expectations about their subsequent response to a placebo are central to the placebo effects, that is, the cognitive expectation triggers the biochemical response.[3] The biochemical placebo effect in conditions like Parkinson's disease is as powerful as the effect of an active drug like apomorphine (dopamine agonist),[4] and also similar in magnitude to the effect of amphetamine in healthy people.[2]

Imaging studies show that placebo enhances the release of dopamine in the mesocortical (prefrontal cortex) and mesolimbic areas (ventral and dorsal striatum),[5,6] these areas involved in attention and working memory function.[7,8]

The hypothesis behind our work is that expectation of stimulant effect enhances dopamine release in the prefrontal cortex and striatum which eventually leads to improvement in attention and working memory capacity.

In this study the psychomotor function evaluated by measuring the critical flicker fusion threshold (CFFT) that measure the frequency at which a flickering light is perceived as a steady light source, changes in CFF are thought to be indicative of changes in CNS activation.[9,10] The choice reaction time (CRT) is used as an indicator of sensorimotor performance, assessing the ability to attend and respond to a critical stimulus.[11]

The working memory capacity is measured by *N*-back task, [12] in which, the participant is shown a series of items (e.g., letters, words or location markers) and is asked to decide, upon presentation of each item, whether a given property of the current item matches the same property of the item N presentations back.[13]

Medical students participated in this trial given placebo in three different occasions; at one time told that it is a stimulant drug to the central nervous system, another time placebo was given as a drug with unknown effects on the CNS, and in the third occasion, the placebo was given as an inert substance with no central nervous system effect.

We wanted to investigate whether placebo-induced dopamine release could enhance the psychomotor function and working memory capacity in healthy adult volunteers.

Methods

This is a prospective, single blind, controlled, cross-over study conducted in the Department of Pharmacology, College of Medicine, Al-Mustansiriya University, Baghdad, IRAQ, from March to April 2011. An independent scientific committee revised and approved the study and oral consent obtained from the participants. Thirty-one (19 females: 12 males) randomly selected from third stage medical students. The were healthy, young volunteers aged between 21 to 23 years were included in the study white those with evidence of eye disease, smokers, diabetic, hypertensive, history of drug therapy in the last 7 days, and those who take beverages within eight hours prior to the study were excluded.

The placebo included sucrose which obtained from local vendor and packed in three different capsule forms (175 mg). The recruited students were told that the trial conducted in three episodes separated by three days wash-out. In each episode, students received different drugs that has different effect on the central nervous system.

Initially, the students were told that they will receive a drug with a stimulant effect, and they were tested before and after 1 hour of taking the drug. In the second time, the same students were told that a new drug was to be examined a new drug with unknown effect on the central nervous system function. At the third occasion, the same students were told that they will receive an inert substance that has no effect on the central nervous system function. The participants were

allowed to practise on both the psychomotor test battery and the *n*-back task to get familiar with it before the beginning of the trial.

Leeds psychomotor tester (Leeds Psychomotor services, York): It is an instrument used to measure choice reaction time (CRT) and critical flicker fusion threshold (CFFT).

Choice reaction time (CRT): The principle of CRT is to respond to a bright red color light that appears randomly by pressing the button where the red light shown. Therefore, the time needed for stimulus to be recognized is called *recognition reaction time (RRT)* which represents the time from stimulus onset to the beginning of motor action; the time from onset of motor action to the end of performance called *motor reaction time (MRT).* Summation of recognition and motor reaction time results in a total reaction time (TRT = RRT + MRT).

The critical flicker fusion threshold (CFFT): measured by asking the subject to concentrate on four illuminated sites and to respond when the illuminated site changed from steady state to flickering and when it changed from flickering to steady state. The median of five trials of flicker descending (i.e. from steady to flickering) is called flicker threshold while the median of flicker ascending (i.e. from flickering to steady) is called fusion threshold.

***N*-back computerized task**: It is a test that uses the visual working memory task of that used by Jaeggi et al.[14] where squares at eight different locations were presented sequentially on a computer screen at a rate of 3 seconds (stimulus length, 500 ms; interstimulus interval, 2,500 ms). A response was required whenever one of the presented stimuli matched the one-presented *n* positions back in the sequence.

In the *1-back* condition, the target was any square position that is identical to the square position immediately preceding it. In the *2-back*, the target was square position similar to another square position two trials back. *3-back* is square position identical to another square position three trials back. Participants made responses manually by pressing on the letter ''A'' of a standard keyboard with their left index finger for visual targets. The computer automatically measured the accuracy rate (number of successful responses).

The above tests were validated and found to be reliable in testing arousal (CFFT), [15] attention (CRT), [16] and working memory capacity (N-back task).[17]

Statistical analysis

Statistical analysis was done by using SPSS (version 11.5), paired t-test was used with significance level of 95%. All the data is presented as (mean ± SD).

Results

Placebo, as stimulant drug, showed significant improvement in TRT, RRT, MRT ($p < 0.05$), no significant change in fusion and flickering threshold was seen (table 1). Regarding n-back task (table 2), placebo, as a stimulant, showed significant improvement in 2 and 3-back working memory task ($p < 0.05$).

When student were given placebo, as unknown, they show no significant change regarding TRT, RRT, MRT, fusion and flickering threshold (table 3), but regarding the n-back task, those students show significant deterioration in the 3-back working memory task (table 4) with $p < 0.05$.

Placebo, when given as inert substance, no change was seen regarding psychomotor performance and working memory capacity with ($p > 0.05$) see table 5 and 6 for details.

Discussion

Placebo, given to students, as a stimulant show significant improvement in choice reaction time parameters (TRT, RRT, MRT) and improvement in 2 and 3-back working memory task, while show no significant change regarding CFFT. Placebo, as unknown, had no significant effect on CRT, CFFT, but showed

Table 1: Placebo, as stimulant, affects the choice reaction time components (TRT, RRT, MRT) and critical flicker fusion threshold.

	TRT (ms)	RRT (ms)	MRT (ms)	Fusion threshold (Hz)	Flicker threshold (Hz)
Before	592.9±73.6	369.3±53.6	223.6±56.9	32.3±3.5	32.8±3
After	550.6±66.3	345±41.3	205.6±55.6	32.8±2.4	32.1±2.6
P Value	0.000*	0.008*	.038*	0.392	0.166

Values presented as (mean±SD). *significant *(P<0.05)* using paired t-test. TRT: total reaction time, RRT: recognition reaction time, MRT: motor reaction time.

Table 2: Placebo, as stimulant, affects the working memory capacity using n-back task.

	1-Back	2-Back	3-Back
Before	96.2±9.1[Ω]	72.7±22.3	50.2±15.9
After	98±8.2	82.7±19.6	68.6±16.6
P Value	.393	.012*	.000*

[Ω] Values represent accuracy rate (%), presented as mean±SD. * significant *(P<0.05)* using paired t-test.

Table 3: Placebo, as unknown affects the choice reaction time components (TRT, RRT, MRT) and critical flicker fusion threshold.

	TRT (ms)	RRT (ms)	MRT (ms)	Fusion threshold (Hz)	Flicker threshold (Hz)
Before	557.9±64.9	360.9±32	197±54	32.7±2.9	32.7±2.2
After	566.4±63.2	353.2±38.6	213.2±48.2	32.7±2.6	32.2±2.1
P Value	0.415	0.270	0.101	0.938	0.172

Values presented as (mean±SD). TRT: total reaction time, RRT: recognition reaction time, MRT: motor reaction time.

Table 4: Placebo, as unknown, affects the working memory capacity using n-back task.

	1-Back	2-Back	3-Back
Before	96.7±8.4Ω	80.2±21.3	54.6±21
After	97.5±7.3	78.9±19.7	43.5±21.7
P Value	0.639	0.773	0.010*

Ω Values represent accuracy rate (%), presented as mean±SD. * significant *(P<0.05)* using paired t-test.

Table 5: Placebo, as inert substance, affects the choice reaction time components (TRT, RRT, MRT) and critical flicker fusion threshold.

	TRT (ms)	RRT (ms)	MRT (ms)	Fusion threshold (Hz)	Flicker threshold (Hz)
Before	545.7±60.9	357.7±40.2	188±41.8	33.2±2.5	33.3±1.9
After	546.4±71.7	359.4±50.6	186.6±45	32.9±2.3	32.6±2.2
P Value	0.975	0.866	0.812	0.376	0.117

Values presented as (mean±SD). TRT: total reaction time, RRT: recognition reaction time, MRT: motor reaction time.

Table 6: Placebo as inert substance effects on working memory capacity using n-back task.

	1-Back	2-Back	3-Back
Before	99.5±3Ω	88.6±14.5	60.3±18.9
After	98.4±7.2	84±11.6	56.6±18.6
P Value	0.463	0.135	0.222

Ω Values represent accuracy rate (%), presented as mean±SD.

significant deterioration in 3-back memory task. When student were told that, they take inert substance, placebo showed no significant difference in CRT components, CFFT and working memory task.

Previous studies have regarding the effect of placebo on cognitive function shown that placebo enhances arousal, reaction time, and short-term memory performance.[18-20] Previous meta-analysis study of working memory and executive attention also reveals similar activation pattern.[21]

In this study, the possible mechanism behind the reduction in choice reaction time is the improvement in attention, [22] placebo, when given as a stimulant, leads to positive expectation and secretion of dopamine in the mesocortical and mesolimbic tracts.[23, 24] The secreted dopamine found to enhance attention indirectly through increasing acetylcholine secretion in the frontal lobe.[25]

Placebo-induced dopamine secretion in the striatum and frontal lobe may enhance working memory capacity because it is well known that both areas are involved in working memory function.[26, 27]

Dopamine enhances working memory function through the following mechanisms: action on D_1 receptors in the prefrontal cortex stimulates pyramidal cells causing online stabilization of task relevant representations, while D_2 receptors stimulation in the striatum leads to flexible updating of these representations in response to novel stimulation.[28]

The role of Dopamine in the striatum and frontal lobe follows inverted-U-shape function, therefore, reduction, or high level

of dopamine may deteriorate working memory capacity. [29] This may explain why placebo, when given as unknown, deteriorates working memory function because this may cause reduction in dopamine secretion through negative expectation. [30] The other possible explanation is that, the higher the uncertainty regarding the drug received, the higher the dopamine secretion, which may also deteriorate working memory capacity.[31]

In our study, placebo has no effect on the degree of arousal (CFFT), while previous studies show that placebo enhances arousal.[18, 19] The reason for this discrepancy between our study and the previous studies may be explained by the following: the previous studies measure subjective arousal (questionnaire) while our study is more objective (CFFT). Second, the response to placebo in the previous studies may relate to conditioning (learned) placebo effect, while our study depends on the level of expectation.[32]

Further, positron emission tomography and imaging studies are required to elucidate the effect of placebo as a stimulant or unknown on the activity and dopamine level within the frontal lobe and basal ganglia.

Conclusion: Placebo as a stimulant enhances attention and improves working memory capacity, while placebo as unknown may deteriorate working memory function.

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Abbreviations:–

CRT: choice reaction time; TRT: total reaction time

RRT: recognition reaction time; MRT: motor reaction time

CFFT: critical flicker fusion threshold

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