

EFFECT OF DECEPTIVE VERSUS NON-DECEPTIVE PLACEBO ON PSYCHOMOTOR AND COGNITIVE FUNCTIONS IN HEALTHY ADULT HUMAN VOLUNTEERS: AN OPEN-LABEL CROSS-OVER RANDOMIZED CONTROLLED TRIAL

Archana Mishra¹, Sudhir Chandra Sarangi², & KH Reeta³

1. Senior Resident, Department of Pharmacology, All India Institute of Medical Sciences, Bhubaneswar, India

2. Additional Professor, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

3. Professor, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

received: 16. 5. 2023;

revised: 15. 11. 2023;

accepted: 18. 12. 2023

Summary

Background: This study was planned to evaluate the effect of a placebo administered with deception vs. without deception on psychomotor and cognitive functions in healthy human volunteers compared to no treatment as placebo responses tend to be circumstantial.

Subjects and Methods: An open-label, 3-period, 6-sequence randomized controlled cross-over trial was conducted with 54 participants in a tertiary care center. After the initial screening for eligibility, the patients were randomized into sequences. Psychomotor, executive, and memory function tests were performed before and 30 minutes after the administration of the intervention on three different days (one intervention each day).

Results: Participants showed a significant reduction in reaction time in most of the computerized tests for evaluation of psychomotor function (simple reaction time: one hand: 47.15; 95% CI: 30.99 to 63.32; $p < 0.001$, both hands: 63.90; 95% CI: 46.23 to 81.57; $p < 0.001$ | choice reaction time (79.83; 95% CI: 41.27 to 118.40; $p < 0.001$) and digit picture substitution test (182.12; 95% CI: 116.0 to 248.24; $p < 0.001$)), executive function and memory with deceptive placebo when compared to nondeceptive placebo. No statistical difference in the paper and pencil tests was observed; however, there was a significant reduction in deceptive placebo over nondeceptive placebo or no intervention groups for trail-making tests for the executive functions. No significant difference was observed for motor functions.

Conclusion: A deceptive placebo has a significant effect on psychomotor function compared to a nondeceptive placebo and no treatment; thus there could be differences in placebo responses in clinical trial versus clinical practice or double blind versus open label placebo. The calculation of actual drug effect in a clinical trial needs the development of an algorithm balancing for placebo response.

Keywords: Placebo response; deception; psychomotor function; executive function; memory

* * * * *

INTRODUCTION

Wolf defined placebo as “any effect attributable to a pill, potion or procedure but not to its pharmacodynamic or specific properties” (Wolf 1959). Placebo is used as a control in randomized controlled trials (RCT), the gold standard for establishing the efficacy and safety of any new drug (Gowdey 1983). Historically, a placebo means a medication given to please rather than benefit the patient. In randomized clinical trials, participants are often informed that they can receive the investigational drug or the placebo. Unlike this, in clinic settings, patients are prescribed a medication or placebo with an implied benefit guarantee. The placebo response rate is 30–50% in antidepressant studies for adults, compared to a pharmaceutical response rate of 4–70%, and it has increased 7% every decade over the previous 30 years (Jakovljević

2014). The data obtained for the efficacy and safety of a drug in clinical trials are extrapolated to the prescribing environment, assuming that both conditions are similar. In reality, both settings differ regarding the expectancies of the patients. It is common to subtract the placebo effects from the total drug effects in calculating the efficacy of the new drug/intervention, assuming the additive model (Kirsch 2000, Kube & Rief 2017). However, in real-life clinical practices, placebo response occurs due to deterministic influences and observation capacities of the patients as well as the communication skills of the physician (Brown 2015, Enck & Klosterhalfen 2013). Thus, a simplistic additive model cannot be used to quantify the effect of a placebo (where we subtract the effect in the placebo group from that in the drug group in a clinical trial to make conclusions on true drug effect). Cognitive expectations of the patients trigger the biochemical

responses (Klosterhalfen & Enck 2006). Both psychomotor function and placebo response cause the release of neurotransmitters like dopamine in the centre of stimulation of the prefrontal and mesolimbic areas of the brain (Zubieta & Stohler 2009). Dopamine is associated with attention and working memory in human beings.

Psychomotor function tests are used for determining the precision, coordination, control, dexterity and reaction time for individuals (Kallus et al. 2005). Along with the mechanical performance, it also assesses the ability to comprehend and follow instructions and perform motor activities (Nakano et al. 1978). The motor responses of an individual vary from an instantaneous reflex response to simple sensorimotor behaviours to skilled and complex motor behaviours. Psychomotor tests are used for quantitative estimation of the effects of drugs on the Central Nervous System (CNS) during the early phases of drug development (Hindmarch 1980, Hindmarch 2004). These tests have been used increasingly in clinical studies of psychiatric and neurological disorders and for testing psychoactive drugs. Besides psychomotor functions, cognitive and affective domains are two other well-known components of human performance tests.

Placebo has been found to have beneficial effects in many psychoneurological conditions like pain, depression, Parkinson's disease and many others (Kirsch 2019, Kisailita et al. 2014, Lidstone 2014). It can be conceptualized as healing power of mind. The effect has been seen in clinical trial as well as clinical practice settings. Alternative therapies with elaborate rituals and distinct environmental cues can have pronounced and clinically significant placebo effect. It is imperative to study the placebo phenomenon from basic science, clinical trial and ethical perspectives to better understand how placebo operate in clinical settings. Intact consciousness, preserved mental faculties and moderate pathological dysfunction are needed for the demonstration of the placebo effect. Drug placebo interaction is known to bias the estimated drug effect, and the effect of active drugs decreases with increasing placebo effect (Hammami et al. 2016). This indicates that the effects of placebo and active intervention may not be simply additive. It has been evidenced earlier that deceptive administration of placebo simulated clinical situations in which subjects were made to believe that they were receiving an active drug (Blease and DesRoches 2021). In contrast, subjects in double-blind conditions are generally aware that they might receive a placebo. Double-blind and deceptive administration of the placebo produced different results in studies of mood, blood pressure, and heart rate (Gould et al. 1981). The placebo effect can be truly quantified when compared with no-treatment groups, which takes care of the Hawthorne effect, regression to mean,

and natural history of disease (Vallance 2006). It would be unethical to recruit a no-treatment group in diseased conditions. Thus, placebo compared to no-treatment has been studied rarely. There is a paucity of studies for quantifying the effect of placebo in psychomotor and cognitive functions. Therefore, this study was planned to evaluate the effect of a placebo response administered with deception versus without deception on psychomotor and cognitive functions in healthy human volunteers when compared to no-treatment.

SUBJECTS AND METHODS

Study design

The study was an open-label, 3-period, 6-sequence cross-over randomized controlled trial conducted in a tertiary care centre at All India Institute of Medical Sciences (AIIMS), New Delhi, India. A written approval from the Institute Ethics Committee (IECPG-531/23.09.2020) was obtained before the commencement of the study. The study was carried out according to the Declaration of Helsinki, Good Clinical Practices guidelines and ICMR's ethical guidelines for biomedical research on human subjects (2017) and was prospectively registered in the Clinical Trial Registry of India (CTRI/2020/10/028474 dated 20.10.2020). Written informed consent was obtained from participants before enrolment.

Study population and eligibility

Healthy volunteers aged 20-45 years of either sex were screened for enrolment in the study. Participants who were free from any medical condition requiring treatment, with an education qualification of at least graduation, and were currently active in their profession or studies were enrolled for the study. Participants who had taken any medicine in last 7 days, had visual or auditory impairment, or had a history of anxiety, depressive, or any other psychiatric illness were excluded. Participants who had substance abuse disorders, including alcohol, tobacco during the preceding one month or took caffeinated drinks in last 4 hours, or had any difficulty understanding given instructions were excluded in the study. Pregnant and lactating women were excluded.

Randomization

Randomization was done using computer-generated random block randomization codes in an equal allocation ratio into one of the six possible sequences: Ps-Pi-Nt;

Pi-Nt-Ps; Nt-Ps-Pi; Ps-Nt-Pi; Nt-Pi-Ps; Pi-Ps-Nt where Ps is placebo as a stimulant (deceptive placebo); Pi is placebo as an inert substance (nondeceptive placebo), and Nt is no treatment. These randomization codes were numbered consecutively. Randomization was done by a third person not involved in the study. Allocation was concealed as a sequence for individual participants were placed in consecutively numbered sealed envelopes and opened by an investigator after screening the participant.

Study intervention(s)

Placebo was given with 240 ml of water, and oral cavity was examined thereafter. The placebo was obtained from Liv-Bio Pharma, Kerala, and consisted only of gelatine used in the formation of the soft gel capsule covering. For placebo as stimulant, participants were told that this would enhance cognition and stimulate central nervous system, thus decreasing participants' reaction time. For the placebo as inert substance, participants were told that this may be a placebo and may or may not enhance cognition and stimulate central nervous system.

Study procedure and data collection

After recruitment, a detailed personal history was taken from the study participants. Three training sessions (one session per day) were given to eliminate effect of practice on psychomotor test prior to randomization. After that, each participant received the study intervention in one of the six possible sequences. The psychomotor

function tests were performed before and half an hour after the intervention. Three interventions (Ps, Pi, and Nt) were delivered over a period of three days with one intervention per day. Participants were asked to take an adequate sleep over previous night. The tests were done using Mindomatics instrument, Psytoolkit software as well as manually using paper and pencil test and hand stadiometer in order of psychomotor, executive and memory functions for all participants in each period. The various tests administered to the participants have been shown in Fig 1. Mindomatics is a computerized psychometric assessment tool which uses a battery of tests that evaluates various aspects of information processing, sensory motor coordination, short term/working memory, reaction time and psychomotor functions (Taur et al. 2014). Psytoolkit is an online software which is used to run cognitive psychological experiments (Stoet 2010, Stoet 2017).

I. Psychomotor function:

A. Computerised t-tests

Psytoolkit

- a. Simple reaction time: One white box appeared on the screen. Participants were asked to press space bar as soon as a cross appeared within the white box. Once this test was over, participants were asked to lay their fingers on z, x, < and > keys of the QWERTY keyboard. Four white boxes appeared on the screen and whenever a cross appeared in any of the box, corresponding finger was pressed. Reaction time and error rate were noted.

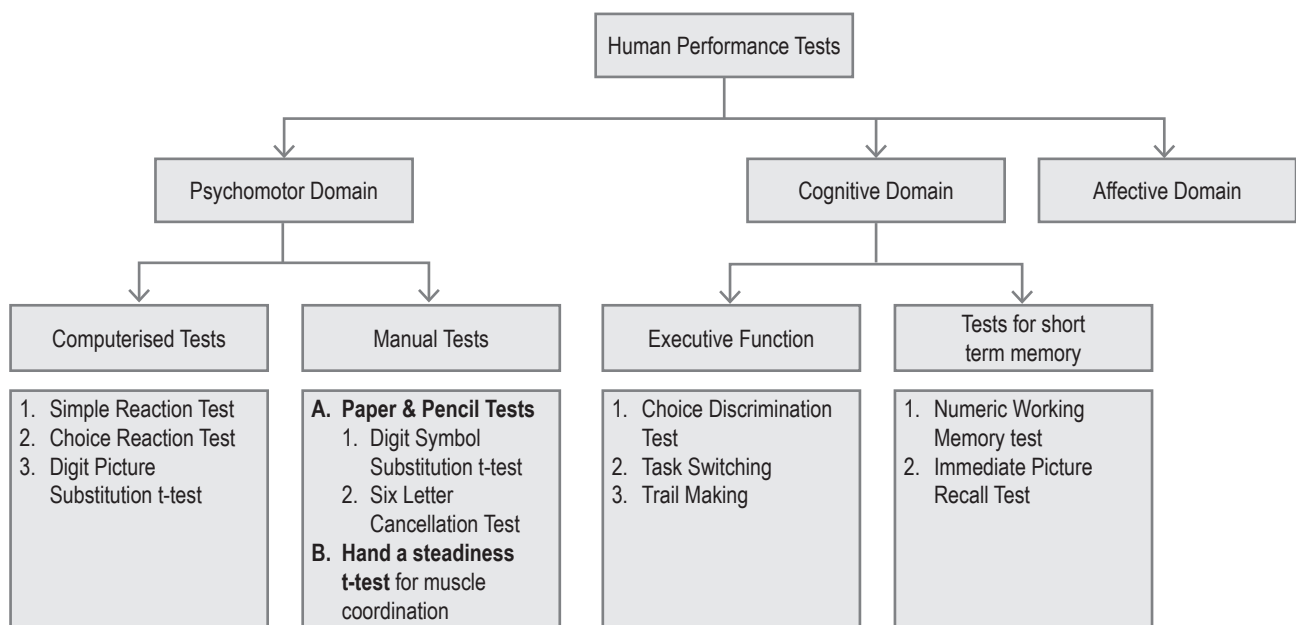


Figure 1.: Classification of human performance tests

- b. Choice reaction time: This test measures impulsiveness of decision making. The participant was expected to make a response within 2 seconds of visualising a “Go” on the screen, while with a “No Go” the expectations were to refrain from making any response. Speed and accuracy of the task completion was measured as output parameters.

Mindomatics

- a. Digit picture substitution test: On the top panel of the screen digits from 1 to 9 and their target pictures were displayed. On clicking start button, pictures from top panel start appearing randomly on the screen one after other. Participants were asked to press the corresponding digit one after other. Reaction time, percentage of right and wrong responses were measured.

B. Paper and pencil test:

- a. Digit symbol substitution test (DSST): Test was applied to evaluate cognitive function, attention and psychomotor speed. Participants were given a code table, displaying the correspondence between pairs of digits (from 1 to 9) and symbols (DSST)/letters (DLST). They were asked to fill in blank squares with the symbol/letter that is paired to the digit displayed above the square. The subjects had to fill in as many squares as possible in 90 seconds.
- b. Six letter cancellation tests (SLCT): This test is a simple and sensitive measure of attention. Participant was presented with a sheet containing randomized letters arranged in columns/rows. Six letters were targeted i.e., they were mentioned to the participant by the investigator. The participant was asked to cancel as many targeted letters as possible in 90 seconds in any selected direction (horizontal/vertical/random). The number of letters correctly cancelled, attempted and errors in selection were recorded.

C. Muscle Coordination:

Hand steadiness test: Hole type

The test is to study the fine motor control of an individual. Participants were instructed to hold the probe in holes numbered seven and nine for 30 seconds each. Number of contacts of the probe with the sides of the hole was automatically measured by the impulse counter.

II. Executive Function

A. Computerized tests

Psytoolkit

- a. Choice discrimination test: In this test, participants were asked to respond to a left or a right pointing arrow as fast as they could, with fingers on alphabets B and N on the keyboard. In second stage of this test, the participant was asked not to respond if a red circle appears around the green arrows. Reaction time and error rates were noted.
- b. Task switching: Ease or difficulty of task switch is a measure of executive function of brain. Participant was asked to perform two sets of ‘task A’, followed by two trials of ‘task B’ and again back to ‘task A’ i.e., a task switch occurs after every two trials. The difficulty to switch between tasks is expressed as the slow down immediately following a task switch.

B. Paper & pencil test

- a. Trail making: This test evaluates the visual attention and task switching ability of an individual. This was conducted in two parts. In the first part, the participants were instructed to sequentially connect the numbers 1 to 25 arranged randomly on a sheet of paper and in the second part, the investigator instructed the participant to connect numbers (1 to 12) and/or alphabets (A to L) in a specified order. The time taken to complete the test was recorded as an outcome measure.

III. Memory

Mindomatics

- a. Numeric working memory test: Three target numbers appear one after the other in the centre of the screen. Pressing ‘Yes’ if the number is target number and ‘No’ for the numbers which appear on the screen, which are not the target numbers was required. This test measured reaction time, right and wrong attempts.
- b. Immediate picture recall test: In this test, few target pictures were displayed initially which the subject had to memorize. Of the random pictures that appeared, press ‘Yes’ if the picture is target picture and ‘No’ for the pictures which were not the target pictures. This test measured reaction time, right and wrong attempts.

Safety evaluation

Participants had free access to investigators for reporting of any adverse events.

Sample size calculation

To the best of our knowledge, there were no studies comparing effect of placebo with no-treatment group in healthy human volunteers till date. Based on a study by Ashor, 2011 where psychomotor effects were compared before and after administration of placebo, taking mean difference as 42 units and standard deviation in two groups as 73 and 66, the sample size was calculated to be 44. Taking an attrition rates of 20%, the present study was planned in 54 healthy volunteers.

Statistical analysis

Continuous variables were presented as mean \pm Standard error (S.E.) and comparison of means of continuous variables was done using mixed model ANOVA followed by post-hoc Bonferroni test. Bias due to carry-over effect was not expected in this study as the intervention was placebo. Statistical analyses were performed using

statistical software SPSS 23.0 (IBM, NY USA) considering a significance level of $p < 0.05$. Sequence effect was considered a covariate in the analysis.

Recruitment of study subjects

The study started in February 2021 and ended in August 2021. The first participant was recruited on 1st February 2021 and follow-up for all participants was completed on 18th August 2021. Healthy participants were screened as per the eligibility criteria. Out of 61 participants screened, six participants did not meet the inclusion criteria and one participant declined to participate. A total of 54 participants were recruited in the study. After recruitment, participants were randomized into six sequences. Each sequence had nine participants. All the participants were included in each of the trial arms. Three participants withdrew after first period as they developed symptoms suggestive of COVID-19 infection before the second period. CONSORT flowchart has been depicted in Fig 2.

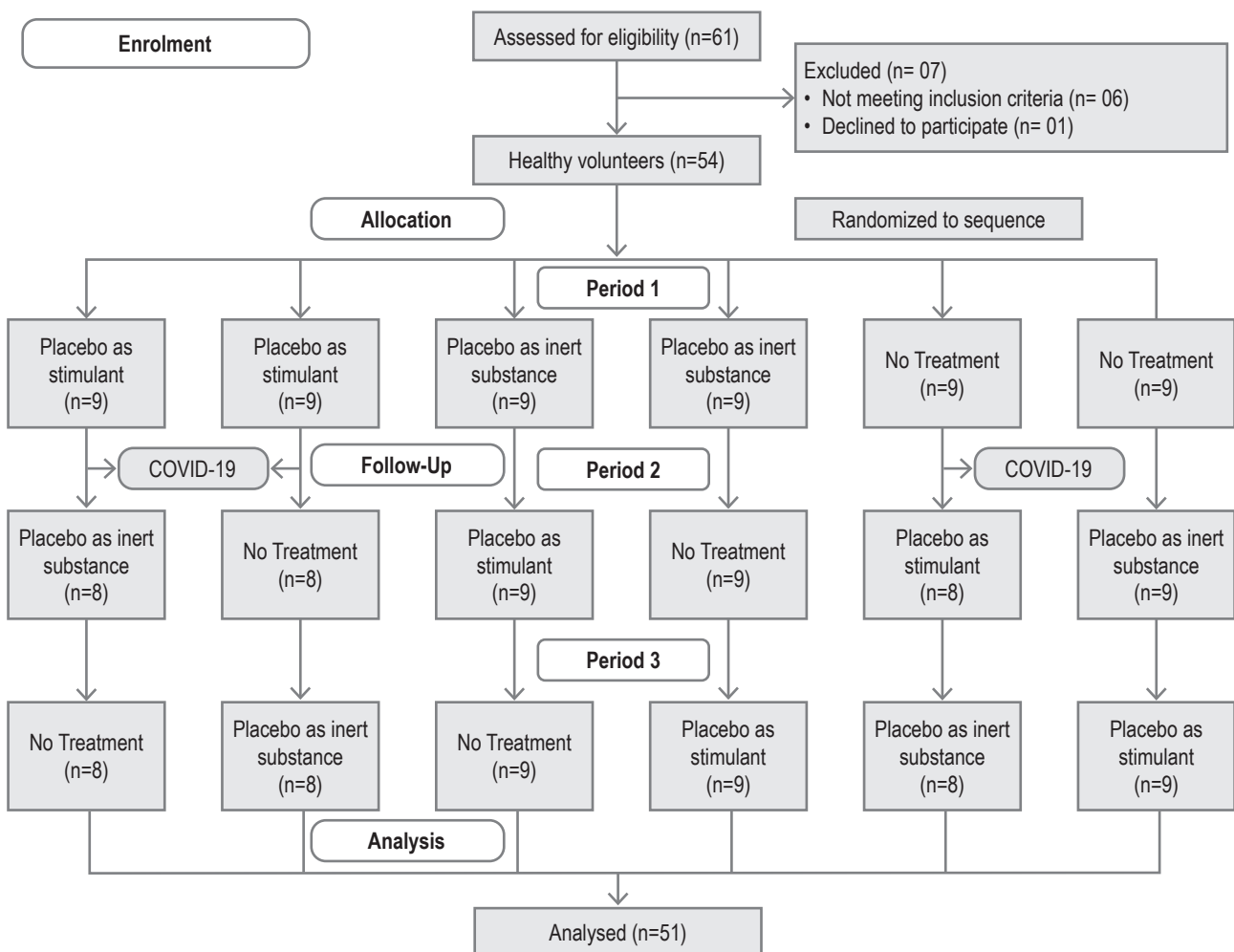


Figure 2.: CONSORT flow diagram

RESULTS

The minimum age of recruited participant was 21 years and maximum age was 35 years. The mean age of the participants included in this study was 28.07 years. Out of 54 participants, 51.9% participants were female, and rest were male.

Comparison of baseline characteristics

The baseline characteristics of participants have been represented in Table 1. Data have been represented in mean (standard error). There was no significant difference in psychomotor function, executive function and memory amongst the groups at baseline.

Table 1. Baseline characteristics

Parameter	Mean reaction time			P value	Errors			P value
	Placebo as stimulant (n=53)	Placebo as inert substance (n=51)	No treatment (n=52)		Placebo as stimulant (n=53)	Placebo as inert substance (n=51)	No treatment (n=52)	
Simple reaction T-time								
One hand	347.22 (6.98)	328.01 (8.99)	330.76 (6.60)	0.728	0.19 (0.19)	0.25 (0.18)	0.00 (0.00)	0.802
Both hands	507.49 (11.72)	487.49 (11.44)	497.64 (10.40)	0.657	3.75 (0.61)	3.47 (0.56)	2.94 (0.52)	0.451
Choice reaction time	431.30 (17.06)	406.15 (15.02)	401.48 (11.89)	0.588	0.59 (0.33)	0.78 (0.43)	0.59 (0.27)	0.533
Choice discrimination time	382.95 (3.46)	380.21 (4.64)	373.38 (4.70)	0.763	20.98 (1.18)	21.20 (1.45)	20.33 (1.45)	0.695
Task switching								
Congruent 1	587.17 (17.97)	567.39 (20.21)	576.96 (23.55)	0.064	4.63 (1.12)	3.38 (0.96)	3.22 (1.01)	0.879
Congruent 2	627.98 (20.11)	597.70 (21.98)	574.25 (21.79)	0.221	4.43 (1.25)	5.36 (1.62)	3.70 (0.96)	0.427
Incongruent 1	689.94 (25.16)	626.47 (25.26)	630.63 (26.07)	0.117	16.50 (2.39)	10.57 (1.83)	10.01 (1.61)	0.894
Incongruent 2	697.72 (29.39)	661.75 (23.72)	652.18 (26.11)	0.059	18.98 (2.37)	17.11 (2.36)	16.68 (2.03)	0.663
Digit picture substitution test	1616.53 (33.14)	1537.04 (24.47)	1562.25 (49.21)	0.380	1.96 (0.59)	1.96 (0.31)	3.22 (1.30)	0.932
Numeric working memory test	360.73 (12.77)	324.04 (15.18)	339.75 (13.51)	0.946	3.43 (0.42)	3.20 (0.42)	4.22 (0.46)	0.426
Immediate picture recall test	668.57 (16.19)	658.92 (22.81)	658.90 (21.15)	0.972	0.78 (0.16)	0.80 (0.23)	1.02 (0.14)	0.174
Digit symbol substitution test	69.00 (1.92)	69.98 (1.94)	70.51 (2.12)	0.506				
Six letter cancellation test	35.39 (1.49)	35.22 (1.54)	35.67 (1.18)	0.770				
Trail making A	20.73 (1.17)	21.00 (1.09)	20.12 (0.99)	0.617				
Trail making B	40.12 (1.97)	42.71 (2.47)	40.96 (2.30)	0.431				
Hand steadiness test 7	11.04 (2.31)	10.63 (1.99)	9.06 (1.41)	0.664				
Hand steadiness test 9	49.71 (4.99)	51.12 (4.64)	49.71 (4.43)	0.480				

Data represented in mean (Standard error)

Table 2. Change in reaction time before and after intervention in psychomotor function

Parameter	Change in reaction time before and after intervention				Group wise comparisons* (Bonferroni)					
	Δ Placebo as stimulant (Ps) (n=51)	Δ Placebo as inert subs (Pi) (n=51)	Δ No treatment (Nt) (n=51)	P value	Δ (Ps) vs. Δ (Pi) (n=51)	Mean difference	P value	Δ (Ps) vs. Δ Nt (n=51)	Mean difference	P value
					Mean difference			Mean difference		
Simple reaction time										
One hand	27.02 (16.79 to 37.25)	-20.13 (-27.88 to -12.38)	-17.04 (-27.40 to -6.68)	0.046	47.15 (30.99 to 63.32)	30.99 to 63.32	<0.001	-3.09 (-17.11 to 10.94)	44.06 (25.54 to 62.58)	0.99
Both hands	42.92 (32.08 to 53.76)	-20.98 (-32.74 to -9.21)	-15.79 (-22.32 to -9.26)	<0.001	63.90 (46.23 to 81.57)	46.23 to 81.57	<0.001	-5.19 (-22.74 to 12.37)	58.71 (44.26 to 73.17)	1.000
Choice reaction Time	54.61 (26.20 to 83.03)	-25.22 (-37.71 to -12.73)	-14.78 (-26.99 to -2.58)	0.006	79.83 (41.27 to 118.40)	41.27 to 118.40	<0.001	-10.44 (-33.48 to 12.61)	69.39 (32.67 to 106.12)	0.801
Digit picture substitution test	117.75 (68.93 to 166.56)	-64.37 (-97.78 to -30.97)	-76.47 (-117.66 to -35.28)	0.001	182.12 (116.0 to 248.24)	116.0 to 248.24	<0.001	12.10 (-56.40 to 80.59)	194.22 (117.74 to 270.70)	1.000
Digit symbol substitution test	-5.63 (-7.70 to -3.56)	-4.72 (-6.59 to -2.84)	-3.67 (-5.75 to -1.59)	0.567						
Six letter cancellation tests	-4.43 (-6.13 to -2.73)	-3.46 (-5.15 to -1.77)	-3.89 (-5.54 to -2.25)	0.823						
Hand steadiness test (Hole 7)	1.72 (-0.72 to 4.16)	-0.84 (-1.89 to 0.21)	-2.54 (-5.08 to -0.00)	0.251						
Hand steadiness test (Hole 9)	9.08 (4.73 to 13.43)	6.00 (1.02 to 10.98)	-2.92 (-8.17 to 2.33)	0.204						

Table 3. Change in reaction time before and after intervention in executive and memory function

Parameter	Change in reaction time before and after intervention				Group wise comparisons* (Bonferroni)					
	Δ Placebo as stimulant (Ps) (n=51)	Δ Placebo as inert subs (Pi) (n=51)	Δ No treatment (Nt) (n=51)	P value	Δ (Ps) vs. Δ (Pi) (n=51)	P value	Δ (Pi) vs. Δ Nt (n=51)	P value	Δ (Ps) vs. Δ Nt (n=51)	P value
Choice discrimination test	11.16 (6.34 to 15.98)	-5.46 (-12.02 to 1.10)	-7.06 (-11.48 to -2.63)	0.003	Mean difference 16.62 (5.76 to 27.48)	0.001	Mean difference 1.59 (-8.47 to 11.66)	1.000	Mean difference 18.22 (9.52 to 26.91)	<0.001
	Task switching									
Congruent 1	55.72 (30.31 to 81.14)	-28.98 (-56.99 to -0.96)	-4.86 (-32.65 to 22.91)	0.026	Mean difference 84.70 (43.36 to 126.05)	<0.001	Mean difference -24.11 (-69.25 to 21.02)	0.575	Mean difference 60.59 (10.23 to 110.95)	0.013
	Congruent 2	66.24 (33.96 to 98.52)	-30.45 (-50.57 to -10.32)	-26.30 (-53.28 to 0.67)	0.041	Mean difference 96.69 (54.44 to 138.93)	<0.001	Mean difference -4.14 (-44.92 to 36.63)	1.000	Mean difference 92.54 (35.03 to 150.05)
Incongruent 1	87.44 (40.80 to 134.09)	-28.62 (-64.42 to 7.18)	-14.09 (-45.49 to 17.32)	0.046	Mean difference 116.07 (44.44 to 187.70)	0.001	Mean difference -14.54 (-56.40 to 27.33)	1.000	Mean difference 101.53 (32.86 to 170.20)	0.002
	Incongruent 2	78.44 (28.15 to 128.72)	-11.66 (-48.55 to 25.22)	-15.42 (-49.98 to 19.14)	0.010	Mean difference 90.10 (13.58 to 167.52)	0.016	Mean difference 3.76 (-58.96 to 66.47)	1.000	Mean difference 93.85 (18.41 to 169.30)
Trail making A	4.28 (2.96 to 5.59)	0.47 (-0.57 to 1.51)	0.29 (-0.48 to 1.07)	0.018	Mean difference 3.80 (1.52 to 6.09)	<0.001	Mean difference 0.18 (-1.45 to 1.80)	1.000	Mean difference 3.98 (2.06 to 5.90)	<0.001
	Trail making B	8.16 (6.23 to 10.08)	1.61 (-0.29 to 3.51)	0.35 (-2.16 to 2.86)	0.022	Mean difference 6.55 (3.10 to 9.99)	<0.001	Mean difference 1.26 (-2.78 to 5.29)	1.000	Mean difference 7.80 (3.98 to 11.63)
Numeric working memory test	36.35 (24.32 to 48.39)	-44.51 (-64.05 to -24.10)	-24.78 (-46.73 to -2.84)	0.286	Mean difference 99.35 (60.54 to 138.17)	<0.001	Mean difference -23.59 (-60.51 to 13.34)	1.000	Mean difference 75.77 (43.56 to 107.97)	<0.001
	Immediate picture recall test	54.04 (34.30 to 73.78)	-45.31 (-72.31 to -18.32)	-21.73 (-42.05 to -1.40)	0.005	Mean difference 99.35 (60.54 to 138.17)	<0.001	Mean difference -23.59 (-60.51 to 13.34)	1.000	Mean difference 75.77 (43.56 to 107.97)

Change in outcome variables

Change in measures of psychomotor function

A significant difference was observed between the Ps and Pi groups for change in score after administration of intervention for simple reaction time (one hand: 47.15; 95% CI: 30.99 to 63.32; $p < 0.001$, both hands: 63.90; 95%CI: 46.23 to 81.57; $p < 0.001$) choice reaction time (79.83; 95%CI: 41.27 to 118.40; $p < 0.001$) and digit picture substitution test (182.12; 95% CI: 116.0 to 248.24; $p < 0.001$); the difference was significant for Ps and Nt groups (Simple reaction test – one hand: 44.06; 95%CI: 25.54 to 62.58; $p < 0.001$, both hands: 58.71; 95%CI: 44.26 to 73.17; $p < 0.001$, choice reaction time: 69.39; 95%CI: 32.67 to 106.12; $p < 0.001$, digit picture substitution test: 194.22; 95%CI: 117.74 to 270.70; $P < 0.001$) but the difference was not significant for Pi and Nt groups. However, no significant difference was found in digit symbol substitution, six letter cancellation test and hand steadiness test. (Table 2)

Change in executive function scores

A significant difference was observed in choice discrimination test (16.62; 95%CI: 5.76 to 27.48; $p = 0.001$), task switching (Congruent 1: 84.70; 95%CI: 43.36 to 126.05; $p < 0.001$, Congruent 2: 96.69; 54.44 to 138.93; $p < 0.001$, Incongruent 1: 116.07; 95%CI: 44.44 to 187.70; $p = 0.001$, Incongruent 2: 90.10; 95%CI: 13.58 to 167.52; $p = 0.016$) and trail making (Trail making A: 3.80; 95%CI: 1.52 to 6.09; $p < 0.001$, Trail making B: 6.55; 95%CI: 3.10 to 9.99; $p < 0.001$) between Ps and Pi groups for change in scores from baseline; the difference in scores were significant for Ps and Nt groups (choice discrimination test: 18.22; 95%CI: 9.52 to 26.91; $p < 0.001$, Trail making A: 3.98; 95%CI: 2.06 to 5.90; $p < 0.001$, Trail making B: 7.80; 95%CI: 3.98 to 11.63; $p < 0.001$) but the difference from baseline was not significant for Pi versus Nt. (Table 3)

Change in memory functions

There was no significant difference amongst the groups in change in scores for numeric working memory test but there was significant difference in change in scores in immediate picture recall test when Ps group was compared with Pi (99.35; 95%CI: 60.54 to 138.17; $p < 0.001$) and Nt (75.77; 95%CI: 43.56 to 107.97; $p < 0.001$). There was no difference in change in scores between Pi and Nt. (Table 3)

There was no significant difference in error rates amongst the groups. No adverse events were reported by any participant enrolled in the study.

DISCUSSION

The present study evaluated the effect of placebo perceived as stimulant on psychomotor, executive and memory functions in healthy volunteers compared to placebo that may be an inert substance and to a situation where no treatment was administered. In deception, patients were convinced that they were being administered a stimulant drug and that it would reduce their reaction time when taking the tests. In this study, participants showed a significant reduction in reaction time in most of the computerized test for evaluation of psychomotor function, executive function and memory. While calculating difference in mean of change in scores after administration of intervention in paper and pencil tests for psychomotor functions, the digit symbol substitution test and six letter cancellation tests showed no statistical difference; however, there was a significant reduction in placebo as stimulant over placebo as inert substance or no intervention groups for trail making tests of executive functions. No significant difference was observed for motor functions in hand steadiness test as well.

As placebo response is dependent not only to patient factors but accounts for physician's convincing ability as well, the difference between the clinical trial and patient care settings becomes obvious. Reward mechanism of brain plays a major role in building expectations (Fromer et al. 2021). This expectancy can be qualitative and quantitative both (Vase et al. 2011). An expectancy for probable occurrence of response is qualitative benefit and the magnitude of that response can be measured quantitatively. True placebo effect can be calculated by comparing effect of placebo against no intervention, but at the same time it will be unethical to perform such an experiment for diseased individuals. In our study, the qualitative expectation of benefit was established by convincing participants that they were receiving a stimulant drug and quantitative measurement of the same was shown by comparison with a probable placebo and no treatment. This is already known that the participants of a clinical trial and a patient in healthcare setting may have different expectations from the drug being administered.

In this study, we have included a no treatment group with an intent to quantify the placebo effect in clinical trial and clinical practice settings. Findings of this study reveal that placebo in clinical practice settings produce a significantly good response when compared with clinical trial settings or when compared to a condition where no treatment is administered. In our study, there was no difference in change from baseline in the groups with respect to error rates in psychomotor, cognitive and executive functions. Apparently, it is not number of choices amongst the stimuli but number of choices amongst responses that slows up

subject's processing activities and complicates decision making ability of an individual. Error rates increase as a function of complexity of psychomotor function and may not be a function of participant's expectations.

In a study by Kirsch et al, deceptive administration of placebo has been shown to have significant effect on alertness, tension, pulse-rate, systolic blood pressure, and subjective probabilities of having consumed caffeine, while no difference was found in motor function (Kirsch & Weixel 1988). They further concluded that the change in response was proportional to the belief of participants on the effect produced by the intervention. Ashor et al conducted a study to evaluate placebo effect on psychomotor function and working memory function when healthy volunteers received placebo as stimulant, unknown and inert substance (Ashor 2011). They compared the change after administration from baseline in each of these situations and found that placebo as stimulant enhanced psychomotor function tests but not critical flicker fusion test (Ashor 2011). Placebo as unknown significantly deteriorated psychomotor function and as an inert substance had no significant effect in that study. But the investigators did not compare the change between the groups (Ashor 2011). To the best of our knowledge, our study becomes first of its kind to compare the change in mean scores amongst the groups and incorporate a no treatment group so that true placebo effect could be identified which is usually not possible with diseased participants.

Our study showed that though reaction time is highly influenced by placebo administration, there was no significant difference in error rates(accuracy) in the tests. Placebo effect has been attributable to expectation of a patient and condition to the environment (clinical set up and presence of a doctor) but is not limited to these. It is not uncommon for clinical trials to yield uninterpretable results, due in part to the placebo response especially for psychopharmacological drugs. A unified model which takes account of expectation-based neurochemical changes and disease specific neurotransmitter release needs to be devised. The calculation of true drug effect in a clinical trial needs development of an algorithm which balances for placebo response in clinical trial and clinical practice settings along with patient expectations based on disease conditions and personal factors. The ability to distinguish between therapeutic and placebo responses in the treatment groups would allow researchers to identify possible placebo responders in randomised control studies (Jakšić et al. 2013). This drug effect can then be generalized to settings of patient care. Most psychiatric disorders, including depression, anxiety, addictions, and, perhaps surprisingly, schizophrenia, are affected significantly by the placebo effect (Požgain et al. 2014).

The main limitation of this study was multiple repetitions of the same tests. Still, increased proficiency due to repetitions was taken care of by training the participants for those tests before start of actual clinical study. This may be similar to conditioning which is believed to teach expectancies to the participants. Secondly, results of this study may or may not be generalizable to diseased condition and other physiological functions as disease severity may be directly proportional to the placebo response. However, the same does not hold true for a drug effect which is always present and is not related to severity and thus, assumptions of additive model may not hold true (Fountoulakis & Moller 2011). Third, Multiple doses of the intervention and multiple timepoints of observation would have added more value to the study results. Fourth, adding a biomarker would have substantiated the study findings.

CONCLUSION

There is a significant difference between deceptive placebo (placebo as stimulant) over non-deceptive placebo (placebo as inert substance) and deceptive placebo over no treatment on psychomotor, executive and memory functions. Thus, we can conclude that clinical trial settings differ significantly from patient care settings and the conventional additive model used to generalize results of a clinical trial to real world patient care needs some modifications. Further studies may be conducted to address placebo effect in other physiological functions and propose evidence-based placebo therapeutics in conditions where definitive treatments are not available at this point of time.

Ethical Considerations: Does this study include human subjects? YES

Authors confirmed the compliance with all relevant ethical regulations.

Conflict of interest: No conflict of Interest

Funding sources: The authors received no funding from an external source

Data availability statement: Data supporting the findings of this study are available from the first author on request.

Authors Contributions: Dr. Archana Mishra: conception and design, literature search, acquisition of data, data analysis and interpretation, first draft, final approval of the manuscript. Dr. Sudhir Chandra Sarangi: literature search, data analysis, and interpretation, critical revision of the manuscript, final approval of the manuscript. Dr. Kh Reeta: literature search, data analysis, and interpretation, critical revision of the manuscript, final approval of the manuscript.

References

- Ashor AW. The placebo effect on psychomotor performance and working memory capacity: randomized single blind cross-over trial. *Ann Neurosci* 2011; 18: 141-4.
- Blease C, DesRoches CM. Open notes in patient care: confining deceptive placebos to the past? *J Med Ethics* 2022; 48:572-574.
- Brown WA. Expectation, the placebo effect and the response to treatment. *R I Med J* 2015; 98: 19-21.
- Enck P, Klosterhalfen S. The placebo response in clinical trials-the current state of play. *Complement Ther Med* 2013; 21: 98-101.
- Fountoulakis KN, Moller HJ. Efficacy of antidepressants: a re-analysis and re-interpretation of the Kirsch data. *Int J Neuropsychopharmacol* 2011; 14: 405-12.
- Fromer R, Lin H, Dean Wolf CK, Inzlicht M, Shenhav A. Expectations of reward and efficacy guide cognitive control allocation. *Nat Commun* 2021; 12: 1030. doi: 10.1038/s41467-021-21315-z.
- Gould BA, Mann S, Davies AB, Altman DG, Raftery EB. Does placebo lower blood-pressure? *Lancet* 1981; 2: 1377-81.
- Gowdey CW. A guide to the pharmacology of placebos. *Can Med Assoc J* 1983; 128: 921-5.
- Hammami MM, Hammami S, Al-Swayeh R, Al-Gaai E, Farah FA, De Padua SJ. Drug*placebo interaction effect may bias clinical trials interpretation: hybrid balanced placebo and randomized placebo-controlled design. *BMC Med Res Methodol* 2016;16: 166. doi: <https://doi.org/10.1186/s12874-016-0269-1>
- Hindmarch I. Psychomotor function and psychoactive drugs. *Br J Clin Pharmacol* 1980; 10: 189-209.
- Hindmarch I. Psychomotor function and psychoactive drugs. *Br J Clin Pharmacol* 2004; 58: S720-40; discussion S741-3.
- Jakovljević MM. The placebo-nocebo response in patients with depression: do we need to reconsider our treatment approach and clinical trial designs? *Psychiatr Danub*. 2014; 26:92-95.
- Jakšić N, Aukst-Margetić B, Jakovljević M. Does personality play a relevant role in the placebo effect? *Psychiatr Danub*. 2013; 25:17-23.
- Kallus KW, Schmitt JA, Benton D. Attention, psychomotor functions and age. *Eur J Nutr* 2005; 44: 465-84.
- Kirsch I. Are drug and placebo effects in depression additive? *Biol Psychiatry* 2000; 47: 733-5.
- Kirsch I. Placebo Effect in the Treatment of Depression and Anxiety. *Front Psychiatry* 2019; 10: 407. doi: <https://doi.org/10.3389/fpsy.2019.00407>
- Kirsch I, Weixel LJ. Double-blind versus deceptive administration of a placebo. *Behav Neurosci* 1988; 102: 319-23.
- Kisaalita N, Staud R, Hurley R, Robinson M. Placebo use in pain management: The role of medical context, treatment efficacy, and deception in determining placebo acceptability. *Pain* 2014; 155: 2638-2645.
- Klosterhalfen S, Enck P. Psychobiology of the placebo response. *Auton Neurosci* 2006; 125: 94-9.
- Kube T, Rief W. Are placebo and drug-specific effects additive? Questioning basic assumptions of double-blinded randomized clinical trials and presenting novel study designs. *Drug Discov Today* 2017; 22: 729-735.
- Lidstone SC. Great expectations: the placebo effect in Parkinson's disease. *Handb Exp Pharmacol* 2014; 225: 139-47.
- Nakano S, Ogawa N, Kawazu Y, Osato E. Effects of antianxiety drug and personality on stress-inducing psychomotor performance test. *J Clin Pharmacol* 1978; 18: 125-30.
- Požgain I, Požgain Z, Degmečić D. Placebo and nocebo effect: a mini-review. *Psychiatr Danub*. 2014 ;26:100-107.
- Stoet G. PsyToolkit: a software package for programming psychological experiments using Linux. *Behav Res Methods* 2010; 42: 1096-104.
- Stoet G. PsyToolkit: A novel web-based method for running online questionnaires and reaction-time experiments. *Teach Psychol* 2017; 44: 8. doi: 10.1177/0098628316677643
- Taur S, Karande S, Saxena AA, Gogtay NJ, Thatte UM. Use of computerized tests to evaluate psychomotor performance in children with specific learning disabilities in comparison to normal children. *Indian J Med Res* 2014; 140: 644-8.
- Vallance AK. Something out of nothing: the placebo effect. *Adv Psychiatr Treat* 2006; 12: 287-296.
- Vase L, Norskov KN, Petersen GL, Price DD. Patients' direct experiences as central elements of placebo analgesia. *Philos Trans R Soc Lond B Biol Sci* 2011; 366: 1913-21.
- Wolf S. The pharmacology of placebos. *Pharmacol Rev* 1959; 11: 689-704.
- Zubieta JK, Stohler CS. Neurobiological mechanisms of placebo responses. *Ann N Y Acad Sci* 2009; 1156: 198-210.

Correspondence:

KH Reeta, M.D.

Professor, Department of Pharmacology

All India Institute of Medical Sciences, New Delhi, India

reetakh@gmail.com / +91-9711204141

Published under



<https://creativecommons.org/licenses/by-nc-nd/4.0/>