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Advanced Central Effects of Yohimbine on the Cognitive Function, Psychomotor Performance Task and Working Memory: A Randomized Controlled Clinical Trial Study

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Authors' contributions

This work carried out between all authors. Author HMAK designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author AIA managed the literature search, analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Systemic administration of yohimbine lead to powerful anxiety-promoting effects and facilitated long-term performances, due to α2- adrenergic receptor action , while its effect on the extinction of reward-related memories are probabilistically independent of their effects on α2- adrenergic receptors. So the objective of presenting study was to evaluate the enhancement effects of yohimbine on psychomotor performance and working memory in normal young healthy volunteers. Twenty subjects (10 females: 10 males) randomly chosen by medical students. They were healthy, young volunteers aged 21 - 23 years were incorporated in the study while those with proof of any disease were excluded. The participants were permitted to practice on both the psychomotor tester

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and the *n*-back task (working memory test) to obtain familiarity with those tests before the commencement of the trial. Yohimbine significantly improve human psychomotor reaction time, and critical flicker fusion threshold significantly ($p<0.05$) also it improve accuracy rates in both 1-Back and 2-Back significantly ($p<0.05$) but produced insignificant effects on 3-Back ($p>0.05$).
In conclusion yohimbine improve psychomotor performances and working memory, thus advance the cognitive function via activation of noradrenergic system.

Keywords: Yohimbine; psychomotor performances; working memory.

1. INTRODUCTION

Yohimbine is an alkaloid agent derived from Pausinystalia, it's used in the management of postural hypotension in autonomic failure and potentiate the antidepressant agents. Yohimbine acts as an antagonist at α_1-adrenergic, α_2-adrenergic, $5HT_{1B}$, and D_2, and as a partial agonist at 5-HT_{1A}. Furthermore, yohimbine decreases glutamatergic transmission in the amygdala [1], and inhibits monoamine oxidase enzymes, though it is not obvious if it is a reversible inhibitors of monoamine oxidase A or B inhibitor and does not require dietary limitations [2-4].

Systemic administration of yohimbine induces anxiety-promoting effects and facilitated long-term performances, due to α2- adrenergic receptor action, while its effect on the extinction of reward-related memories are probabilistically independent of their effects on α2- adrenergic receptors. Moreover, Yohimbine has been second-hand to make possible remind of distressing memories in the management of post traumatic anxiety disorder [5-8].

Presynaptic inhibitory autoreceptors on noradrenergic neurons is aα_2- adrenergic receptor and reserve of these receptors by yohimbine, enhance the release of noradrenalin. The $\alpha_2$adrenoceptors are sub classified into α_2a, α_2b and α_2c.In the brain, the α_2a and α_{2C} subtypes preponderate and majority of the $\alpha_2$adrenoceptor actions, such as low blood pressure, sedation and analgesia are interceded primarily by α_{2a} while α_{2c} could be accountable for stress response and locomotion. Because of noradrenergic network in the prefrontal cortex obtain input from the locus coeruleus, a major centre of noradrenergic neuronal action, and therefore, changes in noradrenalin discharge in the prefrontal cortex imitate activity in the locus coeruleus [9,10].

Additionally, a low dose of the yohimbine enhanced working memory via increased noradrenaline release onto postsynaptic $\alpha_2$adrenoceptors, and the cognitive-enhancing effects of low dose yohimbine so depend on noradrenalin systems. In contrast clonidine improved working memory, but clonidine's useful effects were barren via the postsynaptic antagonists signifying that clonidine acts by directly activating postsynaptic $\alpha_2$adrenoceptors. So, mutual favourable doses of clonidine and yohimbine produced memory enhancement. [11] Noradrenaline released from the locus coeruleus augment working memory, but an excess of noradrenaline might reduce working memory via binding to the low affinity α1 receptors .The locus coeruleus is activated through increasing noradrenalin discharge, which in sequence will modify the cognitive function and psychomotor motivation throughout the prefrontal cortex [12].

Working memory might be a centre of cognitive functions and human intelligence also, working memory submitted for short-term storage of cerebral cortical information. Brain imaging studies have discovered the elevated activity in the frontal lobe when this central function is working. However, several issues are still controversial about working memory, but numerous models of working memory focused on memorization and sequential remember of matters [13,14].

Changes in the preferential concentration of dopamine and noradrenaline might considerably change working memory functions. Moreover; serotoninergic and cholinergic systems are affecting the ascending exciting neuronal systems which may affect working memory in the course of an arousal and attention deficit [15,16].

Psychomotor performance comprises impulses, stimulus and person's performance. The psychomotor performance can be evaluated via reaction time machine. Reaction time is distinct as the time gap between the stimuli and the response of an individual and the reaction time also assess the speed and accurateness of the central cognitive function where the cognition,

denotes the capability of the brain to react, stir up, and control information process. There are three levels of nervous systems throughout which at the stimulus passes; the receptor level, the data processing level and cortical level, destruction of any of these levels will lead to dysfunction in the psychomotor performance and cognitive abilities. The psychomotor performance and cognitive abilities of human beings fluctuate from person to person and can be pretentious by certain factors. These abilities can also decelerate due to aging and it has been reported that cognitive capacities in older age groups are lower as compared to younger age group [17-22].

So, the objective of this work in the present study was to estimate the improvement effects of yohimbine on psychomotor performance and working memory in normal young healthy volunteers.

2. SUBJECTS AND METHODS

This is a study conducted in the Department of Pharmacology, College of Medicine, Al-Mustansiriya University, Baghdad, Iraq, 2014. A self-determining scientific committee revised and permitted the study and oral approval gained from the contributors. Twenty subjects (10 females: 10 males) haphazardly chosen from medical college students. They were fit, youthful volunteers aged 21 - 23 years were incorporated in the study while those with proof of any disease were excluded. The participants were permitted to practice on mutually the psychomotor tested and the *n*-back task (working memory test)to obtain familiarity by way of those tests before the commencement of the trial.

2.1 Subjects Inclusion Criteria

All contributors were healthy volunteers with age ranged 20-23 years and right hand domination.

2.2 Subjects Exclusion Criteria

Any participant that was enrolled in this study with any visual deficits, history of recent medications and with active psychiatric or somatic disorders is excluded from this study.

2.3 Computerized *N*-back Test

(Visual working memory task) where squares next to eight diverse positions were obtainable sequentially on a computer monitor at a rate of 3 seconds. An answer was requisite each time one of the obtainable stimuli coordinated the one-presented *in* the locations backside in the succession. In the *I-back* situation, the goal is any square situation that is the same to the square location instantaneously preceding it. In the *II-back*, the goal is a square position like to an additional square location two checks back. *III-back* is square location equal to a further square location three trials reverse. Participants finished reactions by hand via pressing the letter ‘‘A 'of a typical laptop keyboard with their index finger for visual goals. The computer continually exacting the accuracy rate (number of successful responses) [23]

2.4 Leeds Psychomotor Tester It is a Device Used to Compute Reaction Time (RT) and Critical Flicker Fusion Threshold (CFFT)

2.4.1 Total reaction time (TRT)

The standard of TRT is to respond to a brilliant red colour light so as to emerge haphazardly by urgent the button wherever the red light revealed. Consequently, the time wanted for the incentive to be documented is called recognition reaction time (RRT*)* which correspond to the instance from stimulus beginning with the commencement of motor action; the point from start of motor action to the terminate of concert called motor reaction time (MRT).Summing up of recognition and motor reaction time consequences in a total reaction time (TRT =RRT + MRT).

2.4.2 The critical flicker fusion threshold (CFFT)

Calculated by asking the subject to give attention to on four illumine places and to respond at what time the illuminated site altered because stable state to flickering and when it altered from flickering to steady condition .The mean of four trials of flicker downward is named flicker threshold, although the mean of flicker ascending is named fusion. The best values for fusion threshold should be near 60 Hz, i.e. over 30Hz, while the best values for flicker threshold should be near 1Hz i.e. < 30 Hz. [24].

All reaction time and working memory tasks measured before (control) so the same subjects regarded as control and within five days of taking the yohimbine 5 mg (super 5 ibn hyyanpharm. LTD).

2.5 Statistical Analysis

Statistical analysis was prepared by means of using a paired t - test. All the data are accessible as (mean ± SD) when *the p value* <0.05 regarded significant.

3. RESULTS

A single dose of yohimbine significantly improve human psychomotor reaction time, and critical flicker fusion threshold significantly ($p<0.05$) Table (1).

Regarding the yohimbine effects on working memory it improves the Accuracy rate in both 1-Back and 2-Back significantly ($p<0.05$) but produced insignificant effects on 3-Back ($p>0.05$) Table (2).

4. DISCUSSION

Psychomotor performance, refers to measures of cognitive performance and various choices, making by way of a motor activity, it has been calculated by means of Leeds psychomotor tester that necessitate alertness to the stimuli of the reaction time device [25].

The attendance, study demonstrated that yohimbine considerably advanced the human psychomotor performances in well volunteers and improve the critical flicker fusion threshold after short term yohimbine therapy.

The effects of small dose of yohimbine on psychomotor performance correlate through the augmentations of cerebral functional action mainly at the locus coeruleus which are concerned in the alertness and mood [26]. Also, yohimbine improved cognitive purpose in a non-working form exactness in a dynamic simulator, promotion in the mood events and an unremitting attention task [27].

These facts propose that the cognitive performance enhanced after yohimbine therapy, which are correlated with our findings. It has been designed that there is a contrary association between awakening and performance, because performance is typical approving at medium levels of arousal although deteriorated if much low or much high ,as a result extremely superior motor will be impair as a consequence of high doses of yohimbine since yohimbine has a mild psycho stimulant consequence and improves a wide range of performance variables [28]. This may explain the positive results of the present study via selection of smaller dose 5mg of yohimbine.

Also, yohimbine improves straightforward reaction time and continuous awareness tasks and a little revision have demonstrated improvements on uncomplicated but not choice reaction time [29].

Moreover; the present study showed that yohimbine significantly improves the accuracy rate of the working memory task because the yohimbine regard as a vague stimulant and so chronic yohimbine intake be able to precede working memory and cognitive performances [30]. The majority of articles about yohimbine and memory has not established positive special effects in relative to psycho stimulant effect of caffeine, the caffeine improved verbal analysis, lessening in the unpredictability of intended performance, concentration, improved oral interpretation, and diminution in the changeability of awareness performance between subject matters but here were nix variations in oral or visual memory [31]. These results indicated that any central nervous stimulant similar to caffeine progress, cognitive function and memory and because of yohimbine has central nervous stimulant effects via quickening of central noradrenaline secretions so it augment the cognitive function and memory tasks, but extra studies revealed deceleration in memory concert subsequent a regular yohimbine dose thus these result advise that memory may not be sensitive to the effects of yohimbine [32].

Table 1. Effects of yohimbine on psychomotor reaction time and critical flicker fusion threshold

	TRT (Ms)	RRT (Ms)	MRT (Ms)	Fusion (ascending) threshold (Hz)	Flicker (descending) threshold (Hz)
Before	625.71±73.5	402.8±15.4	222.9±58.1	41.32±0.007	41.44±0.151
After	421.34±32.3	299.7±22.9	121.64±9.40	47.55±1.407	31.435±0.162
P value	<0.01	<0.01*	<0.01*	<0.01*	<0.01*

**significant effects p<0.05, TRT (total reaction time), RRT (recognition reaction time), MRT (movement reaction time).*

Table 2. Effects of yohimbine on working memory accuracy rate using n-back task

Accuracy Rate (%)	I-Back	II-Back	III-Back
Before	88.4±7.3	81.6±16.3	65.6±12.3
After	99.6±11.2	94.5±12.5	66.7±14.3
P Value	<0.01*	<0.01*	>0.01"

**significant effects p<0.05,"nonsignificant effects p>0.05*

Working memory believes to be a decision-making function requiring persons to be mentally controlled. In addition working memory showed differences in spatial working memory, but yohimbine improve working memory performances and advance programming of new sequence in working memory [33].

Also, this study showed that yohimbine improves the flicker threshold more than fusion threshold so it's regarded as a cognitive enhancer. Veerle et al. [34] suggested that working memory is improved during the experience to surplus neural excitation. The brain diagram of a human being, he argues, can be changed via this activation to generate a bigger region of the brain activated by a exacting type of sensory knowledge.

The flicker fusion assesses sum processing capability and change according to the changes in the capability to procedure and the speed of stimuli [35]. As a result, it is probable that alterations to a subject's image surrounds create alterations in CFF verges so as to not connect to the exploitations of that loan. Moreover; flicker fusion is a most reliable procedure for measuring logical and arousal functions and this can evaluate the effects of various drugs on cognitive function and thus the flicker fusion is regarded as a guide of watchfulness and cortical excitement so sedative drugs lessen CFFT while stimulants augment it [36-38].

It has been planned that the diversity between the ascending and the descending threshold reproduce a dissimilar processing of cognitive function due to the presence of diverse pathways for fusion and flicker frequency and this may explain the differential effects of yohimbine on flicker and fusion frequency threshold. Though, upon extended contact to flicker there is a steady attenuation of the cortical reaction and high CFFT is associated with high scores on intelligence tests and prominent cortical arousal [39,40]. Numerous studies display differences in the CFFT between male and female subjects, but the data are extremely conflicting [41]. A numeral of studies revealing higher CFFT values for men than for women, but in various cases the differences be unsuccessful to reach significance and some authors account decreased threshold values for both descending and ascending with increasing age. Male subjects show a higher average CFFT than female subjects, and the sex difference is superior for the flicker than for the fusion [42]. These remarkable variations may possibly be explained by variation of the method and the presentation of the experiments. Older individuals are also more vulnerable to fatigue, both visual and general, and so more probable to knowledge a CFFT decrease during the course of the day [43]. Thus, in the present study young age was selected to exclude age variations and gender factor not regarded as a dependable factor in the present study.

The CFFT are frequently used to measure the impact of drugs like analgesics, sleeping agents and psychoactive drugs on the cognitive function, antihistamines and anticonvulsants are apt to reduce the CFFT [44]. Though, the special effects of a definite drug on the CFFT are usually unfeasible, since drugs affecting the CNS usually have an impact on a lot of CNS functions other than the targeted one so antidepressants lessen or augment CFFT values, also central stimulating agents, like nicotine and amphetamine, increase the CFFT [45]. Nonetheless, to attain substantial effects from stimulant, large doses are required, but in this study small dose of yohimbine used. There seems to be no simple association between the dose and the special effects on the CFFT [46]. There is indication that most favourable working memory concert, cognitive function and psychomotor performances links to the neural capability to focus concentration on task-relevant in sequence and disregard disruption, and that practice linked enhancement in working memory is due to rising neurons aptitudes which are activated via yohimbine that induce modulations in monoaminergic neurons [47].

Thus, yohimbine effects were beneficial in activation of psychomotor performances and working memory via activation of noradrenergic system like other central stimulant effects of nicotine and caffeine regardless of precise mechanism.

5. LIMITATIONS OF STUDY

Many factors limit the present study like numbers of volunteers, new computerized lead

psychomotor tester device and availability of synaptic noradrenalin measurement.

6. CONCLUSION

Yohimbine improves psychomotor performances and working memory, thus advances the cognitive function via activation of noradrenergic system.

CONSENT

All authors and contributors in this experimental clinical study declare written, knowledgeable consent from all volunteers.

ETHICAL APPROVAL

All authors declare that experimental clinical study examined and approved via scientific ethics committee, according to ethical standards of the Helsinki declaration in 1964.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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