Original Article

A Computerized Stroop Test for the Evaluation of Psychotropic Drugs in Healthy Participants

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ABSTRACT

Background: The Stroop paradigm evaluates susceptibility to interference and is sensitive to dysfunction in frontal lobes and drug effects. The aim of the present study was to establish a simple and reliable computerized version of Stroop color-word test, which can be used for screening of various psychotropic drugs. **Materials and Methods:** The standardized method was followed in all cases, by recording the reaction time (RT) in msec in 24 healthy participants using computerized version of Stroop color-word test. Reproducibility of the test procedure was evaluated by recording the RTs by a single experimenter on two sessions (interday reproducibility). Validity of the model was further tested by evaluating the psychotropic effect of Zolpidem 5 mg, Caffeine 500 mg, or Placebo on 24 healthy subjects in a randomized, double blind three-way crossover design. **Results:** The method was found to produce low variability with coefficient of variation less than 10%. Interday reproducibility was very good as shown by Bland-Altman plot with most of the values within ±2SD. There was a significant increase in RTs in Stroop performance with Zolpidem at 1 hr and 2 hrs; in contrast, caffeine significantly decreased RTs in Stroop performance at 1 hr only compared to placebo. **Conclusion:** The Stroop color-word recording and analysis system is simple, sensitive to centrally acting drug effects, and has potential for future experimental psychomotor assessment studies.

Key words: *Attention, cognition, neuropsychology, stroop interference*

INTRODUCTION

"Everyone knows what attention is." wrote William James in 1890. *"It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. It implies withdrawal from some things in order to deal effectively with others".*[1]

Attention is of great importance in human performance, as the ability to select information from the environment and to sustain efficient input is often a major constraint. It refers to a variety of components: (a) initiation or focusing; (b) sustaining attention or vigilance; (c) inhibiting responses to irrelevant stimuli or selective attention; and (d) shifting attention. Psychotropic drugs, especially antidepressants and antipsychotics, may give rise to some concern in clinical practice because of their known ability to induce changes in attention and documentation of such changes is an important part of assessing the deleterious effects of such drugs. The optimum profile of a psychotropic drug should include no detrimental effect on cognitive and psychomotor functions.

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A range of tests are used to measure attention. For example, some tests use faint stimuli close to the threshold of perception, while others use briefly presented stimuli that are easily detected by the alert subject; some use auditory stimuli while others are visual; and some use concentrated attention while others use divided attention or introduce distracters. Although these various measures have been used in many psychological investigations, they have seldom been directly compared and so it is difficult to assess the relative sensitivities of the different types of measure. Tests to analyze attention processes, such as the Gottschaldt Shuffled Figures Test, the Odd Man Out Test, and Stroops color-word procedure, have been related more specifically to selective attention.

The Stroop color-word interference task is one of the most widely used experimental tasks in all of cognitive psychology and is used as a measure of selective attention and inhibitory control.[2] It is a quick and easy test to administer and may be regarded as reflecting different levels of central processing. The Stroop interference effect refers to the increase in response latency observed when an individual is required to identify the color of a color-word when these aspects of the stimulus are incongruent (e.g., the word RED presented in the color blue) compared to the time required to name the color of a neutral (e.g., XXX in blue, or congruent, e.g., the word RED presented in the color red) stimulus. The conflict between the relevant (color of the word) and irrelevant (name of the word) dimensions of the stimulus on incongruent trials presents a particularly difficult task for the selective attentional system. A system that efficiently suppresses the irrelevant dimension (i.e., the word) should exhibit faster color naming than a system in which impaired suppression of the word dimension allows greater competition between the word name and the color name for response output. Thus, the magnitude of Stroop interference has been used as an indicant of the efficiency of the inhibitory system.[3]

In particular, the Stroop paradigm has been employed frequently in neuropsychology and neuropsychiatry. The Stroop effect has been utilized by researchers to explore the nature of automatic and controlled cognitive processes,[4] disturbances in cognition resulting from various psychiatric and/or neurological disorders,[5] the neurocognitive architecture of selective attention,[6] and age-related declines in inhibitory processing.[7] This test has been used in a number of studies and has proved to be sensitive to a variety of factors, including drug effects, particularly drugs acting on central nervous system (CNS), especially those with arousing or dearousing effects.[8-12] It is possible, therefore, that performance change on the interference task after taking the drug is likely to be due to some influence that the drug has on the CNS.

Numerous different Stroop test versions have been developed with tests differing in the number of cards used, color dots or XXX, number of items in each card, number of colors used, paper and pencil task or computerized ones. After Stroop version, the two most used in clinical practice and research are the Dodrill's and Victoria's formats. With the development of computerized versions of the task, two response modes were used. A verbal response mode equivalent to the original version of the task was enabled using voice key device, registering the onset of a verbal response and signaling the computer recording the reaction times (RTs). Along with verbal response mode, manual response mode has become frequently used as well. The task of participants in the manual version of the task is to respond by pressing a predefined key, signaling the color of the stimuli or the meaning of the word. The Stroop-like computerized forms include blocks of incongruent, congruent and neutral trials, using colors, pictures, or words of super-ordinate categories. Because of its short administration time, the Victoria-based Stroop test seems particularly appropriate for use in geriatric populations and with those suffering from dementia and who are prone to fatigue during neuropsychological examination. Considering that computer technologies provide a higher degree of accuracy for the measurement and control of presentation of stimuli in comparison with pencil- and paper-based tests, the current study was undertaken to establish and standardize a simple and reliable computerized Stroop color-word test with the verbal version for assessing CNS effects of drugs. The effects of 5 mg Zolpidem and 500 mg caffeine were tested vs placebo.

MATERIALS AND METHODS

Twenty-four healthy male participants aged 18 to 35 years took part in the study. Following a full medical history (including smoking habits) and physical examination, which included hematological and biochemical screening, and an electrocardiogram, volunteers were excluded if there was any evidence of physical illness or drug abuse. Each subject was approached personally and if they agreed to participate, written informed consent was taken after a full explanation of aims, procedures, and risks of the study. The study was approved by the Institutional Ethics Committee and conducted in conformity with the Declaration of Helsinki. Three sets of practice Stroop color-word test were conducted after the medical examination and prior to the test day to introduce the subjects to the testing procedure and to make them familiar with the testing method. Data acquired in this training session were recorded, but not included

in analysis. Alcohol, nicotine, chocolate, or caffeine containing drinks were prohibited prior to (12 hours for caffeine and nicotine; 24 hours for alcohol) and during the test day. All the recordings were carried out during the early morning between 8:00 to 10:00 AM after a light breakfast. All participants had normal or corrected-to-normal vision and all participants completed formal education ranged from 12 to 14 years.

Apparatus and stimuli

The block diagram of real-time Stroop test assessment system is shown in Figure 1, major instrumentation consisted of stimulus presentation software (SuperLab 4, Cedrus Corporation, San Pedro, CA 90734 - USA) incorporating a dedicated response pad (RB-730 Model) and a separate Signal acquisition module (MP 30, Biopac Systems, Santa Barbara, USA) with a voice recorder, hand switch transducer (TSD116A), and personal computer-based analysis system (BSL Pro software), which captures the participants' response to the stimulus, stimulus onset, and the error response given by investigator to subjects wrong response.

The present computerized Stroop test consists of three parts and is based on the Victoria version. The first part consists of computerized presentation of the names of four colors (yellow, blue, green, and red), written in capital letters, Times New Roman font, size 72, in black. Each word appears six times and the order is semi-random, so that the same word never appears two consecutive times throughout the test. The subject's task is to read each word as quickly as possible. This part of the test is intended to obtain a baseline to evaluate the reading ability and determine whether this ability is high enough so as not to hinder the interference effect.
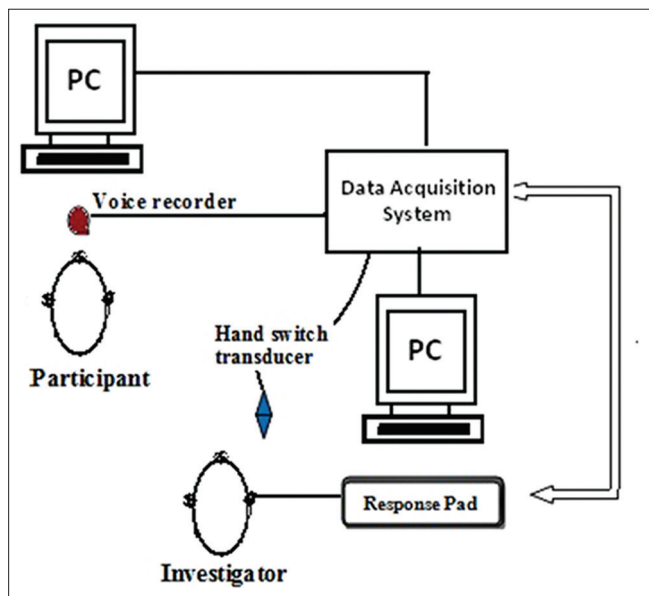

Figure 1: Computerized stroop test diagnostic system

This is because the effect of color-word interference may be absent if the reading ability is lower than expected.

In the second part, 24 colored circles are presented, 6 circles for each of the four colors (yellow, blue, green, and red), distributed semi-randomly. The task is similar to the first part, having to name the color of the circle, to provide a baseline for the analysis of RT in the third part.

In the third part, the circles are replaced by written words, corresponding to the four colors; however, the words are printed in colors that do not correspond to the written word (for example, the word "green" written in red letters). The subject must name the color in which the word is written, ignoring the meaning of the written word.

Test procedure

The Stroop test was administered individually to each participant, taking about 5 minutes, using a computer. The recordings were obtained in a uniformly/adequately lit room, in a noise-free environment with controlled temperature to avoid distraction and increase the comfort level of the subject. At the beginning of the test, participants were told that they would be presented by a series of stimuli printed in colors (yellow, blue, green, and red) and the test is made of three parts, the first one consisting of the reading of words, the second and third ones consisting of naming the colors as quickly as possible. Participants were instructed in each condition to give their verbal response to the stimulus as quickly and as accurately without making errors. The test started with Part-1, and then Part 2, and Part 3 and the order was same for all the participants. When it was clear that the participants understood the entire procedure (particularly Part 3), the test was started with screen instructions. Following the instructions for a task, the stimuli were presented with a key press on the response pad by the experimenter. Each task was followed by a short break of 10 seconds. The experimenter initiated instructions to the next task by pressing the key on the response pad. The participant task was to name the color in which the stimuli were presented by speaking the names aloud (verbal response mode). Their responses are to be as quick and accurate as possible. Each stimulus remained on the screen for 4000 msec or until a response was collected. If there was no response within 4000 msec or response given by the participant was incorrect, that trial was scored as incorrect response with the press of a hand switch by the experimenter and the next trial was generated after a delay of 2-3 seconds by a key press on the response pad by the experimenter. The software records the time of the stimulus onset by a signal triggered by a key press on the response pad by the experimenter. Similarly, the responses of the

participant to the stimulus were co-registered using a microphone attached to the Biopac amplifier. The response latency (the time elapsed between the onset of stimulus presentation and the vocal response) for each stimulus was then extracted using Biopac software looking for a significant change in the co-registered signal. An average of three readings was taken with a brief rest of 2 minutes in between. After each trial, subjects received feedback regarding their responses. In addition, to assess the interday variability and reproducibility of the method, the test was performed in 12 participants at the same time in the morning on two occasions with an interval of 3 days by a single experimenter.

Data analysis

As stated, one of the main goals for the study was to use the response latency (RT) results as a guide in analyzing the data. The software records RT for each stimulus.

RT was measured as the time between stimulus onset and the participant response [Figure 2]. Trials in which the participant's RT, that fell below 250 msec or falling beyond 3000 msec, were considered to be lapses of attention and were eliminated from the analyses.

For the purpose of analyzing RT, four measurements were taken:
a. Mean RT in word reading
b. Mean RT in naming of the color circles
c. Mean RT in naming of the colors of the printed words and
d. Mean color word interference score was calculated by subtracting the average time needed to complete the first two subtasks from the time needed to complete the third subtask (interference score=Sroop III- [(Stroop I + Stroop II)/2].[13]

The error rate was very low; therefore, no analysis was performed on these data (this was true in all parts of the Stroop test). In this study, only the mean color-word interference score was considered, as it reflects most appropriately the mean color-word interference effect.
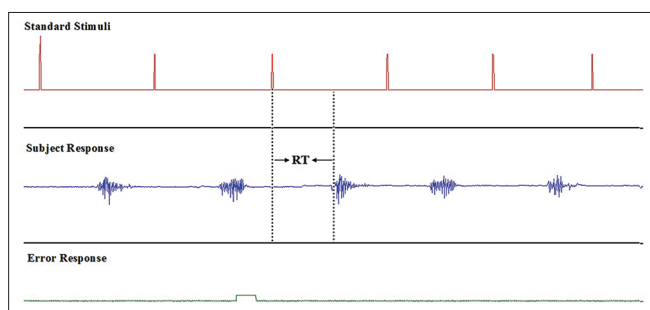
Figure 2: Signal generated by the standard stimuli given by the experimenter, voice response by the subject, error response given by the experimenter to incorrect response

Method validation

Twenty-four healthy male participants aged 20 to 40 years took part in the study after they were trained on the test procedure. The study was performed in a double blind three-way crossover design with subjects randomized to receive either a single oral dose of 5 mg Zolpidem or 500 mg caffeine or matching placebo capsule. The treatments were separated by an interval of one week. Subjects arrived at the laboratory following an overnight fast and abstinence of caffeine containing beverages or alcohol (12 hours for caffeine and nicotine; 24 hours for alcohol), confirmed by a questionnaire at the beginning of the session. The procedure as described earlier for performing computerized Stroop test was carried out during the early morning between 7:00 AM to 11:00 AM after a light breakfast, at 0 hr, 1 hr, 2 hrs, and 3 hrs by a single investigator. Subjects were asked to report any side effects during the study. Drug preparation and administration was done by staff members who did not participate in subject observation or data acquisition. The drug assignments for each subject were prepared by a staff member otherwise not involved in the present study using a randomization program (Statistica: Stat Soft, Inc, USA). After the study, the drug assignments were unblinded for statistical analysis. The data analysis comprised of two sessions, one in which Zolpidem and placebo were compared at 0 hr, 1 hr, 2 hrs, and 3 hrs and a second in which the treatments were Caffeine and placebo at 0 hr, 1 hr, and 3 hrs time points.

Statistical analysis

All statistical tests were processed using graphpad prism software, Version 4. Mean±SEM values were calculated for each variable. Demographic details were summarized for all subjects using descriptive statistics.

The Kolmogorov-Smirnov test was used to assess if data had a normal distribution.

ANOVA for repeated measures were employed for the mean RT to all conditions for which response latency was recorded.

Bland-Altman plotting was performed for the assessment of method validity and reproducibility. The relative (positive or negative) difference between each pair of measurements were plotted against the mean of the pair to make sure that no obvious relation appeared between the estimated values of mean and difference. The Bland-Altman analysis was done to confirm the reproducibility by comparing the RT obtained in each part for two consecutive days. ANOVA for repeated measures (averaged F) with Bonferroni correction was carried out to detect significant changes in variables over time within each session separately. Pair-wise comparisons between the two treatments (Zolpidem

vs Placebo and Caffeine vs Placebo) were tested for statistical significance using the paired Student's *t*-test. Statistical significance was at *P*<0.05.

RESULTS

The equipment was standardized by recording the Stroop RT in 24 healthy male subjects. The mean age of the overall sample was 26.42±3.60 years, with a mean BMI of 23.64±1.20 kg/m^2.

Table 1 summarizes the descriptive statistics for the three conditions studied, in terms of naming time (mean, SEM and coefficient of variation (CV)). ANOVA with repeated measure showed a significant condition effect (F (2,23)=513.1, *P*<0.0001). The subjects were slower to name the colors in the incongruent condition, both compared to the color condition (*t* (2,23) =11.48, *P*<0.001) and the word condition (*t* (2,23) =18.22, *P*<0.001). Naming time of the color was also longer than the word condition (*t* (2,23)=6.74, *P*<0.001).

To study the interday variability, mean RT was recorded to all conditions on two different days by the same observer. The variability was minimal in both the times and the data were highly reproducible with CV below 10%. There was good reproducibility between the difference among the time periods which is shown as Bland Altman Plot in Figure 3 for RT in all tasks of Stroop test respectively. These figures shown as Bland-Altman Plot also clearly show less variation in reproducibility with most of the points lying within Mean±2SD.

Validation results
To confirm the validity of the above method, Zolpidem 5 mg and caffeine 500 mg were used as reference study medication in 24 healthy male individuals. Two subjects due to drowsiness and vomiting in Zolpidem group and two subjects from caffeine group due to gastric irritation were excluded. Data of 20 subjects were analyzed, of which participants were of average height and weight for their age (29.75±3.98 years) and their mean BMI was 22.4±2.6 kg/m^2.

There were no significant differences in baseline characteristics between the three sessions [Table 2].

Effect of Zolpidem on response latency RT and interference score
Results for the outcome measures are depicted in Table 2.

The results of the study showed that Zolpidem significantly increased response latency to all conditions of the computerized Stroop test.

ANOVA performed on the response latency data revealed significant treatment effects on Stroop task condition {word naming: F (3,19)=6.11, *P*=0.01, color naming: F (3,19)=19.02, *P*<0.0001, incongruent color/word naming: F (3,19)=13.92, *P*<0.0001}.

Table 1: Mean response latencies and color word interference score as a function of stroop task condition

	Part-1 (Word naming RT)	Part-2 (Color naming RT)	Part-3 (incongruent color/word naming RT)	Color word interference score
Mean±SEM	553.5±9.27	660.8±10.40	843.3±13.75	236.2±14.57
CV (%)	8.21	7.71	7.99	30.22

RT – Reaction time, CV – Coefficient of variation
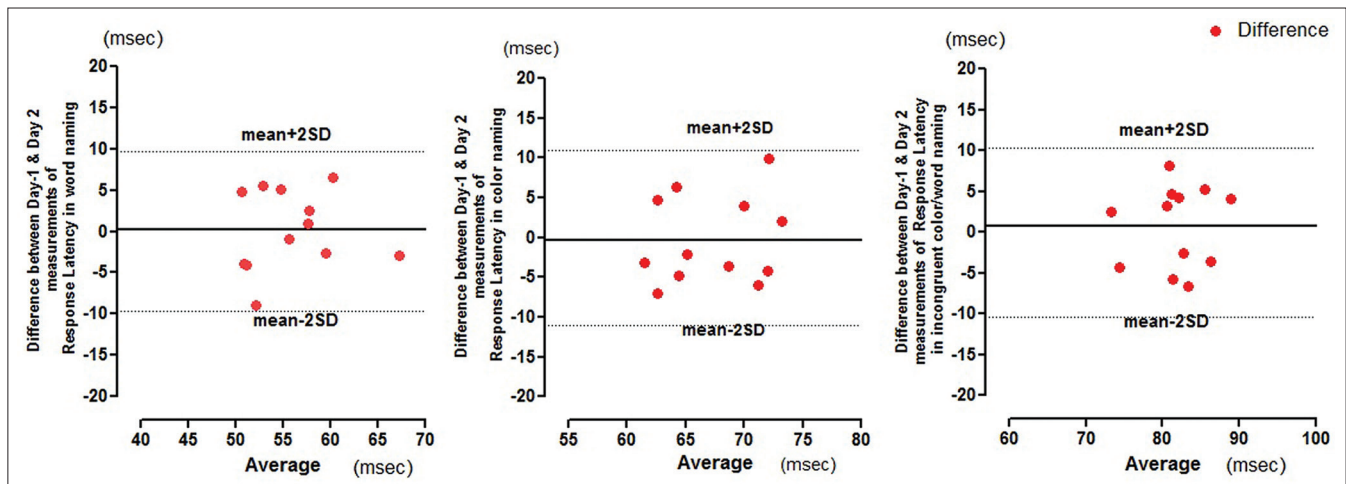
Figure 3: Bland Altman plot showing session 1 and session 2 difference in measurements of stroop color-word test

Table 2: Mean response latencies and color word interference score in the stroop task conditions before and after intake of study medication

	Part-1 (Word naming RT)	Part-2 (Color naming RT)	Part-3 (incongruent color/word naming RT)	Color word interference score
Placebo				
0 hr	599±17.22	669.6±19.43	835.2±22.21	200.9±15.23
1 hrs	599.9±18.2	675.3±16.93	828.3±21.21	190.7±14.82
2 hrs	590.2±17.65	651.5±15.18	819.9±20.84	196.9±17.06
3 hrs	607.0±19.93	671.1±17.02	824.9±19.2	185.8±15.58
Zolpidem				
0 hr	596.2±19.22	657.8±16.23	825.2±19.54	198.2±13.65
1 hrs	631.2±24.62**#	736.4±25.5***##	947.3±40.06***###	263.5±17.02**##
2 hrs	615.4±23.47	701.7±23.44**#	894.7±36.2**#	236.1±19.2
3 hrs	599.9±19.26	674.5±20	853.1±25.79	215.8±15.58
Caffeine				
0 hr	597.3±18.29	667.9±21.98	821±21.63	188.4±13.04
1 hrs	565.7±17.37***##	623.4±19.25***##	754.1±17.01***##	159.4±11.3**#
3 hrs	584.0±21.16	641.3±18.79*	793.2±16.41**	180.6±12.61

Mean values ($\pm$SEM) of 20 participants, *$P<0.05$, **$P<0.01$, ***$P<0.001$ as compared to baseline, #$P<0.05$, ##$P<0.01$, ###$P<0.001$ as compared to placebo; RT – Reaction time

Compared to baseline, a significant effect was observed for word naming at 1 hr (t (3,19)=3.82, $P<0.01$). No significant effect was noticed at 2 hrs and 3 hrs.

In case of color naming, a significant effect was observed at 1 hrs (t (3,19)=7.05, $P<0.001$) and 2 hrs (t (3,19)=3.94, $P<0.01$); however, no effect was noticed at 3 hrs. Similarly, a significant effect was observed for incongruent color/word naming at 1 hr (t (3,19)=6.06, $P<0.001$) and 2 hrs (t (3,19)=3.44, $P<0.01$); however, no significant effect was noticed at 3 hrs.

Specific time points at which significant Zolpidem vs placebo differences occurred were identified by two-tailed paired t-tests. Word naming RT differed significantly at 1 hr (t=2.44, df 19, $P<0.05$) only. In case of color naming, RT decreased significantly at 1 hr (t=3.33, df 19, $P<0.01$) and at 2 hrs (t=2.64, df 19, $P<0.05$).

Similarly, incongruent color/word naming RT differed significantly at 1 hr (t=4.38, df 19, $P<0.01$), and 2 hrs (t=2.54, df 19, $P<0.05$) only.

ANOVA-detected Zolpidem induced significant increase in the interference score (F (3,19)=5.67, $P<0.01$). A significant increase in the interference score was observed at 1 hr only compared to baseline (t (3,19)= 3.92, df 19, $P<0.01$). Compared to placebo, a significant increase in the interference score was observed at 1 hr (t=3.52, df 19, $P<0.01$) only. The latter results did not reach any statistical significance [Figure 4].

Effect of Caffeine on response latency RT and interference score
Results for the outcome measures are depicted in Table 2.
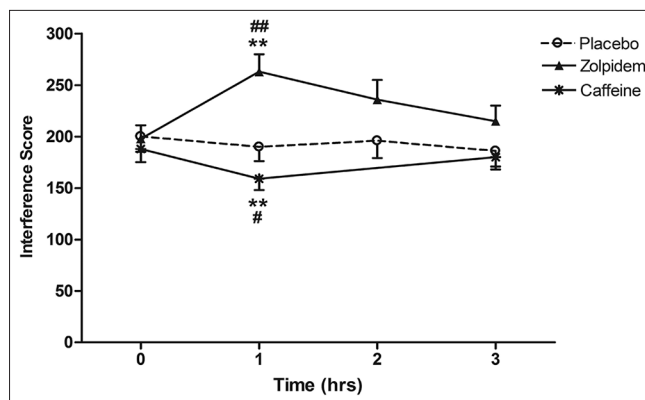
Figure 4: Color word interference score before and after oral intake of Study Medicament. **$P<0.01$, as compared to baseline. #$P<0.05$, ##$P<0.01$, as compared to placebo

Caffeine significantly decreased response latency to all conditions of the computerized Stroop test. ANOVA performed on the response latency data revealed significant treatment effects on Stroop task condition {word naming: F (2,19)=13.05, $P<0.0001$, color naming: F (2,19)=12.85, $P<0.0001$, incongruent color/word naming F (2, 19)=31.94, $P<0.0001$}.

Compared to baseline, a significant effect was observed for word naming at 1 hr (t (2,19)=5.08, $P<0.001$). No effect was noticed at 3 hrs.

Similarly, a significant effect was observed in case of color naming at 1 hr (t (2, 19)=5.03, $P<0.001$) and 3 hrs (t (2,19)=4.46, $P<0.001$).

A significant effect was observed for incongruent color/word naming at 1 hr (t (2,19)=7.95, $P<0.001$) and 3 hrs (t (2,19)=3.31, $P<0.01$).

Specific time points at which significant caffeine vs placebo differences occurred were identified by two-tailed paired *t*-tests. RT decreased significantly in all tasks of Stroop test at 1 hr only, word naming RT (t=3.62, df 19, P<0.01), color naming RT (t=2.99, df 19, P<0.01). Similarly, incongruent color/word naming RT (t=3.62, df 19, P<0.01).

ANOVA-detected caffeine induced significant decrease in the interference score (F $(2,19)$=5.61, P<0.01). A significant decrease in the interference score was observed at 1 hr only compared to baseline (t=3.24, df 19, P<0.01).

Compared to placebo, a significant decrease in the interference score was observed at 1 hr (t=2.22, df 19, P=0.04) only. The latter results did not reach any statistical significance [Figure 4].

DISCUSSION

Many researchers report that chronic use of psychoactive substances is associated with widespread deficits in neuropsychological function.[14] Deficits are pronounced in the executive domain including decision-making, response inhibition, planning and working memory. These deficits may be associated with prefrontal cortex dysfunction and their extent and nature is likely to depend on the substance of abuse. A variety of experimental methods like Rule Shift Cards Test, the Trail Making Test, Continuous Performance Test, Gottschaldt Shuffled Figures Test, the Odd Man Out Test, and the Stroop Test, which measure cognitive flexibility and inhibitory control in healthy human participants and patients, have been reported in medical literature.

At present, due to development of technology, computerized neurocognitive tests may be appropriate in new and developing fields of psychological testing. One such method is computerized application of the Stroop color-word test which provides a great advantage to the analysis of time measurements, as it allows precise recording of RT in thousandths of a second, increasing its sensitivity. Furthermore, computerization improves standardization of the conditions for presenting the stimuli and collecting responses, allowing greater rigor in the control of the conditions for the evaluation, making the test a more trustworthy resource for neuropsychological evaluation.

The purpose of the present study was to further develop a simple computerized Stroop test measure, which is most sensitive and specific to changes in sustained human performance. Although previous attempts at developing a neurophysiological measure of sustained human performance have produced solutions that have better informed research on the sustained attention process, such solutions have typically possessed a number of technical limitations that have reduced their usefulness, particularly as clinical diagnostic tool. The results of the present study provides evidence for the validity of the computerized Stroop measure that is more sensitive and specific to changes in sustained human performance.

The normative values for the Stroop tasks (word naming, color naming, and incongruent color/word naming), that were collected from 24 healthy subjects, was found to be reliable and accurate. These results are in line with previous studies, i.e., naming times on the Stroop task systematically increased from the color through the word and finally to the incongruent condition. This is the classical pattern found on the Stroop tasks both with adults, adolescents, and children.[15] These results are explained in terms of the difficulty of inhibiting a pre-potent over-learned response (reading), in favor of naming the color the word is printed in, a much less automatic response.[16]

A review of the extensive literature concerning the mechanisms underlying Stroop performance is clearly beyond the scope of this article.[17] Early explanations of Stroop interference usually embodied the idea of a race between the color code and word code to reach an output selection stage. Because word reading is faster than color naming, the word information arrives at the response buffer before the color information and thus competes with the color for output. However, explanations only in terms of the difference in speed between word reading and color naming are now viewed as inadequate in light of studies that have manipulated the relative speed and practice for the relevant and irrelevant dimensions of the stimulus.[18,19]

In the present study, the data obtained for response latencies for the Stroop tasks (word naming, color naming, and incongruent color/word naming) on two alternate days was to evaluate the reproducibility of the computerized Stroop model. The test was carried by a single experimenter, which was highly reproducible with CV less than 10%.

To test the sensitivity, reproducibility, and predictability of the present method, we investigated the effect of Zolpidem (5 mg) and caffeine (500 mg) in healthy human subjects. Computerized Stroop test was recorded frequently to provide a measure of the time course of drug action. Peak effects were seen between 1 to 2 hours for both drugs with the onset of action being 1 hr after drug intake.

The Stroop color-word test appears to be especially sensitive to drug effects,[8-12,20-28] as indicated by previous work and Zolpidem and caffeine may affect any of a number of cognitive skills used on such a complex task as the Stroop color-word test. Arnett *et al.*[29] suggest that such skills include "selective, sustained, or divided attention; working or long-term memory; or speed of information-processing." However, the selective attention task used in the present study, i.e., the Stroop color-word test showed significant effect of Zolpidem and caffeine. Compared to placebo, we found that acute administration of a low dose of zolpidem (5 mg) induces a significant increase in RT latencies of Stroop task and interference score, whereas caffeine showed a significant decrease in RT latencies and interference score in computerized Stroop test. For the interference score, the more negative the score, the greater the interference effect, that is the lower the capacity to respond quickly and correctly to a target stimulus (i.e. the color in which the word was presented) in the presence of distracting stimulus (i.e., written word that names a color).

A similar effect was shown by Desager JP *et al.*[20] in which Zolpidem (20 mg) produced increase in RT latencies up to 3 hours after drug intake in Stroop test. The effect of benzodiazepines on Stroop interference demonstrated a variety of results. Boulenger *et al.*[21] also found no effects of diazepam on Stroop interference. They tested 12 young, healthy volunteers, all women, with single doses (10 mg) of diazepam, buspirone (a nonbenzodiazepine that lacks anticonvulsant and muscle-relaxant properties and interacts minimally with CNS depressants), and placebo. Drugs were administered to individual subjects in random orders at 1- or 2-week intervals between administrations. None of the drug seemed to have an effect on Stroop interference. Griffiths *et al.*[22] studied effects of three benzodiazepines (flurazepam, lormetazepam, and triazolam) and one nonbenzodiazepine, zopiclone. The four drugs and a placebo were administered in a random order, with 7-day intervals between drugs, to 10 young male volunteers. Subjects were tested several times after each drug ingestion (0, 1, 4, or 10 hours). The authors computed an unusual measure of interference, which was the difference between the incongruent and the neutral conditions divided by time to read color names in black. They found a significant interaction between time after drug ingestion and drug type but noted that "despite this interaction being significant there were no significant differences between any of the treatments and placebo."

Studies on the effects of stimulants on Stroop interference have yielded somewhat inconsistent results. As to nicotine, both a decreasing effect[23] as well as no (clear) effects have been reported.[12,24] The same holds for methamphetamine[23] while the one study on ephedrine found no effect.[25] Results from caffeine studies using the Stroop color-word test have been mixed, with caffeine resulting in improvement,[10,26,27] hindrance,[9] or no significant effect on performance.[28] However, Foreman *et al.*[9] found caffeine to actually increase Stroop interference, Hasenfratz and Battig[10] reported a reducing effect. Although task parameters were highly comparable across the two studies, there were clear differences with respect to more general aspects of the procedure.

Foreman *et al.*[9] gave subjects 125 or 250 mg caffeine, or placebo, and reported that the higher dose of caffeine significantly increased the magnitude of the Stroop effect in a numerical version of the task, compared to placebo. It was suggested that this apparently clear finding is in contrast to the variability seen in much of the previous work on the cognitive effects of caffeine, may be explained by the demanding nature of the Stroop task, involving the processing of ambiguous or confusing stimuli, which may make it particularly sensitive to high levels of caffeine. Unfortunately, however, because only difference scores for performance in the neutral condition and the confusing Stroop condition were given, it is impossible to evaluate whether the observed differences in Stroop effect magnitude were due primarily to differences in performance in the confusing Stroop condition or in the neutral condition. However, Hasenfratz and Battig[10] contradicted the findings of Foreman *et al*. They included four groups in their experiment – 250 mg caffeine only, smoking only, caffeine plus smoking, and control-in a numerical version of the task. They reported that when the interval between the presentations of successive Stroop stimuli was 1 sec, the treatments, when compared to control, had no effect on the general Stroop performance improvements observed between pretreatment and post-treatment testing. When the inter-stimulus interval was 0 sec, the improvements observed in post-treatment testing compared to pretreatment testing were significantly greater in subjects in the smoking-only and caffeine-only groups than in the control group, although there was no difference between control and the smoking plus caffeine group. These results corroborate the interference effect on RT in the Stroop Test as a valid measurement to discriminate between groups with and without treatment.

A number of factors should also be investigated in greater detail, because, according to the literature, many external variables may interfere in the evaluation of results, such as type of school, age, sex, the use of medication, and comorbidity, among others. It is important to study, as well, the intrinsic characteristics of each version of the Stroop Test. In the current version, for example, presentation is computerized, so

each stimulus is presented isolated on the screen, and the next stimulus is only presented after the participant has responded to the previous stimulus. This eliminates interference from the distraction of presenting various stimuli simultaneously, as occurs, for example, in the Regard[30] pencil-and-paper version. If, on one hand, this eliminates interference from distraction, on the other hand, it restricts the possibility of erroneous responses, and increases RT.

CONCLUSION

Attention is one of the therapeutic areas of greatest clinical need where there are few existing therapies and have the least well-validated models or surrogate markers. The present study investigated the sensitivity of a computerized Stroop color-word test to drug-induced effect on attention function in healthy subjects. This study showed reproducible data in healthy volunteers with some subtle differences. This Computerized Stroop Test, which is sensitive and specific to changes in sustained human performance, may be a very good alternative approach for testing of drugs in healthy subjects and in patients who do not respond to conventional paper-based methods.

ACKNOWLEDGMENT

REFERENCES

1. Gazzaniga MS, Ivry RB, Mangun GR. Cognitive neuroscience: The biology of the mind. New York: W. W. Norton and Company; 2002.
2. Spieler DH, Balota DA, Faust ME. Stroop performance in healthy younger and older adults and in individuals with dementia of the Alzheimer's type. J Exp Psychol 1996;22:461-79.
3. Dempster FN. The rise and fall of the inhibitory mechanism: Toward a unifield theory of cognitive development and aging. Dev Rev 1992;12:45-75.
4. Henik A. Paying attention to the Stroop effect ? J Int Neuropsychol Soc 1996;2:467-70.
5. Rafal R, Henik A. The neurology of inhibition: Integrating controlled and automatic processes, In: Dagenbach D, Carr TH, editors. Inhibitory Processes in Attention, Memory, and Language. San Diego: Academic Press; 1994. p. 1-52.
6. Rebai M, Bernard C, Lannou J. The Stroop's test evokes a negative brain potential, the N400. Int J Neurosci 1997;91:85-94.
7. West R, Alain C. Age-related decline in inhibitory control contributes to the increased Stroop effect in older adults. Psychophysiology 2000;37:179-89.
8. Harvey PG, Clayton AB, Betts TA. The effects of two antidepressant agents on performance on the Stroop color word test in normal male volunteer subjects. Br J Clin Pharmacol 1978;5:305-12.
9. Foreman N, Barraclough S, Moore C, Mehta A, Madon M. High doses of caffeine impair performance of a numerical version of the Stroop task in men, Pharmacol Biochem Behav 1989;32:399-403.
10. Hasenfratz M, Battig K. Action profiles of smoking and caffeine: Stroop effect, EEG, and peripheral physiology. Pharmacol Biochem Behav 1992;42:155-61.
11. Parrott A, Wesnes K. Promethazine, scopolamine and cinnarizine: Comparative time course of psychological performance effects. Psychopharmacology 1987;92:513-9.
12. Wesnes K, Revell A. The separate and combined effects of scopolamine and nicotine on human information processing. Psychopharmacology 1984;84:5-11.
13. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Stroop Color-Word Test- Influence of Age, Sex and education; and normative data for a large sample across the adult age range. Assessments 2006;13:67-79.
14. Rogers RD, Robbins TW. Investigating the neurocognitive deficits associated with chronic drug misuse. Curr Opin Neurobiol 2001;11:250-7.
15. Comalli PE Jr, Wapner S, Werner H. Interference effects of Stroop color-word test in childhood, adulthood and ageing. J Gen Psychol 1962;100:47-53.
16. Spreen O, Strauss E. A compendium of neuropsychological tests. New York: Oxford University Press; 1998.
17. Dyer FN. The Stroop phenomenon and its use in the study of perceptual, cognitive, and response processes. Mem Cogn 1973;1:106-20.
18. Dunbar K, MacLeod CM. A horse race of a different color: Stroop interference patterns with transformed words. J Exp Psychol 1984;10:622-39.
19. MacLeod CM, Dunbar K. Training and stroop-like interference: Evidence for a continuum of automaticity. J Exp Psychol Learn Mem Cogn 1988;14:126-35.
20. Desager JP, Hulhoven R, Harvengt C, Hermann P, Guillet P, Thiercelin JF. Possible interactions between zolpidem, a new sleep inducer and chlorpromazine, a phenothiazine neuroleptic. Psychopharmacology 1988;96:63-6.
21. Boulenger JP, Squillace K, Simon P, Herrou M, Leymarie P, Zarifian E. Buspirone and diazepam: Comparison of subjective, psychomotor and biological effects. Neuropsychobiology 1989;22:83-9.
22. Griffiths AN, Jones DM, Richens A. Zopiclone produces effects on human performance similar to flurazepam, lormetazepam and triazolam. Br J Clin Pharmacol 1986;21:647-53.
23. Jensen AR, Rohwer WD. The Stroop color word task: A review. Acta Psychol 1966;25:36-93.
24. Provost SC, Woodward R. Effects of nicotine gum on repeated administration of the Stroop test. Psychopharmacology 1991;104:536-40.
25. Mair RG, McEntee WJ. Cognitive enhancement in Korsakoff'spsychosis by clonidine: A comparison with L-dopa and ephedrine. Psychopharmacology 1986;88:374-80.
26. Kenemans JL, Wieleman JS, Zeegers M, Verbaten MN. Caffeine and stroop interference. Pharmacol Biochem Behav 1999;63:589-98.
27. Patat A, Rosenzweig P, Enslen M, Trocherie S, Miget N, Bozon MC, *et al*. Effects of a new slow release formulation of caffeine on EEG, psychomotor and cognitive functions in sleep-deprived subjects. Hum Psychopharmacol 2000;15:153-70.
28. Edwards S, Brice C, Craig C, Penri-Jones R. Effects of

caffeine, practice, and mode of presentation on Stroop task performance. Pharmacol Biochem Behav 1996;54:309-15.

29. Arnett PA, Rao SM, Bemardin MS, Grafman J, Yetkin FZ, Lobeck L. Relationship between frontal lobe lesions and Wisconsin Card Sorting Test performance in patients with multiple sclerosis. Neurology 1994;44:420-5.

30. Regard M. Cognitive rigidity and flexibility: A neuropsychological study. In: Spreen O, Strauss E, editors. A compendium of neuropsychological tests. Oxford, MA: Oxford University Press; 1998.

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