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Effect of Caffeine, Gender, and Time of Day on Working Memory in Medical Students

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ABSTRACT

This study investigates the effects of caffeine on working memory in medical students. Furthermore, the study determines whether an effect of caffeine could be attributed to differences in the gender of participants and the time of day that the tests were taken. The study was based on the administration of 200mg of caffeine or placebo given to the participants and their results on verbal, auditory, and both verbal and auditory digit span tests were recorded and analyzed. The tests were given in two separate trials, one in the morning between 07:00 hours (h) and 08:15h and one in the afternoon between 15:00h and 16:15h. Analysis of the data revealed that for the morning trial, while 200mg dose of caffeine had no effect on male test scores when compared to the test scores of males taking the placebo, female subjects taking placebo recorded significantly ($P<0.05$) longer scores across each of the three tests as compared to the tests scores of caffeine exposed females. In the afternoon trial, while 200mg dose of caffeine had no effect on male test scores when compared to the test scores of males taking the placebo during individual audio and visual tests, females taking 200mg dose of caffeine similarly had no significant difference ($P>0.05$) in test scores when compared to females on placebo in all tests. This study thus reveals statistically significant results in the digit span test between gender and time of day trials.

Keywords: Caffeine; Memory; Digit Span Test; Gender; Time of Day

Introduction

Numerous studies have looked at psychopharmacological and electrophysiological effects of caffeine on the human brain and heart [1-4]. Effects of caffeine in humans have been found to enhance mental performance, alertness, and mood especially when subjects are fatigued [5-7]. However, many variations exist in literature among the subjects assessed and results achieved. Firstly, some studies show that, in free recall tasks, caffeine either has no effect [8-11], a beneficial effect on cognition and memory [12-14] or can impair performance in tasks involving working memory [8].. Studies have attributed these differences in cognition to variations of mental performance in response to caffeine between the methods used in testing short term memory, the amount of caffeine given, sex and age of participants as well as the time of day for testing [15,16]. First, when testing the effect of caffeine on short-term memory, a discrepancy exists among research studies. In 1958, Kirchner conducted an experiment to measure very short-term retention in younger and older Ss utilizing a visual display involving a rapidly moving light; the results indicated that older Ss slumped in performance, make more errors of omission and more random responses much sooner than younger Ss, in both relative and absolute terms; thus indicating the inability to organize incoming and outgoing information as rapidly as the younger Ss [17]. Since then, other studies in the past have used multiple variations of memory tasks, causing a large percentage of previous data on short-term memory to be incomparable [18-20]. Repovs and Baddeley have established a working theory for a multi-component model of working memory [21].

They define working memory as being composed of three aspects: a phonological loop, visuospatial sketchpad, and a multimodal store, the episodic buffer which allows integration of short term and long-term memory. This article proposes the testing of all aspects of short-term memory defined by Repovs and Baddeley [21], through the integration of a visual, auditory, and combined audio and visual digit span test, which has been established as one of the most accurate tests in predicting working memory progress [22]. Second, a wide range of research has been performed to determine a concentration of caffeine for studies that best mimic natural caffeine levels consumed by most of the regular population. Cheng and colleagues have determined that caffeine levels between 70mg to 300mg show a significant decrease in the clearance of caffeine as the dose increases; thus, indicating saturable caffeine metabolism in the dose range tested [23]. Also, around 150mg-200mg of caffeine has been found to imitate moderate caffeine intake by subjects, the majority of whom consume around three cups of coffee per day [24]. This study, therefore, proposes to use 200mg of caffeine, in a one-tablet dose, which best reenacts natural conditions for subjects. To achieve the full influence of the caffeine dose, it is also proposed that subjects wait 30 minutes, since between 15 minutes to 120 minutes caffeine shows an effect in humans [25].

Additionally, studies in the past have proven that sex and age of participants have varying results, with females and males performing at different scales from each other depending on the amount of caffeine given, time of the study, and type of test used [26]. Furthermore, differences in the age of participants have also shown variable results, with subjects over the age of fifty found to be more sensitive to the objective effects of caffeine when compared with individuals below 50 years of age [9]. Due to such variation in participant qualities, this study proposed to maintain a separate comparison between the effects of caffeine in males and females and to use subjects below 50 years of age, to eliminate discrepancies and allow for more accurate comparisons between groups. Lastly, as discussed by Ryan and colleagues, caffeine can have a different effect on individuals if the memory task is performed in the morning versus the afternoon [14]. The performance depends on numerous obstacles, such as whether the participant is a morning person or whether their natural decline in function that accompanies the afternoon overlies the time frame for the mental assessment. It is thus proposed for this research that we conduct two trials, one in the morning and one in the afternoon to account for individual differences in performance on the memory tests.

Methods

Study Design

We conducted two randomized double-blind trials lasting one week in duration (one in the morning and one in the afternoon) involving healthy participants at the St. James School of Medicine. Each participant consented to participate and was compensated for participation. The study protocol was approved by the institutional review board. The authors vouch for the fidelity of this report and the accuracy and completeness of the data and the analyses.

Study Procedure

Before the first round of testing, each participant completed a survey recording their age, sex, race, the average duration of sleep per night, and average caffeine use in a normal week. Eighty-one participants (40 in the morning trial and 41 in the afternoon trial) were randomly assigned into groups receiving caffeine (one 4 everfit 200mg tablets) and groups receiving placebo (one 400IU tablet of Nature's Bounty vitamin D). Each day during the study, the participants were given a pill with water then asked to wait for a half-hour to allow the contents to be absorbed. After the half-hour waiting period, each subject was administered three-digit span tests (auditory stimulus, visual stimulus, and both auditory and visual stimuli) via a computer program design for this study. This process was repeated every day for the duration of the study. Their results were recorded by the program and analyzed at the end of the study using Microsoft Excel.

Program Specifics

A program was created to present the digit span test to the participants; results were collected and maintained consistently with the use of Microsoft Visual Studio 2010 Visual Basic Net and Microsoft Excel software. The software runs using Windows 7 32-bit operating system. The volume of the PC is set by the user before the trial began and is not controlled by the program other than to either use or not to use an auditory presentation. The visual presentation of the integers is displayed in a black background and a white foreground with a 14-point Times New Roman font. The window completely covered the screen of the monitor to reduce distractions. The generated number is displayed in the center of the screen for one second and removed before the next number is generated and presented. When an auditory presentation is selected, a soft feminine voice announces the generated number in English with the annunciation of each number lasting one second. If both an auditory and visual presentation is selected the number is displayed and announced at the same time. Each number in the series is presented in the same manner for the duration of the trial. Each integer is presented separately in one-second intervals beginning with a minimum series of three integers for three seconds. After the last integer is presented, the program clears the screen and displays a new screen with instructions for the subject to enter the numbers just revealed into the response box in the order in which the integers were presented. There is no time limit to enter the values into the response box.

The test subject must press the enter key when the last number is entered into the response box. The program will store in a database the series of integers presented, the test subject's responses, and the results of the comparison of the generated series to the test subject's entered values. If the response is the same as the generated series the program will increase the series of integers to present to the subject in the next round by one integer. If the response differs, the program will in the next series give the test subject another attempt at the current number of generated integers in a series (up to a maximum of two attempts). After the second attempt at the designated number of integers in a series, the program decreases the series length by one integer until the minimum number of integers to display to the test subject in the series is reached (currently the minimum series length is three integers). The program will present a total of fourteen series of numbers and after each series, it determines and store the results for that test subject. After each completed trail the total number of correct responses and the maximum length of integers presented for a correct response is recorded for each test subject.

Statistical Analysis

We estimated that our sample of eighty-one participants would provide 95% power to detect a significant difference for the primary endpoint at a two-sided significance level of 0.05, assuming a normal distribution.

Analyses were performed on each data set and differences between the treatment groups were evaluated with the use of a two-tailed unpaired uneven variant student t-test. All reported P values are two-sided; a P-value of 0.05 or less was considered to indicate statistical significance. All analysis was done using Microsoft Excel.

Results

(Table 1 & Figure 1) shows the mean raw scores for digit span tests and the mean longest recorded test score with p-value, respectively. (Figures 2 & 3) show the graphic presentation of caffeine trial in the morning and afternoon, respectively. (Figure 4) shows a graphical presentation of the time frame and gender against p-value. (Figures 5-8) show the Histograms demonstrating the frequency of the longest recorded scores for caffeinated and placebo males and females in the morning and afternoon sessions, respectively.

Table 1: Mean raw scores for digit span tests.

Time of Day	Sex	Test Type	Caffeine			Placebo		
			Mean	SD	p-value	Mean	SD	p-value
Morning	Male	Audio	8.34	1.06	0.006	8.6	1.39	0.478
		Visual	8.46	1.01	8.37×10^{-3}	8.6	1.39	0.69
		Audio/Visual	8.6	0.91	0.052	8.75	1.12	0.613
	Female	Audio	7.53	1.22	5.63×10^{-4}	8.62	1.2	0.954
		Visual	7.73	1.11	3.02×10^{-3}	8.59	1.16	0.988
		Audio/Visual	8.13	0.97	0.019	8.75	1.17	1
Afternoon	Male	Audio	8.12	1.34	0.352	8.34	1.22	3.42×10^{-2}
		Visual	7.23	1.42	0.17	7.59	1.26	4.73×10^{-2}
		Audio/Visual	7.7	1.33	2.58×10^{-2}	8.28	1.31	1.21×10^{-2}
	Female	Audio	7.8	1.39	0.934	7.82	1.38	6.31×10^{-3}
		Visual	6.92	1.22	0.546	7.07	1.51	2.78×10^{-2}
		Audio/Visual	7.49	1.25	0.498	7.65	1.28	1.43×10^{-2}

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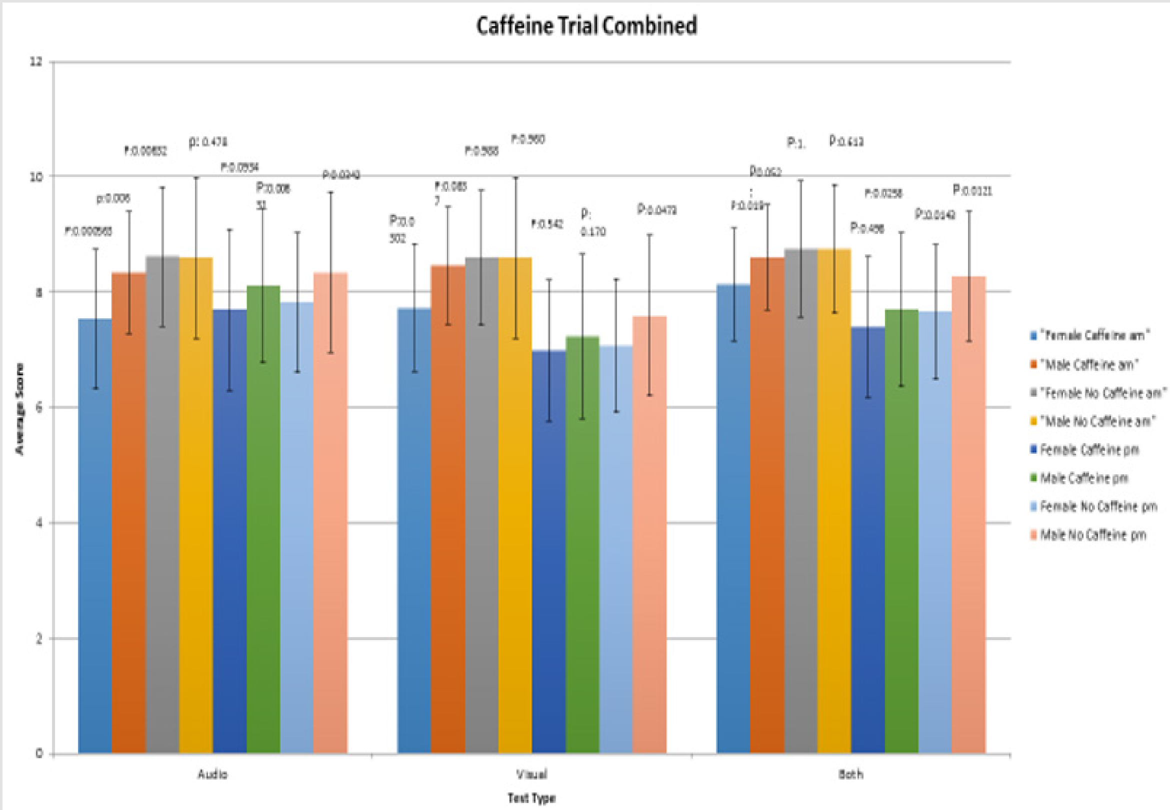


Figure 1: Mean longest recorded test scores showing comparison Morning (am) versus Afternoon (pm) trial with the p-values. Error bars are representative of the standard deviation.

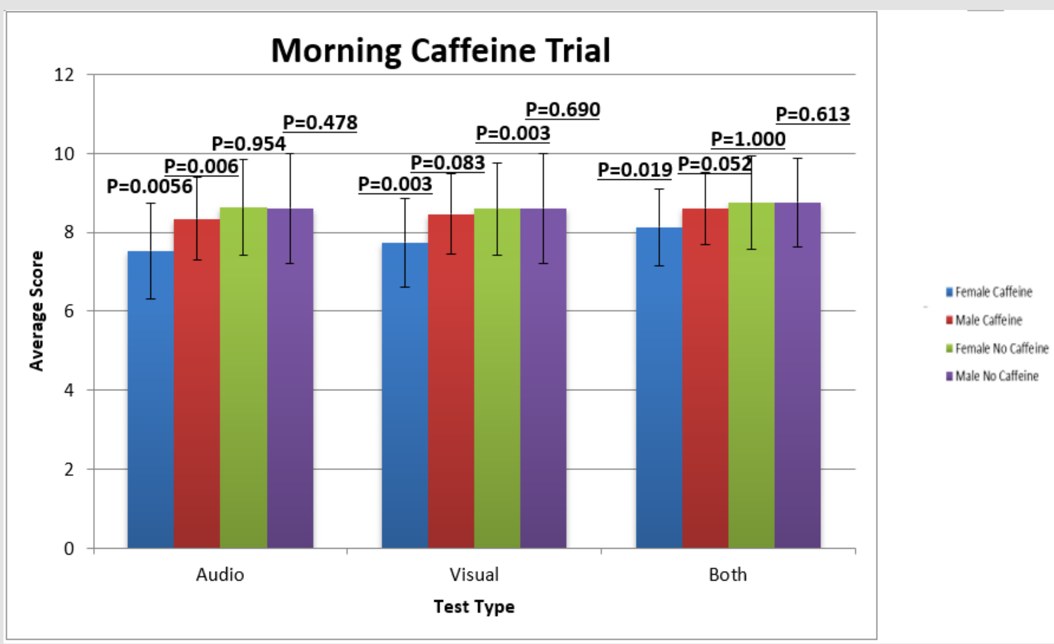


Figure 2: Graphic presentation showing 200mg dose of caffeine has no effect on male test scores when compared to the test scores of males taking the placebo (No caffeine); also showing female subjects taking placebo (No caffeine) having significantly longer scores across each of the three tests as compared to the tests scores of caffeine exposed females, and lastly caffeinated males performing significantly better during the individual audio and visual tests than caffeinated females in the morning trial.

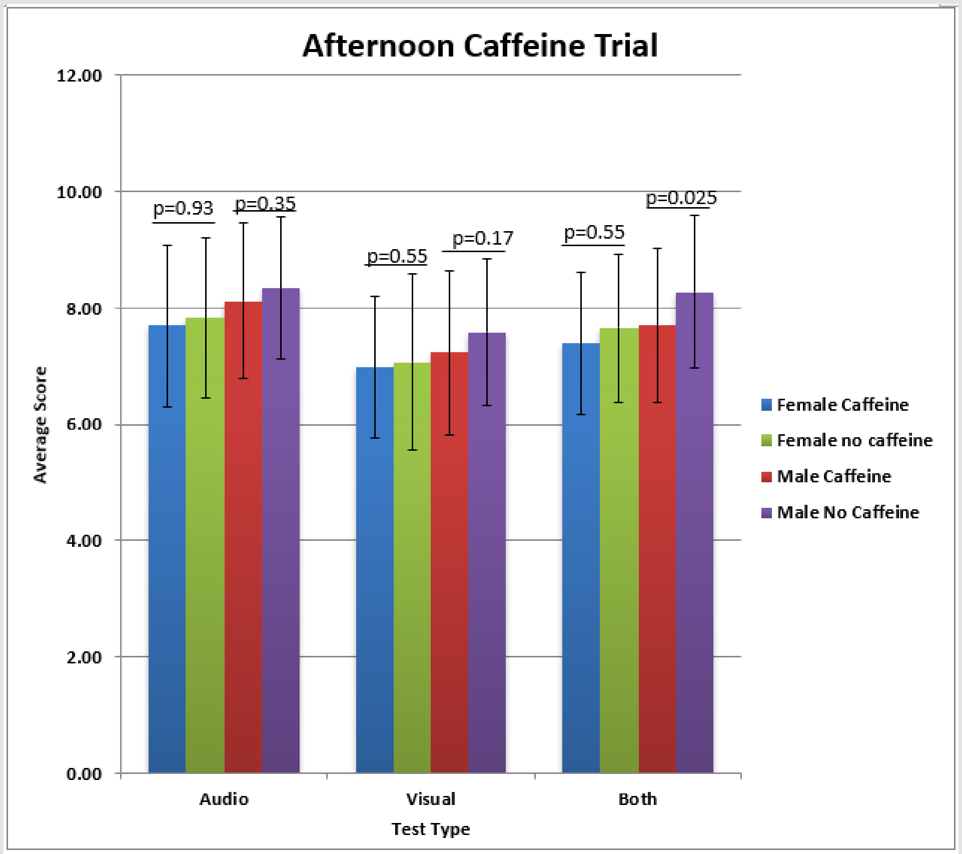
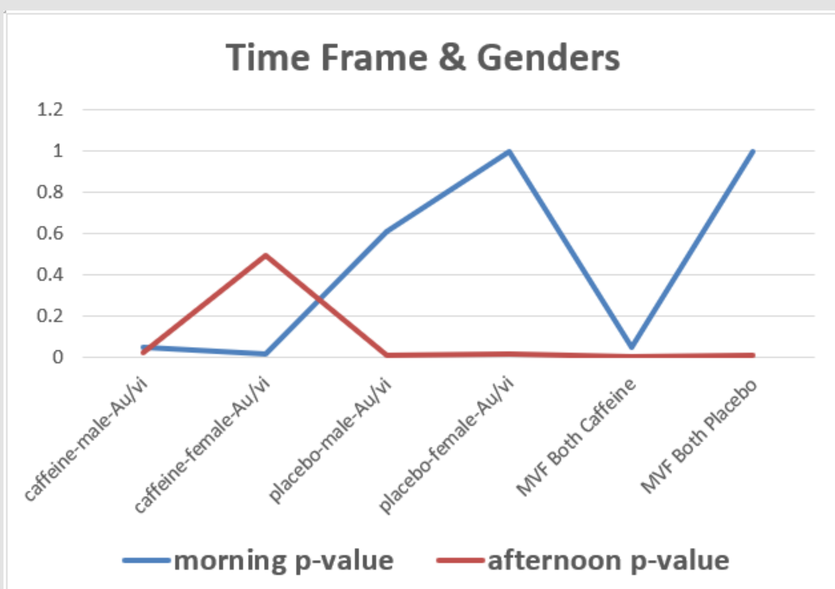


Figure 3: Graphic presentation with p-value showing the effect of 200mg dose of caffeine on male and female test scores compared with placebo (No caffeine) in the afternoon trial.



Note: AU: audio; VI: visual; MVF: male versus female.

Figure 4: Graphic presentation of the time frame and gender against p-values

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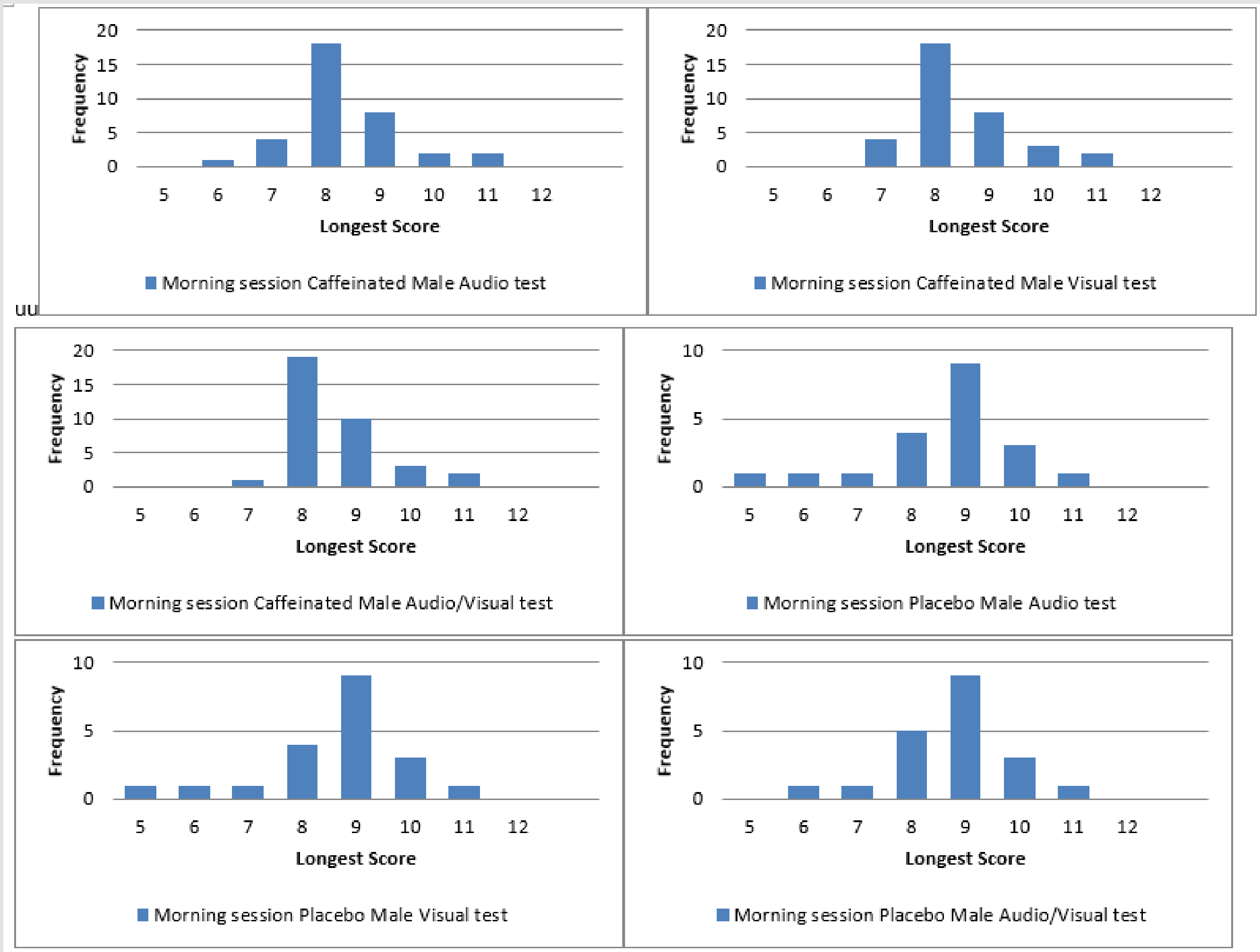

Figure 5: Histograms demonstrating frequency of longest recorded scores for caffeinated and placebo males in the morning session.

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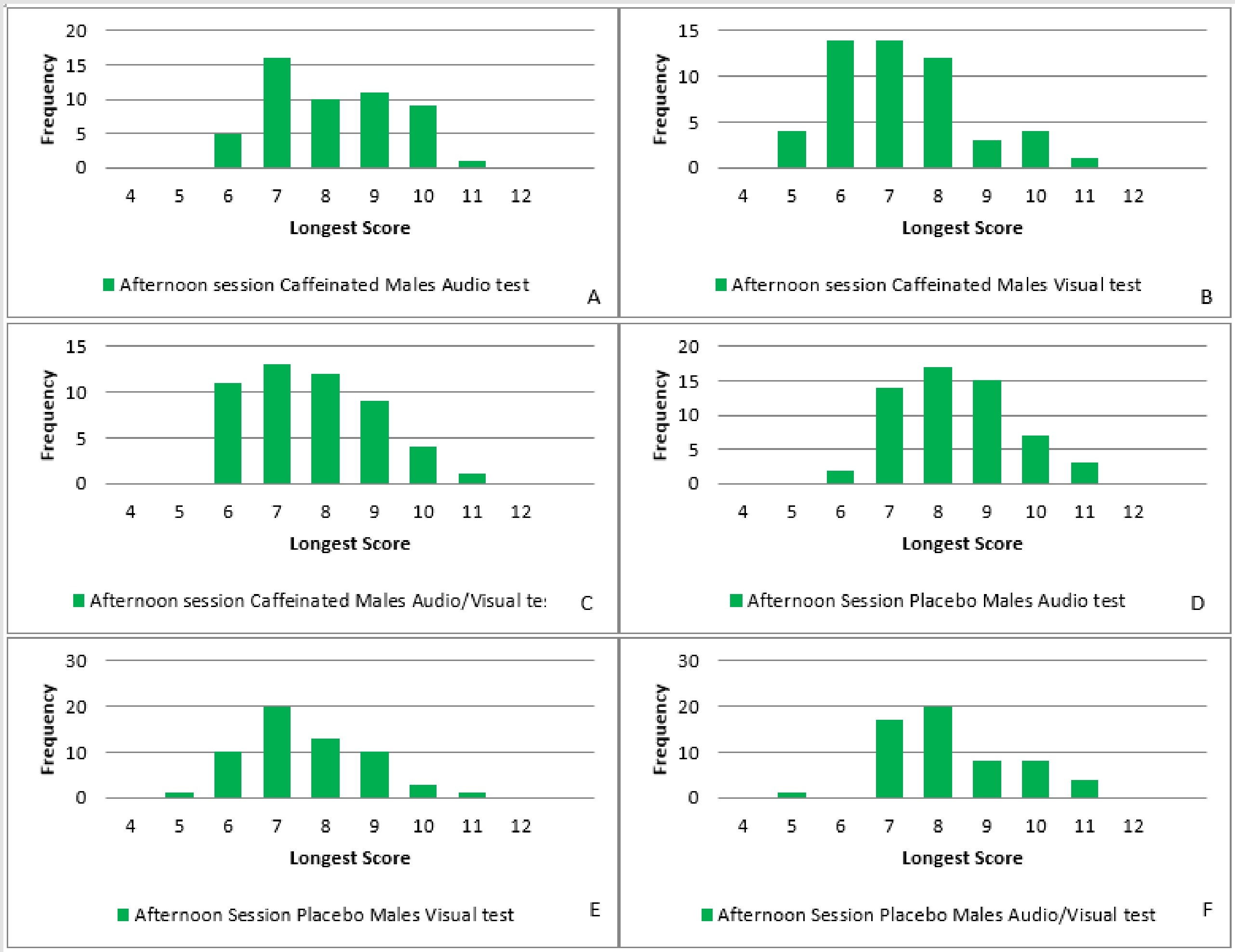

Figure 6: Histograms demonstrating frequency of longest recorded scores for caffeinated and placebo males in the afternoon session.

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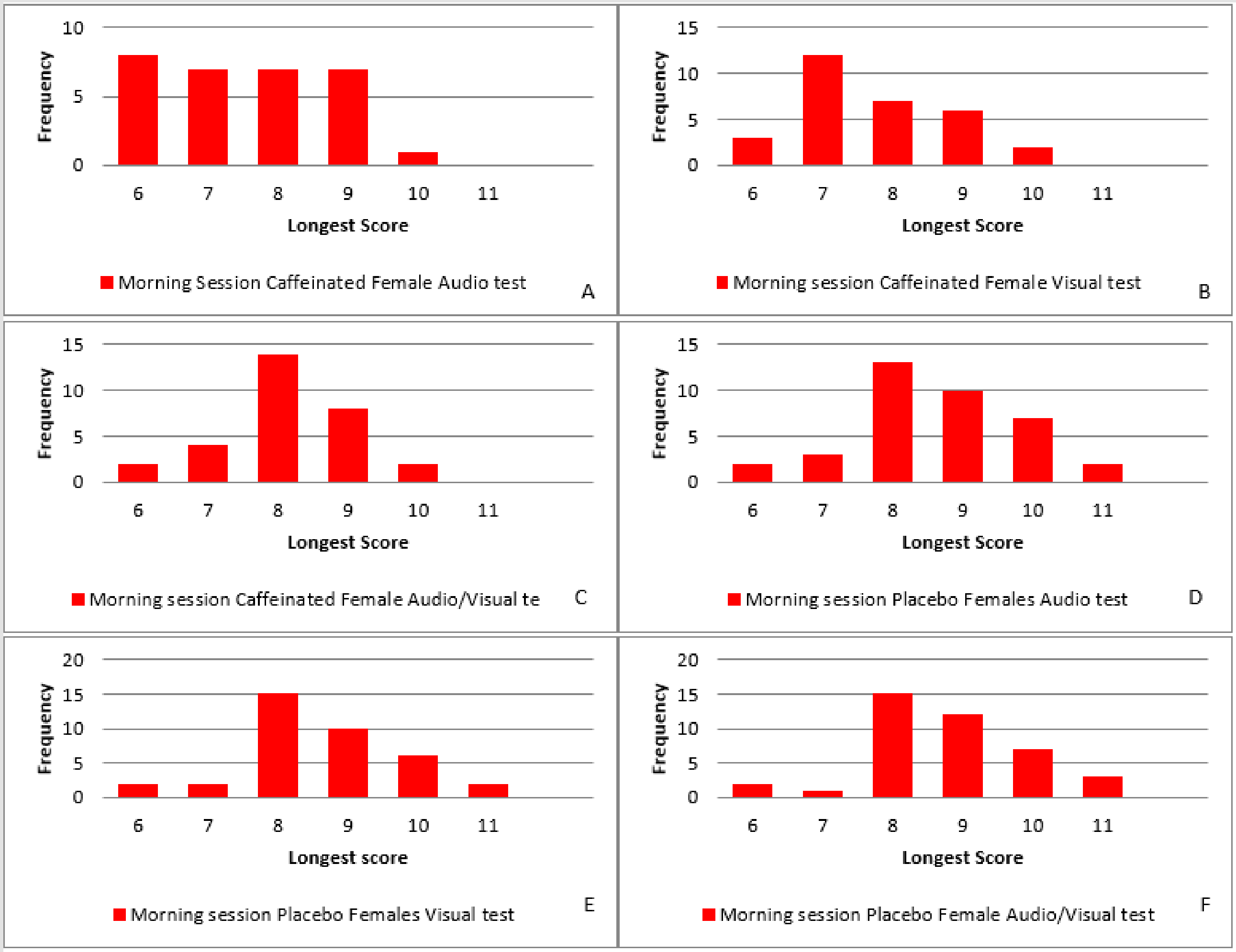

Figure 7: Histograms demonstrating frequency of longest recorded scores for caffeinated and placebo females in the morning session.

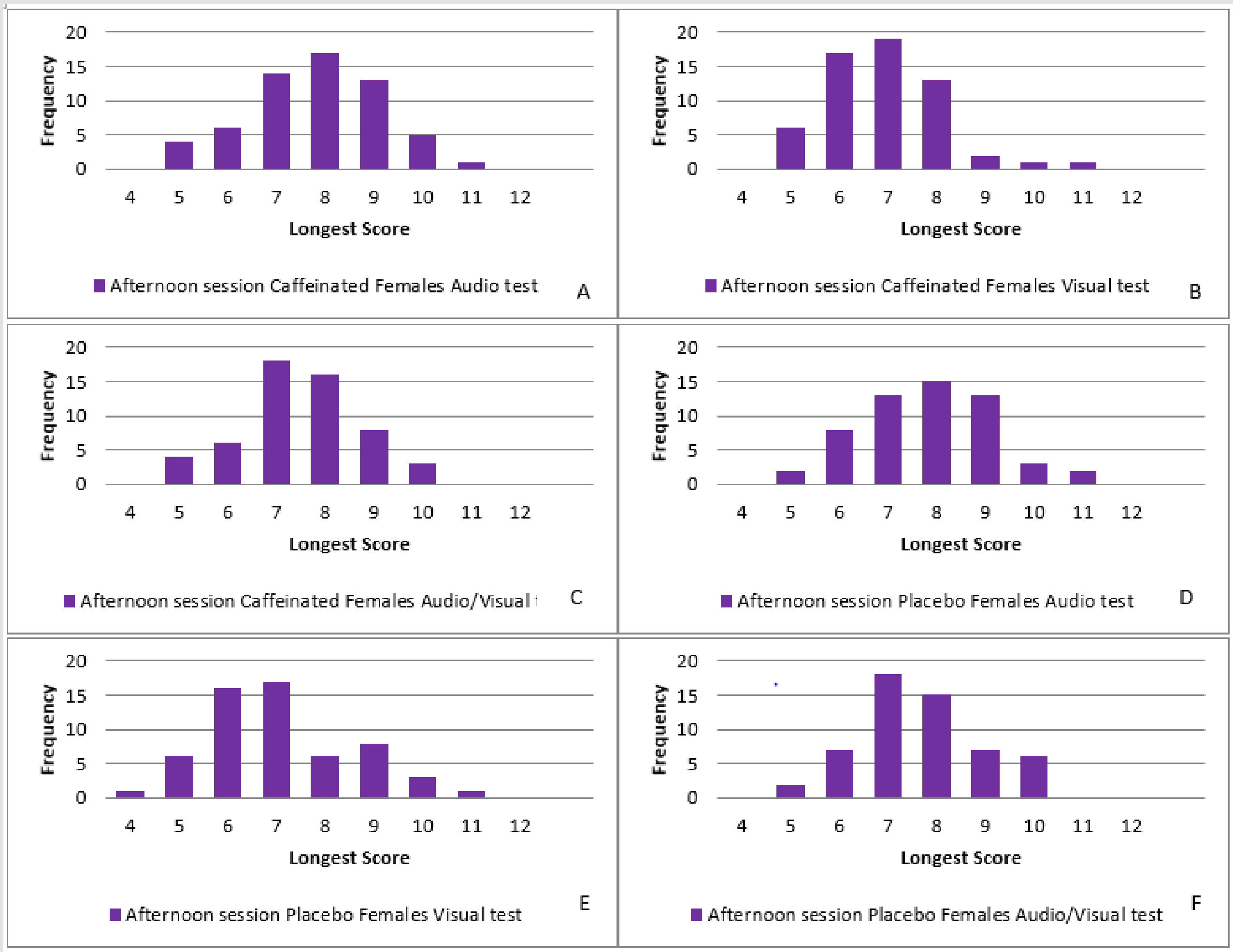

Figure 8: Histograms demonstrating frequency of longest recorded scores for caffeinated and placebo females in the afternoon session.

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Morning Trial

No significant difference was observed in male test scores for both the caffeine (Audio vs. Visual p=0.645, Audio vs. Audio/Visual p= 0.279, Visual vs. Audio/Visual p=0.537) and placebo (Audio vs. Visual p=1, Audio vs. Audio/Visual p=0.709, Visual vs. Audio/Visual p=0.709) groups. No significant difference was observed in female test scores for both the caffeine (Audio vs. Visual p=0.510, Audio vs. Audio/Visual p=0.402, Visual vs. Audio/Visual p=0.144) and placebo (Audio vs. Visual p=0.922, Audio vs. Audio/Visual p=0.638, Visual vs. Audio/Visual p=0.562) groups. 200mg dose of caffeine had no effect on male test scores when compared to the test scores of males taking the placebo (Audio p=0.478, Visual p=0.690, Audio/Visual p=0.613). Female subjects taking placebo recorded significantly longer scores across each of the three tests as compared to the test scores of caffeine exposed females (Audio $p=5.63x10^{-4}$, Visual $p= 3.02x10^{-3}$, Audio/Visual p=0.019). Caffeinated males performed significantly better during the individual audio and visual tests than caffeinated females (Audio p=0.006, Visual $p=8.37x10^{-3}$). The combined audio/visual test showed no significant difference between males and females (Audio/Visual p=0.052). No significant difference was noted during any of the tests between males and females exposed to the placebo (Audio p=0.954, Visual p=0.988, Audio/Visual p=1.00).

Afternoon Trial

Both caffeinated and placebo males performed significantly better on audio tests as compared with visual tests (p= 1.49x10-3, $p=1.31x10^{-3}$ respectively), while placebo males also performed significantly better on audio/visual combination tests as compared with visual tests ($p=4.55x10^{-3}$). No significant difference was observed in any other test for caffeinated (Audio vs. Audio/Visual p=0.119, Visual vs. Audio/Visual p=0.088) or placebo (Audio vs. Audio/Visual p=0.769) males. No significant difference was observed in the placebo or caffeinated females when comparing audio and audio/visual combination tests (p=0.509 and p=0.211 respectively). However, significant differences were noted between all other tests for both placeboes (Audio vs. Visual $p=6.31x10^{-3}$ and Visual vs. Combined $p=2.78x10^{-2}$) and caffeinated (Audio vs. Visual $p=3.39x10^{-4}$ and Visual vs. Combined $p=1.43x10^{-2}$) females. In each case, females recorded a lower mean score for visual tests than either the auditory or auditory/visual tests. 200mg dose of caffeine had no effect on male test scores when compared to the test scores of males taking the placebo during individual audio and visual tests (Audio p=0.352, Visual p=0.170). Placebo males performed significantly better than males on caffeine during the combined audio-visual test (Audio/Visual $p=2.58x10^{-2}$). Females taking 200mg dose of caffeine had no significant difference in test scores when compared to females on placebo in all tests (Audio p=0.934, Visual p=0.546, Audio/Visual p=0.498). Males taking placebo performed significantly better than females taking placebo (Audio $p=3.42x10^{-2}$, Visual $p=4.73x10^{-2}$, Audio/Visual $p=1.21x10^{-2}$). No significant difference was seen between males taking caffeine and females taking caffeine (Audio p=0.224, Visual p=0.216, Audio/Visual p=0.409).

Morning vs. Afternoon

When comparing males from the morning session to males in the afternoon session no significant difference was noted in test scores for males exposed to caffeine during audio tests (Audio p=0.379), or males taking the placebo during audio and combined audio/visual tests, (Audio p=0.471, Audio/Visual p=0.126). Males in the caffeine group performed significantly better in the morning than the afternoon during visual and combined audio/visual tests (Visual $p=9.92x10^{-6}$, Audio/Visual $p=3.87x10^{-4}$). Males taking placebo in the morning also performed better during visual tests than males taking placebo in the afternoon ($p=7.31x10^{-3}$). When comparing females from the morning to the afternoon no significant difference was seen in females taking caffeine during the audio tests (p=0.355). Females taking placebo performed significantly better in the morning in all tests (Audio $p=4.07x10^{-3}$, Visual $p=3.09x10^{-7}$, Audio/Visual $p=3.97x10^{-5}$). Females also performed significantly better in the morning as compared to the afternoon when taking caffeine in visual and combined audio-visual tests (Visual $p=2.33x10^{-3}$, Audio/Visual $p=1.04x10^{-2}$).

Discussion

The effect that caffeine has on memory functions in humans has been noted in numerous separate studies that, perplexingly, arrive at differing and sometimes opposed conclusions. The truth is that the end effect of this compound's ability to add or detract from mental functioning is dependent on the various parameters of these experiments that most, if not all, of these conclusions, are correct. More importantly, not only can the results be supported by the various data, but the differing of the conclusions can be explained. An anecdotal conclusion is that caffeine has been shown to both improve and impair working memory. There is a plethora of variables, many interdependent, that make quantifying working memory often an almost insurmountable task. Parameters include weight, gender, hormone levels, time of day, fatigue, and age. To begin, according to the U.S. Department of Health and Human Services, the average U.S. woman is 5' 3.7" (162 centimeters) tall and weighs 152 pounds (69 kilograms). This is with respect to a Body Mass Index of 26.3 $kilograms/meters^2$, which is slightly less than the average men. The average U.S. male stands 5' 9.1" (175 centimeters) tall and weighs 180 pounds (82 kilograms), with a Body Mass Index of 26.5 kg/m^2. Therefore, on the average, the same standard dose provides at onset 18.42% more caffeine per unit of body mass in females than it does to males. As our study looked at the difference in male and female immediate responses to caffeine, it did not account for weight variances between subjects.

In other words, equal concentrations had been given in this study to determine the instant response to caffeine, without noting that weight variance between participants could have had a fast-immediate effect on the study results. It is therefore possible that, given on average the lower weights of female participants as compared to male participants, there could have been a difference in mg of caffeine / kg, which potentially contributed to the statistically significant memory impairment seen in the caffeinated females but the precariously absent effect in the caffeinated males. Differences between males and females regarding caffeine intake can also be attributed to the metabolism of caffeine, normally executed by cytochrome P450 1A2 (CYP1A2) enzyme. In females, numerous studies have hypothesized that estrogen might play a role in the metabolism of caffeine. Pollock and colleagues assessed the effects of exogenous estrogen on caffeine metabolism [27]. They placed women on eight weeks of estrogen replacement and measured their caffeine metabolic ratios (CMR) before and after the therapy. For all participants, CMR levels were decreased after the estrogen therapy as opposed to before beginning the therapy, which suggests that estrogen might hinder the metabolism of caffeine by CYP1A2. Similar results were demonstrated by Hong and colleagues, where CMR in premenopausal and postmenopausal women was decreased by 22% and 15% with high levels of free circulating estradiol as opposed to women with low levels of free circulating estradiol [28].

CYP1A2 was also negatively associated with the percentage of circulating free estradiol. Thus, estrogen could influence CYP1A2, and further decrease the metabolism of caffeine by the enzyme. This connection between the different metabolism of caffeine in males and females can likewise be supported by Scandlyn and colleague, who shows that there exists a sex-specific difference between CYP1A2 activity in males and females, with males having a higher enzyme activity than females [29]. Since CYP1A2 metabolizes caffeine, higher levels of the enzyme in males and a more suppressed enzyme under the influence of estrogen in females can explain the difference in sex in performance on mental tasks. This is especially important when recalling that high doses of caffeine can negatively impact working memory [15]. These factors could provide an alternative or compounding reason for the difference between performance in males and females on our digit span test. Estrogen is not the only hormone that could contribute to altered working memory. It is known that human physiology is influenced by natural circadian rhythms in which an increase in alertness occurs in the early morning and declines throughout the day demonstrating low levels of alertness in the early afternoon independent of food intake [30]. In our study, placebo males performed equally well in the morning and afternoon in auditory and combination tests. However, during the visual test, men recalled longer strings of numbers in the morning relative to the afternoon.

Interestingly, females in the placebo group performed significantly better in the morning than in the afternoon in each test. These results indicate some time-of-day effects where male's visuospatial memory and female's visuospatial and phonological loop may be more prone to inhibitory effects that occur during a day. This observed decline may be associated with the maximal concentrations of glucocorticoids found in the blood in the morning, which follow alertness by declining levels as the day continues. According to Lupien and colleagues working memory tasks decreased significantly under the highest dose of hydrocortisone [31]. Additionally, curve fit estimations exhibit a "U-shaped" relationship between working memory task performance and changes in glucocorticoid levels after hydrocortisone infusion. Furthermore, there is an upper limit to the point at which caffeine can provide enhanced mental capabilities. This upper limit of how well you can perform is in the typical case: if you are well-rested and awake then you are already at the upper limit of your functioning capabilities; thus the caffeine probably does not result in enhanced performance; but paradoxically, it probably lowers your performance because it makes you 'jittery' and being 'too aware' because of heightened senses which reduce your ability to focus. So, the benefits of caffeine are greatest neither for those test subjects that are well rested nor for those in total exhaustion, but for the mildly exhausted or fatigued subject [32].

As such, both cortisol levels and fatigue could have contributed to the differences observed between the morning and afternoon groups. Finally, it has been seen in past research that varying amounts of caffeine have a positive or negative effect on tasks testing working memory. For example, Kaplan and colleagues have concluded that caffeine in low doses enriches working memory, while at high doses caffeine impairs it [15]. Furthermore, Rogers in his study has found that the effects of varying concentrations of caffeine show different results depending on the fatigue or sleep deprivation, with low doses of caffeine increasing alertness while high doses increase both alertness and performance on tasks testing working memory [33]. Our study demonstrates caffeine's potential ability for having an enhancing effect on an aspect of auditory processing and/or rehearsal in working memory. Both caffeinated males and females recalled significantly fewer digits in visual and combination tests from morning to afternoon while being conserved for the auditory tests. A similar result was seen in a study in which a group of older adults who were exposed to caffeine 30 minutes before testing were able to perform on a California Verbal Learning test (CLVT) equally as well in the late afternoon as they did in the morning, whereas participants not exposed to caffeine showed a significant decline [14]. An alternative explanation is discussed by Kemtes and Allen who demonstrated an auditory superiority effect in younger and older populations during exposure to WAIS digit span tests [34].

This phenomenon was observed in our afternoon study where placebo males and females recorded significantly higher scores during auditory tests than visual tests. Several limitations should be noted when considering the study results. Due to time constraints, only two trials were run. Like all drugs administered orally, stomach content can affect absorption levels, which was not considered. Due to time constraints, subjects were only given thirty minutes between administration of their pill and the beginning of their tests, although this timetable falls between the average maximum time and minimum time needed to achieve peak serum caffeine levels, actual levels are unknown due to inability to test blood directly. Due to resource constraints, the school library was used as a testing center, only ten participants could take the test simultaneously and the testing environment was not always quiet. All participants in the study were medical students, although they were all healthy there might be a selection bias skewing the results.

Conclusion

In conclusion, past studies have demonstrated discrepancies among the effects of caffeine. Previous authors attributed these differences to a plethora of variables including, but not limited to, gender, age, fatigue, hormone levels, and time of day, weight, test type, and dosage of caffeine. Our study reveals statistically significant results in the digit span test between males and females as well as the morning and afternoon trials. Much of our data and research suggests that innate differences between test subjects can provide a potential explanation for these findings.

Data Availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

The studies involving human participants were reviewed and approved by the Saint James School of medicine Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Competing Interests

None.

Funding

None.

Authors' Contributions

D.H.: Conceptualization, and design, approval of the final version, responsibility for the accuracy, and integrity of all aspects of research. M.C.: Study administration, writing—review, and editing. D.D.: Study administration, writing—review, and editing. D.S.: Data acquisition, writing—review, and editing. I.B.: Review for intellectual content and verified data analysis and interpretation. D.H.: Analyzed and interpreted the data. RP: Review for intellectual content and Resources. A.S.: Supervision and revising the article for intellectual content; editing, manuscript submission for publication. All authors read and approved the final manuscript.

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