The impact of caffeine use across the lifespan on cognitive performance in elderly women

Clinton S. Perry III, M.Sc.

Ayanna K. Thomas, Ph.D.

Holly A. Taylor, Ph.D.

Paul F. Jacques, D.Sc.

Robin B. Kanarek, Ph.D.

Affiliations: Tufts University

Corresponding Author: Clinton Perry, Department of Psychology, 490 Boston Avenue, Medford, MA 02155, clinton.perry@tufts.edu, phone: 530 574 5825

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Abstract: Habitual caffeine consumption has often been associated with decreasing age-related cognitive decline. However, whether habitual caffeine use preferentially spares different cognitive processes is unclear. Furthermore, whether basing habitual caffeine consumption patterns on current consumption or on a lifetime measure better represents an individual's use remains unclear. In the present study, we collected information from women, aged 56 – 83, about their current caffeine consumption patterns and history of use, including age they began consuming caffeine. Regression models assessed the relationship between caffeine consumption and performance on batteries designed to probe speed of processing, inhibition, memory, and executive function. While we found no direct associations between caffeine exposure and cognitive performance, we found that caffeine consumption and participant BMI interacted for inhibitory function and speed of processing performance. We discuss possible protective effects of long term caffeine use as well as the possibility of dose dependent effects.

Keywords: Caffeine; Aging; Individual Differences; BMI

Introduction

The nearly ubiquitous use of caffeine has prompted extensive research directed at elucidating both the health and psychological impact of its acute and, to a lesser degree, habitual consumption. The latter has produced an inchoate body of literature suggesting that caffeine consumption may protect against, or at least delay, the inevitable cognitive declines with normal aging (Hameleers et al., 2000; Jarvis, 1993; Johnson-Kozlow, Kritz-Silverstein, Barrett-Connor, & Deborah, 2002; Ritchie et al., 2007; van Boxtel, Schmitt, Bosma, & Jolles, 2003; van Gelder et al., 2007). However, methodological differences across studies make drawing strong conclusions about the nature of the relationship difficult. One potential significant methodological difference across studies is outcome measure. Task choice and how underlying latent variables have been defined vary widely across studies. As one example, the broad construct of memory has been operationalized using tasks that likely assess widely disparate and potentially independent memory systems. The present study employs psychometric testing in order to assess a broad range of cognitive abilities. Several tests were considered in combination in order to provide a more comprehensive assessment of cognitive function than any one test could provide. Through self-report measures designed to improve the resolution of life-time caffeine consumption and administration of several individual tests with the intention of identifying hypothetical latent factors, we sought to further elucidate the impact of long-term caffeine use on cognitive performance.

Task vs. Construct Effects of Habitual Caffeine Use

While effects of long-term caffeine exposure have been less well studied in humans, animal studies provide insight into cortical and behavioral changes resulting from chronic caffeine exposure. Specifically, chronic exposure appears to provide some protection against both normal and pathological aging. For example, long-term caffeine results in protection against the onset of memory deficits in a mouse model of Alzheimer’s (Arendash et al., 2009; Chu et al., 2012) and generally better memory performance in healthy mice (for a review see: Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999). In addition, there is evidence that chronic caffeine consumption provides protection against cognitive impairment in models of exposure to stress (Cunha & Agostinho, 2010) as well a high fat diet in rats (Alzoubi et al., 2013). In general, this apparently protective role of caffeine appears to hold true for humans as well, with studies indicating that high levels of caffeine consumption are associated with fewer negative health outcomes (Corley et al., 2010). For example, caffeine consumption through coffee has been found to be inversely associated with risk of certain types of cancer, type two diabetes, and Parkinson’s and Alzheimer’s disease; though its impact on cardiovascular function, bone density, and reproductive function is still controversial (for a review see Butt & Sultan, 2011; de Mejia & Ramirez-Mares, 2014; Nawrot et al., 2003). Caffeine has also been associated with generally preserved cognitive ability in older adults (Cao et al., 2012; Hameleers et al., 2000; Jarvis, 1993; Johnson-Kozlow et al., 2002; Ritchie et al., 2007; van Gelder et al., 2007). However, inconsistencies in cognitive tasks across studies make the nature of the cognitive preservation unclear.

Indeed, of the seven studies to date, six have included a memory measure. Of these, four found a positive association with caffeine consumption and memory performance (Corley et al., 2010; Hameleers et al., 2000; Jarvis, 1993; Johnson-Kozlow et al., 2002), while the remaining two found no relationship (Ritchie et al., 2007; van Boxtel et al., 2003). Four studies included a response speed measure, all of which found a positive association between response speed and habitual caffeine use (Corley et al., 2010; Hameleers et al., 2000; Jarvis, 1993; van Boxtel et al., 2003). Four studies used verbal fluency measures, two of which found a positive association between habitual caffeine use and verbal fluency, but only in women (Johnson-Kozlow et al., 2002; Ritchie et al., 2007) while the other two found no relationship (Hameleers et al., 2000; van Boxtel et al., 2003). Three used the Mini Mental State Exam (MMSE) and two of which found a positive association with habitual caffeine use (Johnson-Kozlow et al., 2002; van Gelder et al., 2007). It is important to note that MMSE is intended as a quick screening device for dementia and draws from a wide array of cognitive resources and thus provides little insight into the particular underlying cognitive processes. Overall, these studies provide strong evidence of preserved speed of processing and some evidence for memory preservation.

With one notable exception (Corley et al., 2010), previous studies have employed a single cognitive test to measure differences associated with habitual caffeine use. As such, the findings may be task specific rather than reflecting sustained ability in a particular cognitive domain (e.g., memory, processing speed, executive function). That is, while a single measure may appear sensitive to a particular function, no task is a pure measure of an underlying cognitive construct and will include the recruitment of other cognitive processes necessary to complete the task. By compiling a set of tasks that all purportedly rely on the same core underlying cognitive system into a single composite score we can more effectively focus on the cognitive processes involved (Tucker-Drob & Salthouse, 2009).

Corley and colleagues (2010) used just such an approach by focusing on three main factors: a general factor, processing speed, and memory performance. Their memory factor was comprised of two long-term memory tasks (verbal paired associates and logical memory) as well as three working memory tasks (letter-number sequencing, backward digit span, and spatial span). Their processing speed factor consisted of five tasks: a simple reaction time task, two choice reaction time tasks, a symbol search task, and a digit symbol substitution task. Finally, the general factor was composed of two working memory tasks (letter-number sequencing and backward digit span) the two paper-based speed tasks (symbol substitution and symbol search) as well as the matrix reasoning and block design tasks from the Wechsler Adult Intelligence Scale. Corley and colleagues (2010) collected measures of habitual caffeine consumption across a range of contexts including caffeinated and decaffeinated coffee, tea, and soda. While total caffeine consumption was associated with memory performance, IQ, and reading ability only, the researchers found that coffee consumption was positively associated with performance for all three factors. However, due to the makeup of the memory factor (i.e., containing both working memory and long term memory components) it is impossible to determine which memory system may be affected by habitual caffeine consumption.

Defining and Measuring Habitual Consumption

In addition to discrepancies in task choice, there is also some discordance in how "habitual" consumption is defined. All but one study have relied on questions such as "How many cups of coffee do you usually drink in a day?" (e.g., Jarvis, 1993), or will go so far as to ask participants to consider the past year to make a general judgment of intake. Yet, this measure only takes into account recent caffeine consumption trends to define "habitual" use and ignores long term patterns. Johnson-Kozlow and colleagues (2002) recognized this shortcoming and included a "lifetime use" measure by asking how long a participant had been consuming caffeinated and decaffeinated coffee only. This allowed them to calculate a value representing coffee consumed throughout the participant's life, or "Lifetime Cups", by dividing average daily consumption by the amount of caffeine per serving and then multiplying the result by the number of years consuming. While the researchers found no associations with any measure of caffeine consumption in men, they did find a trend-level positive association between current coffee consumption and both MMSE scores and word memory in women. Of interest, the lifetime cups measure in female participants was significantly associated with word and shape memory, MMSE score, and category fluency scores. This finding suggests that accounting for the length of caffeine exposure may provide a more sensitive measure of the impact of habitual caffeine exposure on cognitive performance in the elderly. However, as the lifetime measure used in this study was calculated using current levels of consumption, it may not account for fluctuations in patterns of consumption, such as increases or decreases in use across time, resulting in an inaccurate representation of lifetime consumption.

The Present Study

In the present study we expand upon Corley and colleagues' (2010) approach by employing factor batteries previously established in cognitive aging research (e.g., Glisky & Kong, 2008; Glisky, Polster, & Routhieaux, 1995; Glisky, Rubin, & Davidson, 2001), and by testing the impact of habitual caffeine consumption on a new exploratory factor. Specifically, to focus more directly on one component of memory we adapted a Medial Temporal Lobe (MTL) battery used previously to explore cognitive decline in older adults (Glisky & Kong, 2008). This battery consists of a Verbal Paired Associates, Logical Memory, and Face Recognition tasks from the WMS-III (Wechsler, 1997b). As research has reliably suggested a relationship between habitual caffeine consumption and processing speed, we also used a speed of processing battery commonly employed in cognitive aging research (Salthouse, 2005; Tucker-Drob & Salthouse, 2009). This battery consists of the Digit Symbol Substitution Task from the WAIS-III (Wechsler, 1997a) as well as Line and Letter Comparison tasks (Salthouse, Hancock, Meinz, & Hambrick, 1996). We also included a Frontal Lobe Function (FLF) and an Inhibitory Function battery to explore the possible relationships between long-term caffeine exposure and executive function in the elderly. The FLF battery was adapted from Glisky & Kong (2008) and consisted of the Digit Span task from the WAIS-III (Wechsler, 1997a), a computerized version of the Wisconsin Card Sorting Task, and the Mental Control task from the WMS-III (Wechsler, 1997b). Our Inhibitory Function battery was exploratory in nature and consisted of a word Stroop task (Golden, 1978), the Stop Signal Task (Verbruggen, Logan, & Stevens, 2008), and a Flanker task (Eriksen, 1995).

In addition, we included measures of both current habitual as well as long-term caffeine consumption. Current caffeine consumption patterns were assessed using the NHANES Food Frequency Questionnaire's (Thompson et al., 2002) items concerning caffeinated beverage consumption. To address life-long habits, we borrowed Johnson-Kozlow and colleagues' (2002) methodology and asked participants to provide an estimate of age when they first started consuming caffeine habitually and then calculated a "lifetime cups" measure. By including these measures we sought to replicate Johnson-Kozlow and colleagues' findings and determine if a long-term exposure measure is more sensitive to caffeine's relationship with cognitive performance.

Our primary goal was to determine the impact of long-term caffeine exposure on current cognitive performance of elderly participants. We hypothesized that performance on the cognitive batteries would be associated with caffeine intake such that higher levels of habitual intake would be associated with the better composite scores on each battery.

Methods

Participants

As previous research has found relationships between caffeine consumption and cognitive performance mainly in women (Johnson-Kozlow et al., 2002; Ritchie et al., 2007), we recruited only healthy women aged 55 to 85 years (*N* = 67;), though the age range of our actual sample was 56 – 83 years. Participants living in the greater Boston area were recruited, by phone, from a database of individuals maintained by the Cognitive Aging and Memory laboratory at Tufts University. Participants were community dwelling, had normal or corrected vision, suffered from no learning or cognitive disorders (e.g., schizophrenia, bipolar disorder, etc.), had no history of alcohol or drug abuse, and had no history of head trauma, stroke, or seizure. Of those enrolled in the current study, four failed to return for the follow up cognitive testing session and were omitted from all analyses. The average age of the remaining 63 participants was 68.7 years (*SD* = 5.7). The ethnicity of our sample was relatively homogenous: 58 participants identified as Caucasian, 3 as African American, 1 as Hispanic, and 1 provided no indication of her ethnicity. All participants were fluent English speakers. Average body mass index (27.0 kg/m^2; BMI) was calculated from self-reported height and weight: 46.0% of participants had a BMI in the healthy range (18.5 – 24.9 kg/m^2), the majority of the participants were either overweight (25.0-29.9 kg/m^2, 25.4%) or obese (>30 kg/m^2, 27.0%) and only one participant was considered underweight (BMI <18.5 kg/m^2).

Participants provided signed, informed consent prior to commencement of study procedures. All recruitment and enrollment procedures were approved by the Social, Behavioral, and Educational Research Institutional Review Board at Tufts University.

Caffeine consumption questionnaire.

Caffeine consumption habits for the twelve months preceding the participant's first visit to the lab were assessed using a subset of questions from the NHANES dietary questionnaire (Thompson et al., 2002). The included questions determined consumption frequency of both caffeinated and de-caffeinated sodas, coffee, and tea, as well as energy drinks; however for reporting simplicity, only caffeinated products will be reported in the results section. Because participants were asked to maintain normal caffeine consumption patterns, they recorded all caffeinated beverages consumed from the morning prior to and through the morning of cognitive testing to control for acute consumption in our analyses. Participants also indicated whether they had ever habitually consumed caffeine pills either currently or in the past. If the participant answered “yes”, they were asked to elaborate by providing the age at which the habit started, duration of the habit, and quantity consumed during this time.

In addition to collecting details about the previous twelve months’ consumption, we collected responses regarding prior longer-term caffeine consumption patterns. Participants indicated the age at which they started habitually consuming caffeine (defined in the questionnaire as a pattern lasting greater than three months). This age was used to calculate a lifetime measure of caffeine consumption in line with the methods used by Johnson-Kozlow and colleagues (2002), described later. In addition, participants indicated periods of abstinence from caffeine consumption, if any, including age and the length of abstinence.

To further define the general caffeine consumption patterns across the lifespan, we provided a series of visual analog scales (VAS) to approximate caffeine intake. Seven scales were provided. The first six scales corresponded to different decades of life, “20 – 30 years of age”, “30 – 40 years of age”, “40 – 50 years of age”, “50 – 60 years of age”, “60 – 70 years of age”, and “70 – 80 years of age”, the final scale corresponded to the “Last 12 months”. Participants only filled out the decade scales which were relevant to their own age (e.g., 50 – 60 years of age was the last scale a 54 year old would complete). After completing each scale, participants indicated their primary and secondary sources of their caffeine consumption during that decade (e.g., coffee, tea, soda). However, these data will not be presented in the current manuscript.

Cognitive Test Battery

Cognitive tests consisted of a range of verbal, paper and pencil, and computerized tasks. All testing was done individually in a quiet room. Computerized tasks were run on a laptop with a USB attached mouse and keyboard. The instructions for each task were provided in writing as well as read aloud by a trained researcher. In addition to two general function tasks, the MMSE (Folstein, Folstein, & McHugh, 1975), described earlier, and Shipley's Institute of Living Scale (Zachary, 1986), a vocabulary test to provide an additional measure of mental faculty, participants completed twelve tasks designed around specific cognitive systems.

The MTL battery consisted of three standardized tasks from the Wechsler Memory Scale (Wechsler, 1997b): Verbal Paired Associates, Logical Memory I, and Face Recognition I. The Verbal Paired Associates task required participants to listen to 10 word pairs read aloud and produce the second word of the pair when prompted with the first. The outcome measure was the number of correctly recalled associates. For the Logical Memory task, participants listened to short stories and then recalled as many details as possible. The outcome measure was the number of correctly recalled story details. The face recognition task requires that participants view 24 color pictures of faces presented one at a time from a booklet. Participants then viewed 48 face pictures, half old and half new, and provided a "yes/no" response to indicate whether they had seen the faces before. The outcome measure was the number of correctly recalled faces.

Our Inhibitory battery included 3 computerized tasks: a Stroop task (Golden, 1978; Mueller & Piper, 2014), a Stop Signal task (Verbruggen et al., 2008), and a Flanker task (Eriksen, 1995; Mueller & Piper, 2014). The Stroop task consisted of seven blocks: the first block was practice, with all word names being consistent with the font color; the following six blocks contained a mixture of congruent and incongruent stimuli (i.e., mismatch between word name and printed color) with alternating response focus (i.e., button push for word name or printed color). The outcome measure for this task was the mean reaction time for correct responses on incongruent trials. To rule out any false start responses and to eliminate response times reflecting other factors (e.g., confirming task demands), only responses between 200 MS and 4000 MS were considered (Davidson, Zacks, & Williams, 2003). The Stop-Signal task required participants to provide a push button with their index finger to the visual presentation of a go stimulus (a blue circle or square), but to inhibit this response if the stimulus was followed by an auditory stop stimulus (a loud "beep"). The outcome measure for this task was the number of accurately inhibited responses. The Flanker task required participants to provide a push button response indicating the direction of a center arrow in three conditions: no flanking distractor arrows, two flanking distractor arrows on either side pointing the same direction as the target arrow (congruent), or in a direction opposing the central target arrow (incongruent). The outcome measure for this task was mean response time for correct responses on incongruent trials.

The Speed of Processing battery consisted of the Digit Symbol Substitution task from the Wechsler Adult Intelligence Scale (WAIS – III; Wechsler, 1997a) as well as the Letter and Line Comparison tasks used in previous works to research age related cognitive decline (Salthouse et al., 1996). In the Digit Symbol Substitution task, participants have 120 seconds to populate all of the blank boxes with a symbol corresponding to a number printed in a box directly above. The outcome measure was the number of correctly copied symbols within the allotted time. The Letter and Line comparison tasks required participants to indicate whether paired sets of letters and lines, respectively, were the same or different by placing a check mark or “x”, respectively, in the blank next to the pair. For both of these tasks the outcome measure was the number of correctly judged pairs within the allotted time (20 seconds per page).

Finally, the FLF consisted of the Backward Digit Span (WAIS-III; Wechsler, 1997a), the Wisconsin Card Sorting Task (Mueller & Piper, 2014), and the Mental Control task (WMS-III; Wechsler, 1997b). In the Backward Digit Span participants hear series of single digit numbers at a rate of one number per second and repeat them back in reverse sequence. The outcome measure for this task was the number of correctly recalled number sequences. We used a computerized Wisconsin Card Sorting Task wherein participants sorted cards depending upon one of three rules (color, shape, or number) by clicking on the card pile matching the current rule which would change periodically. They received feedback regarding their accuracy. The outcome measure for this task was the total number of perseverative errors. For the Mental Control task, participants had to mentally sequence or manipulate information such as numbers, days of the week, and months of the year or a combination (e.g., counting up by 6’s and listing the days of the week in order: 6 – Sunday, 12 – Monday, etc.). The outcome measure for this task was the cumulative points across items.

Procedure

To reduce strain on the participants, the experiment consisted of two sessions separated by one to seven days. During the first session, researchers explained the study details and obtained informed consent. Participants then completed the aforementioned questionnaires after which they received monetary compensation ($15), confirmed the follow up appointment, and received the food diary and were instructed how to complete the diary for the day prior to and morning of the second visit. Participants were instructed to maintain normal dietary and living patterns during the intervening time.

During the second visit, participants completed the cognitive testing battery. Testing sessions lasted approximately two hours. After the completion of the cognitive testing battery, participants received monetary compensation ($30; for a total $45), were debriefed regarding the goals of the study, and thanked for their participation.

Statistical Analysis

All statistical analyses were computed using SPSS. Participant SES was calculated based on their responses regarding their highest degree earned, residential status, income, and current occupational status. We used a bivariate correlation analysis to determine the relationship between SES response measures. After variable selection, we ran a Cronbach's-α to verify reliability of the chosen variables. The scores were then transformed into Z-scores and averaged to create the SES composite.

We next turned our attention to the caffeine consumption variables. A cross tabulation analysis was first used to determine whether participants were exclusive in their caffeinated beverage type consumption. As consumption was not exclusive for any caffeinated beverage type, we next ran a bivariate correlation analysis to determine whether the amount of consumption for each beverage type was related. We then calculated the relative caffeine consumption amount for each beverage type and combined them to create an overall consumption value. This value was used, in conjunction with participants' reported age of first use, to create a lifetime consumption value.

As cognitive measures differed in outcome type, all scores were z-transformed and age was 0 centered to the youngest age in the sample: 56 years old. We then screened for missing and outlier data. Using these z-scores we next ran an exploratory factor analysis using principle component factor extraction with Varimax rotation and Kaiser Normalization to verify the composition of our latent variable factors. We used a Mahalanobis distance analysis to look for multinomial outliers for each latent variable. Unfortunately, multinomial outliers for each latent variable were unrelated and, due to our already small sample, we elected to retain these participants in the sample. The z-scores for each component of the latent variables were then averaged. Regression coefficients for analyses were only reported if the model was significantly different from zero.

For our latent cognitive variables, the regression analyses first involved a set of single predictor linear regressions to determine the relationship between our habitual caffeine consumption measures and task performance. We then added two additional blocks to the regression. The first block contained the control variables (i.e., age, SES, BMI, and number of health conditions), the second block contained the measure of habitual caffeine consumption, and the final block contained variables of interaction between the control variables and habitual caffeine use measures. The analyses proceeded by first adding age as a control variable in the first block and age x habitual caffeine consumption measure in the third block. The next model set added SES to the control variables in the first block and the associated interactions to the third block and so on with BMI and number of current health conditions. Initially, the interaction block contained all possible interactions. If any interactions reached significance or suggested a trend toward significance ($p < .1$), we removed all other interactions terms from the model to determine the nature of the interaction in isolation. Follow up slopes analyses followed the procedures outlined by Field (2013) using the PROCESS version 2.13 macro created by Andrew Hayes (2015). This macro calculates regression equations for the predictor and outcome measures as well as the average level of the moderating variable and one standard deviation above and below this average.

Because we allowed participants to continue normal intake patterns on the testing day, many participants were under the effects of acute caffeine consumption. To determine to what degree this consumption might be affecting performance and the associations within our models, we first ran a series of regressions using the amount of caffeine consumed on test day as the sole predictor for each outcome measure. This was then added to the previous models as an additional control variable. Because we were also interested if any of our control variables might mitigate this effect, we added the amount of caffeine consumed on test day in a new block after the other control variables. These modified model sets had the basic layout of general control variables in block 1, caffeine consumed the morning of testing in block 2, habitual caffeine consumption in measures block 3, and the interactions in block 4.

Results

In general, our participants were well-educated, the majority owned a home, and were working part time. Reported current annual household income was positively correlated with education ($r = 0.34$, $p = .01$) and with residential ownership ($r = 0.46$, $p < 0.01$). We found no significant correlations between any measure and current occupational status. This measure was therefore omitted from further analyses. The remaining three measures, highest degree earned, annual income, and residential ownership were transformed into Z–scores to create a composite SES variable. Cronbach’s α was computed for all three variables together as well as for highest degree earned and annual income alone; the values were .57 and .50 respectively. The composite variable was calculated as the average of the three Z–scores and will be referred to as SES.

Caffeine Use

Daily overall caffeine consumption was calculated as the sum of caffeine consumed from each individual source based on an estimated level of caffeine from each source (100 mg per 8 oz cup of coffee, 25 mg per cup of decaffeinated coffee, 30 mg per cup of tea, 35 mg per can of soda, and 200 mg per serving of energy drink; averages compiled from Somogyi, 2010). Daily overall caffeine consumption was calculated only for those participants who provided a response for each individual source of caffeine consumption (*n* = 55). Details of the average caffeine consumption reported in this sample can be found in Table 1. A cross-tabulation of caffeine consumption by source (data not shown), indicated that participants rarely drank any caffeinated beverage type exclusively and tended to drink multiple types of caffeinated beverages. Corollary analyses revealed a positive association between both the amount of decaffeinated coffee consumed and the amount of caffeinated coffee consumed ($r = 0.35$, $p < 0.01$) and the amount of tea consumed ($r = 0.42$, $p < 0.01$). We found no other significant correlations between amounts of caffeine consumed by source.

	N	Mean	*SD*	Minimum	Maximum
Coffee	63	127.15	146.51	0.00	600.00
Decaffeinated Coffee	61	10.29	19.03	0.00	62.50
Tea	58	18.90	36.16	0.00	180.00
Soda	62	13.44	29.28	0.00	157.50
Energy Drink	63	0.32	1.43	0.00	6.67
Overall Consumption	55	167.26	145.38	0.00	601.00

Table 1. Average daily caffeine consumption from each individual source. All listed values are in milligrams.

In addition to traditional caffeine sources, participants also indicated whether they currently, or had ever, habitually consumed caffeine pills. Four participants reported having habitually consumed caffeine pills at some point. Of these participants, none reported current habitual use. The average age of starting caffeine pill use was 16.75 years (*SD* = 1.26) and average length of 2.17 years (*SD* = .29). As no participants reported current habitual use, caffeine pill consumption was omitted from analyses.

Historical caffeine use patterns. Participants provided an estimate of the age at which they began habitually consuming caffeine; five participants failed to provide a response to this question. The average reported onset age was 17.40 years old (S.D. 6.78) with minimum age of 6 and a maximum of 50. Years of habitual caffeine consumption were computed by subtracting the age of onset from the age at testing. The average number of years of habitual caffeine consumption was 51.33 years (*SD* = 9.15) with a minimum length of 25 and a maximum of 75 years.

To maintain consistency with previous work (Johnson-Kozlow et al., 2002), lifetime caffeine consumption measures were estimated by first calculating a standard unit of caffeine per day for each source (dividing the daily consumption by the average amount of caffeine per serving) and multiplying by the number of years consuming. For example, a participant with a calculated daily intake of 200 mg of caffeine from coffee and a reported 40 years of consumption would be calculated as having 80 lifetime cups. We defined a single unit of overall caffeine consumption at 250 mg. Descriptive statistics for lifetime caffeine consumption can be found in Table 2.

Twenty-three participants indicated that they had undergone a period of abstinence from caffeine. The average caffeine abstinence duration lasted 47.31 months (*SD* = 111.03), though this included four participants who indicated ongoing abstinence. Of those not currently abstaining, the average abstinence length was 29.48 months (*SD* = 69.07) with a minimum length of 4 days and a maximum length of 25 years. Of the four participants who indicated ongoing caffeine abstinence, one stopped a year prior, two stopped two years prior, and one stopped 39 years prior to testing. However, all four of these participants later indicated some caffeine intake (overall consumption: *M* = 19.58, *SD* = 26.52) with most of the intake coming from decaffeinated coffee (*M* = 31.46, *SD* = 35.85).

	Caff. Per Serving	n	M	SD	Min.	Max.
Coffee Cup Years	100 mg	60	66.33	77.75	0.00	330.00
Decaffeinated Coffee Cup Years	25 mg	59	21.99	43.34	0.00	187.50
Tea Cup Years	30 mg	55	33.12	65.65	0.00	324.00
Soda Can Years	35 mg	58	21.85	46.89	0.00	234.00
Energy Drink Can Years	200 mg	62	0.05	0.29	0.00	1.80
Overall Consumption Unit Years	250 mg	51	35.66	31.19	0.00	132.22

Table 2. Descriptive statistics for lifetime unit years for each caffeine source based on current caffeine consumption patterns. Caffeine per serving size is based on estimates provided in Somogyi (2010).

An adjusted lifetime caffeine consumption measure was also computed by subtracting periods of abstinence from the lifetime caffeine consumption measure (data not shown). However, the difference between lifetime caffeine consumption measure and adjusted measure was negligible and provided no additional resolution in the regression analyses. As such, these measures are not discussed further.

Cognitive performance.

On the two general cognitive measures, mean performance score for the MMSE was 28.37 (*SD* = 1.47) out of 30 possible points. The majority of participants (*n* = 49) scored 28 or above. Of those scoring below 28 (n=14), the minimum score was 24. The mean score for the Shipley’s Institute of Living task was 35.35 (*SD* = 3.01) out of 40 possible points with a minimum score of 27 and a maximum score of 40. No relationship was found between age and MMSE or the Shipley’s Institute of Living performance. However, there was a positive correlation between performance on these two tasks (*r* = 0.31, *p* = 0.01) such that as performance on one task increased, so did performance on the other.

Descriptive Statistics for all other main outcome measures can be found in Table 3. Two participants failed to provide any correct responses for incongruent trials on the Flanker task, part of the inhibition battery. As such, these participants were omitted from further analysis of the inhibitory battery.

Task	Outcome Measure	*N*	*M*	*SD*
Stop Signal Task	Percent of correctly suppressed responses	63	0.50	0.14
Stroop	Incongruent mean reaction time (ms)	63	1327.21	355.20
Flanker	Incongruent mean reaction time (MS)	61	606.32	51.96
Visual Paired Associates	Number of words correctly recalled	63	18.03	8.29
Logical Memory	Number of correctly recalled story details	63	42.22	8.90
Face Recognition	Number of correctly recognized faces	63	34.17	4.82
Digit Symbol Substitution	Number of correctly copied symbols	63	62.33	15.15
Letter Comparison Task	Number of correctly judged letter sets	63	21.03	5.30
Line Comparison Task	Number of correctly judged line patterns	63	23.03	5.11
Backward Digit Span	Number of correctly recalled number sequences	63	7.46	2.24
Card Sorting Task	Percent of perseverative responses	63	15.23	11.05
Mental Control	Number of correctly provided item sequences	63	25.54	4.72

Table 3. Descriptive statistics for the main outcome measures for each task. Note that reaction time data are presented in milliseconds.

Factor Batteries. As a reminder to the reader, the Inhibition battery consisted of the Stop Signal, Stroop, and Flanker Tasks, the MTL battery consisted of the Visual Paired Associates, Logical Memory and Face Recognition tasks, the Speed of Processing battery consisted of the Digit Symbol Substitution, Letter Comparison, and Line Comparison tasks, and the FLF Battery consisted of the Backward Digit Span, Wisconsin Card Sorting, and Mental Control tasks.

In order to verify that the cognitive battery tasks loaded on to the expected latent factors, we conducted a factor analysis. Results showed four latent variable structures (Table 4). Three of the factors conform relatively well to our expectations. Factor 1 reflected our speed of processing battery, receiving the strongest loadings from the Letter and Line Comparison tasks and to a lesser degree the Digit Symbol Substitution of the Speed of Processing Battery as well as the Mental Control task of the FLF Battery. Given that participants can receive bonus points on the

Mental Control task for finishing the items quickly, it is unsurprising that this task would contribute to what appears to be our speed factor. For the latent variable we chose to include only the Letter and Line Comparison tasks as they were the most strongly associated with the latent variable.

		Factor			
Anticipated Factor		1	2	3	4
Inhibition	Stop Signal Task	0.296	0.364	-0.059	-0.021
	Stroop	-0.654	-0.333	0.610	-0.029
	Flanker	-0.397	-0.105	0.396	0.031
Medial Temporal	Visual Paired Associates	0.248	0.798	0.009	0.087
	Logical Memory	0.040	0.661	-0.033	0.344
	Face Recognition	0.189	0.233	-0.127	0.674
Speed of Processing	Digit Symbol Substitution	0.510	0.226	-0.723	-0.067
	Letter Comparison Task	0.862	0.219	-0.339	0.052
	Line Comparison Task	0.892	0.305	-0.169	0.112
Frontal Function	Digit Span Backward	0.095	0.202	-0.442	0.352
	Card Sorting Task	-0.003	-0.111	-0.183	-0.004
	Mental Control	0.424	0.208	-0.212	-0.168

Table 4. Exploratory factor analysis factor loading.

Factor 2 reflected our memory battery, receiving the strongest loadings from the Visual Paired Associates and Logical Memory tasks and was thus used to create the latent memory variable. Factor 3 reflected a latent inhibition factor in that it received the strongest loading from the Stroop outcome variable with the Flanker outcome variable contributing to much lesser degree. While the factor loading of the Flanker outcome variable was relatively low, the fact that nearly every other variable was negatively loaded onto Factor 3 led us to include both the Stroop and the Flanker outcome variables in the latent Inhibition variable.

Factor 4 did not conform to our anticipated FLF latent, receiving the strongest loadings from the Face Recognition, Logical Memory, and Backward Digit Span outcome variables. While our FLF battery did not seem to tap an underlying frontal function component, these measures have been used in previous studies of aging and have been found to tap a single underlying element in a much larger sample (Glisky & Kong, 2008). As such, rather than dropping this factor battery, we proceeded to use task performance on the Backward Digit Span, WCST, and Mental Control tasks as a composite variable to investigate the relationship between frontal function and caffeine consumption. The component scores from these factors were then used as the dependent measure in our regression analyses.

Battery performance, caffeine, and other individual differences.

After controlling for caffeine consumption outliers, habitual caffeine consumption measures were not associated with MTL or FLF performance. In addition, performance on the MTL and FLF batteries was not associated with the amount of caffeine consumed by participants the morning prior to testing nor did controlling for the impact of this caffeine consumption prior to testing reveal any associations.

Inhibition. It should be noted that the inhibition latent measure is based on reaction time data and, as such, negative relationships indicate better performance. Habitual caffeine consumption measures were not directly associated with inhibitory battery performance. After controlling for age, SES, BMI, and average caffeine consumption in previous blocks of the model, the interaction between BMI and average current caffeine consumption was associated with inhibitory battery performance (ß = -0.50, $df = 47$, $p < 0.01$). A follow up slope analysis (Figure 1) revealed that at lower BMI (BMI < 24.21), average caffeine consumption was significantly, positively associated with inhibitory battery performance (ß = 0.41, $t = 3.93$, $p < 0.01$). At mean BMI, average caffeine consumption was not associated with inhibitory battery performance (ß = -0.08, $t = -0.70$, $p = 0.49$). At high BMI (BMI > 31.62), average caffeine consumption was significantly negatively associated with inhibitory battery performance (ß = -0.57, t = -2.24, p = 0.03).

Similar associations with inhibitory battery performance were found for the interactions between BMI and lifetime caffeine consumption (ß = -0.46, df = 44, $p < 0.01$). Similar to average caffeine consumption, follow up slope analyses indicated that when BMI was low, lifetime caffeine consumption was positively associated with inhibitory battery performance (ß = 0.38, t = 3.16, $p < 0.01$). For mean BMI in our sample, lifetime caffeine consumption was not associated with inhibitory battery performance (ß = -0.08, t = -0.61, p = 0.54), and when BMI was high, we found a marginally significant negative association between lifetime caffeine consumption and inhibitory battery performance (ß = -0.53, t = -2.00, p = 0.05).

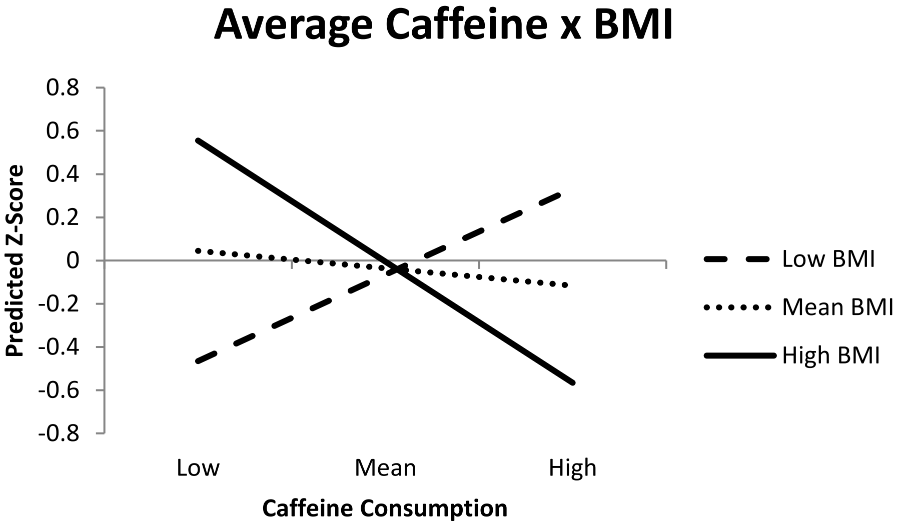

Figure 1. Interaction between average caffeine consumption and BMI on Inhibitory battery performance based on *Process Macro* (Hayes, 2015) analysis. Note that lower values indicate better performance.

We found a similar interaction between average coffee consumption, as well as its lifetime measures, and BMI with inhibitory battery performance. A slope analysis of the interaction between average coffee consumption and BMI (ß = -0.42, df = 48, $p < 0.01$) revealed that when BMI was low, average coffee consumption was significantly positively associated with inhibitory battery performance (ß = 0.56, $t = 2.39$, $p = 0.02$). For mean BMI in our sample, average coffee consumption was not associated with inhibitory battery performance (ß = 0.13, $t = 0.81$, $p = 0.42$), and when BMI was high, we found a trending association between lifetime caffeine consumption and inhibitory battery performance (ß = -0.31, $t = -1.68$, $p = 0.10$). A slope analysis of the interaction between lifetime coffee consumption and BMI (ß = -0.44, $df = 46$, $p < 0.01$) revealed a similar interaction. When BMI was low, lifetime coffee consumption was positively associated with inhibitory battery performance (ß = 0.66, $t = 2.78$, $p < 0.01$). For mean BMI in our sample, average coffee consumption was not associated with inhibitory battery performance (ß = 0.19, $t = 1.16$, $p = 0.25$). Here, however, for high BMI lifetime caffeine consumption was not associated with inhibitory battery performance (ß = -0.28, $t = -1.42$, $p = 0.16$). Caffeine consumed the morning of testing was not associated with inhibitory battery performance or the interactions described above.

Speed. After controlling for outliers, habitual caffeine consumption measures were not associated with speed battery performance. Caffeine consumed the day of testing was also not associated with speed battery performance. However, controlling for the effects of caffeine consumed the day of testing did reveal an interaction between lifetime caffeine consumption measures and BMI. After controlling for age, SES, BMI, caffeine consumed the morning of testing, and lifetime caffeine consumption in previous blocks, we found that speed battery performance was associated with the lifetime caffeine consumption interaction with BMI (ß = 0.45, $df = 41$, $p = 0.03$). Slope analyses (Figure 2) revealed that when BMI was low, there was a trending negative relationship between lifetime caffeine consumption and speed battery performance (ß = -0.30, $t = -1.67$, $p = 0.10$). At mean BMI, there was no relationship between lifetime caffeine consumption and speed battery performance (ß = 0.17, *t* = 1.30, *p* = 0.20), and when BMI was high, there was a positive association between lifetime caffeine consumption and speed battery performance (ß = 0.65, *t* = 2.07, *p* = 0.05).

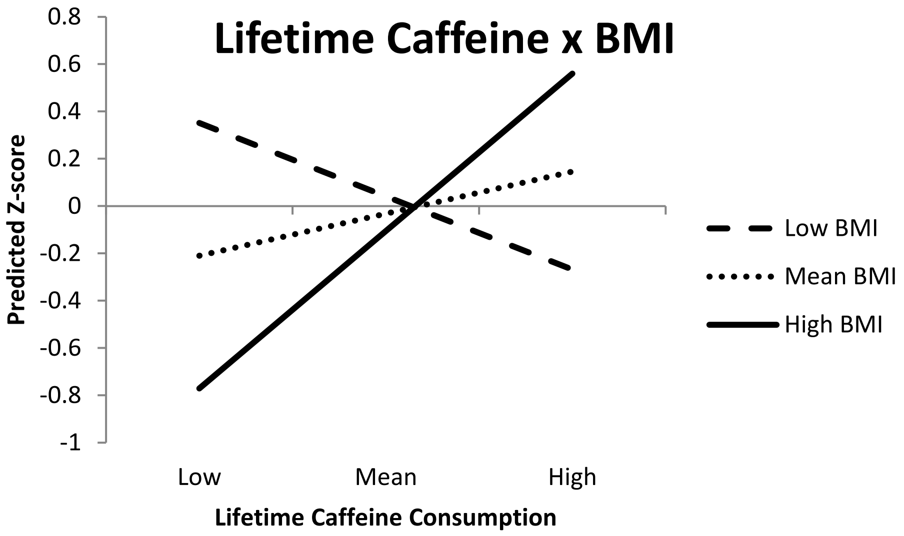

Figure 2. Interaction between lifetime caffeine consumption and BMI on speed battery performance based on *Process Macro* (Hayes, 2015) analysis. Note: vertical axis speed battery performance in z-score.

Discussion

We hypothesized that increased caffeine use would be positively associated with cognitive performance, specifically for memory and speed of processing. Our findings do not support this hypothesis. However, we found intriguing interactions between caffeine consumption and BMI for inhibitory and speed of processing performance. Specifically, our analyses support a positive association between caffeine consumption (habitual and lifetime) and both inhibitory performance and speed of processing (lifetime consumption only) for participants with high BMI, no association for participants with normal BMI, and a negative association for those with a low BMI. This would appear to be in line with the idea that habitual caffeine use provides protection against cognitive decline, at least in the overweight and obese.

Previous work has found that high BMI is often associated with decreased cognitive performance (Cournot et al., 2006; Groppe & Elsner, 2015 for a review see Prickett, Brennan, & Stolwyk, 2014), specifically with executive function deficits (Groppe & Elsner, 2015; Reinert, Po'e, & Barkin, 2013; Wolf et al., 2007), and not surprisingly is associated with decreased prefrontal metabolism (Volkow et al., 2009; Willeumier, Taylor, & Amen, 2011). However, animal studies have found that habitual caffeine may mitigate the deleterious impact of a high fat diet on both weight gain and cognitive performance associated with high BMI (Alzoubi et al., 2013; Moy & McNay, 2013). Taken together this affords the possibility that habitual caffeine exposure may buffer against the negative cognitive impact of high BMI, rather than providing general preservation of cognitive function. This is an interesting prospect that, to our knowledge, has not been systematically explored in a human population.

Yet, this does not account for the negative association with "low" BMI predicted by the interaction. It is important to note that in the predicted interaction, the negative association became significant at a BMI of 24.21, well within the normal range, indicating that individuals of healthy body weight may experience a detrimental effect of high levels of habitual caffeine consumption. That is, although two individuals reporting the same average consumption (2-3 cups of coffee per day) are estimated to consume 250 mg of caffeine from coffee per day, on average, the effective dose will vary considerably based on the individual's body mass. For example, 250 mg of caffeine for an obese participant (e.g., BMI of 30.22 and weight of 87.54 kg) would be approximately a 2.86 mg/kg dose, whereas for a healthy weight participant (e.g., BMI of 21.43 and weight of 54.88 kg), would be approximately 4.56 mg/kg; a little over one and a half times the effect dose. As such, the effect driving the positive association of higher levels of habitual caffeine consumption in obese individuals may be similar to that seen in the low consumers with normal BMI, indicating that moderate levels of habitual caffeine consumption, relative to one’s body mass, may be generally positive in nature. Due to the small scale of the current sample, we are unfortunately limited in our ability to explore this prospect. Further investigation is warranted.

However, to accept an association between BMI and executive function (Groppe & Elsner, 2015; Reinert et al., 2013; Wolf et al., 2007) would suggest that we should also find an interaction effect for performance on our FLF battery. This was not the case. One possible explanation is that our FLF battery may not actually be measuring a unitary latent variable. That is, we found that the three tasks were not associated with any single latent factor despite having been used in previous work with older adults (Glisky & Kong, 2008). This may be due, in part, to our choice to use the number of perseverative errors as the outcome measure for the WCST instead of the number of categories successfully completed, as was done in the previous studies (Glisky & Kong, 2008). This was done for two reasons. First and foremost, the number of perseverative errors increases with normal aging (Daigneault, Braun, & Whitaker, 1992; Foldi, Helm-Estabrooks, Redfield, & Nickel, 2003; Rhodes, 2004) and is indicative of frontal dysfunction (Joseph, 1999; Nagahama, Okina, Suzuki, Nabatame, & Matsuda, 2005) leading us to reason that it would be a better measure of the underlying frontal function. Second, when we included the number of categories completed in the exploratory factor analysis, as the card sorting task outcome measure, instead of the number of perseverative errors, the factors loadings were quite weak for all four factors and thus made the determination of the underlying factors more difficult. In addition, ad-hoc analyses (data not reported) using the number of categories completed on the WSCT as part of the FLF latent variable revealed no additional associations with caffeine consumption suggesting that battery composition may not be the underlying issue.

Indeed, a more likely explanation is that our sample size may not have been sufficient to tease apart the effects of long-term caffeine consumption from other individual differences. Previous work has included sample sizes well in excess of 500 participants (Hameleers et al., 2000; Jarvis, 1993; Johnson-Kozlow et al., 2002; Ritchie et al., 2007; van Boxtel et al., 2003; van Gelder et al., 2007). The current sample size was chosen with the anticipation that effects would be robust enough within a sample set particularly susceptible to caffeine, namely women (Johnson-Kozlow et al., 2002; Ritchie et al., 2007; Smith, D., Davidson, & Green, 1993; Stonehouse, Adachi, Walcott, & Jones, 2003). Yet it is possible that the direct effect of caffeine is relatively weak in comparison to other factors and may, in part, explain the variability in findings across studies. Further, previous studies finding significant associations between caffeine and task performance have had quite small beta weights for caffeine’s association across task types, with most below 0.08, indicating that the effect of caffeine may be quite subtle (Hameleers et al., 2000; Johnson-Kozlow et al., 2002; van Boxtel et al., 2003) and it is likely that our rather small, healthy, and homogenous sample was insufficient to detect this effect.

Caffeine and Memory Performance.

Unlike previous habitual caffeine consumption studies (Corley et al., 2010; Jarvis, 1993; Johnson-Kozlow et al., 2002; Ritchie et al., 2007), we found no associations between caffeine consumption and memory performance. Task demands provide an intriguing explanation for this disparity; specifically delay duration before retrieval. Whereas the current study, in an endeavor to focus our memory battery, included only tasks of immediate recall and omitted the delayed memory tests, previous studies have included delayed recall measures. Indeed, in studies that looked at individual measures of memory performance, the associations with caffeine were nearly always with delayed recall measures (Hameleers et al., 2000; Jarvis, 1993; Johnson-

Kozlow et al., 2002). Immediate recall measures have not shown such associations (Hameleers et al., 2000; van Boxtel et al., 2003). It is difficult to tell to what degree delayed recall drove the relationship in Corley and colleagues' (2010) battery as it included a range of working memory and immediate recall tasks. Together this seems to suggest that long-term caffeine consumption may have a focal impact on delayed recall or long-term memory. However, a systematic comparison of habitual caffeine consumption's impact on immediate or delayed recall in older adults has yet to be undertaken to the best our knowledge, leaving room for further exploration of this effect.

Summary. The current experiment found no support for previous findings of caffeine's general ability to protect against cognitive deficits associated with normal aging. However, we are the first to report an interaction between caffeine use and participant BMI on task performance and thus provide evidence that caffeine's effect may not be one of broad preservation, but may provide focal defense against the deleterious impact of social and dietary stress on cognitive performance. In conclusion, we suggest that caffeine's effect may be directly influenced by measures of individual difference such as BMI and thus more studies should explore the possible interaction effects between these factors when looking at the long term effect of caffeine.

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