Working Memory Performance Following Acute Alcohol: Replication and Extension of Dose by Age Interactions

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ABSTRACT. Objective: Despite the substantial number of older adult drinkers, few studies have examined acute alcohol effects in aging samples. We have explored these interactions across a variety of neurobehavioral domains and modalities and have consistently observed age-contingent vulnerabilities to alcohol-associated decrements in neurobehavioral functions. However, these studies have not been sufficiently powered to address sex differences, and, thus far, no attempt has been made to replicate results. The current study addresses these gaps. **Method:** The study used a double-blind, placebo-controlled, factorial design with two age groups (older, 55–70 years; younger, 25–35 years) and three doses (target breath alcohol concentrations: .00, .04, and .065 g/dl). Replication analyses used an independent sample (n = 90) to replicate age-contingent alcohol effects reported by Boissoneault (n = 90). Samples were combined (N = 180; 91 women) to enable sex

analyses. The dependent measure was performance efficiency in a visual working memory task. **Results:** A complex interaction between sex, age, and dose, F(2, 178) = 4.15, p = .02, appeared driven by age-contingent divergence in working memory performance, which was most pronounced between women at the .065 dose, t(28) = 4.61, p < .01, d = 1.68. Replication analyses revealed a pattern of age differences consistent with previous results, although the previously reported age by alcohol interaction failed to reach statistical significance. **Conclusions:** Results provide further support for the hypothesis that neurobehavioral effects of acute alcohol are age dependent and offer evidence that this interaction may be moderated by sex. Extensions of this work are needed to identify underlying processes and ascertain the functional impact of these effects on the health and well-being of aging adult drinkers. (*J. Stud. Alcohol Drugs*, 80, 86–95, 2019)

GING ADULTS REPRESENT a rapidly expanding Aproportion of the global population. Projected estimates indicate that by 2030, adults age 65 years and older will represent 12% of persons worldwide (He et al., 2016) and more than 20% of the U.S. population (Colby & Ortman, 2015). Among this latter group, nearly half report current alcohol consumption, with recent work indicating ongoing increases in their drinking prevalence (Breslow et al., 2017). A substantial epidemiological literature has examined consumption patterns among aging adults, with attention to both health risks (e.g., Holahan et al., 2017) and potential benefits (e.g., Ilomaki et al., 2015). Much of this work has focused on "moderate" drinking patterns, including average consumption of no more than one or two standard drinks per day for women and men, respectively (U.S. Department of Health and Human Services & U.S. Department of Agriculture, 2015). In contrast, few empirical investigations have

examined the neurobehavioral effects of acute consumption in older adults.

Examinations of neurobehavioral alterations following acute alcohol administration frequently use intoxicating doses (i.e., blood alcohol concentrations [BACs] \geq .08 g/dl). Although subintoxicating doses consistent with moderate consumption have received less attention, a limited literature suggests alterations in a range of processes, including visual perception, attentional control, and inhibitory functions (e.g., de Wit et al., 2000; Dougherty et al., 2008; Fillmore, 2007; Friedman et al., 2011; Holloway, 1994; Oscar-Berman & Marinkovi, 2007; Reed et al., 2012). However, these investigations typically limit age ranges or include insufficient samples of aging adults for meaningful analysis. Although some investigations have focused on postural control, suggesting age-associated deficits in stability at subintoxicating doses (Jones & Neri, 1994; Vogel-Sprott & Barret, 1984; Wu et al., 2017), a significant gap in the literature remains regarding acute neurobehavioral effects in aging adults.

To address this gap, our research group has conducted several investigations of acute effects in older and younger adults at subintoxicating doses (target breath alcohol concentrations [BrACs] of .04 and .065 g/dl). We have reported alcohol-associated vulnerabilities among older adults in behavioral tasks involving set-shifting (Gilbertson et al., 2009), attention (Sklar et al., 2012), and working memory (Boissoneault et al., 2014). We have also observed alcohol-associated decrements among older adults in electroencepha-

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lographic (EEG) indices of these processes across a variety of tasks (Boissoneault et al., 2016; Lewis et al., 2013; Sklar & Nixon, 2014). This pattern persists in ecologically relevant simulated driving behavior (Price et al., 2018; Sklar et al., 2014) and EEG measures gathered during driving (Lewis et al., 2016). These studies are consistent with our overarching hypothesis of age-related vulnerability to alcohol, but more provocatively, also commonly demonstrate age-contingent divergence of alcohol effects across measures (e.g., Boissoneault et al., 2014; Lewis et al., 2016; Price et al., 2018). Although these investigations included men and women as research participants, they were insufficiently powered for meaningful analysis of complex interactions between age, alcohol, and sex. This limitation is addressed in the current study.

Although the aforementioned works support our hypothesis of age-associated vulnerabilities to alcohol effects, the paucity of related work limits our capacity to compare and contrast results with independent samples. Given the novelty of the findings, their relevance to public health, and recent concerns with reproducibility in scientific research (e.g., Baker, 2016; Nosek et al., 2015), replication analyses are crucial.

Thus, the current study was constructed with two aims: (a) to replicate, in an independent sample, a prior observation (Boissoneault et al., 2014) of alcohol-associated differences in performance between older and younger adults (Aim 1: replication analyses) and (b) to explore three-way interactions between alcohol, age, and participant sex (Aim 2: sex analyses) that were previously infeasible because of restricted sample sizes. Although age- and sex-contingent effects of acute alcohol are hypothesized across a broad range of neurobehavioral processes, the current study focused on working memory because of its functional import and integration with other executive processes (e.g., attention, inhibitory function).

Given our interest in working memory as an integrated process, an "attend/ignore" working memory task (Gazzaley et al., 2005) was used in which participants attended to a pair of relevant visual stimuli while ignoring a pair of irrelevant stimuli, then subsequently indicated whether a "probe" stimulus matched either of the previously presented relevant images. In replication analyses, given our prior observation (Boissoneault et al., 2014), and consistent with our overarching hypothesis, we expected age differences in performance under active dose conditions when probe stimuli did not match targets. In contrast, Boissoneault et al. (2014) also detected evidence for alcohol-associated performance gains among older adults in trials with matching probes. Such gains are inconsistent with our general hypothesis and much of our work to date. Thus, performance in this condition was of specific interest but remained an empirical question. In sex analyses, based on extant literature reporting greater vulnerability to acute alcohol effects among women (e.g.,

Miller et al., 2009), we hypothesized three-way interactions driven by performance decrements among older women administered active doses of alcohol. Whether these potential interactions would be sensitive to task conditions remained an open question.

Method

Study design

The study used a double-blind, placebo-controlled, factorial design (2 [Age: Older vs. Younger] × 2 [Sex: Men vs. Women] × 3 [Dose: .00 vs. .04 vs. .065 g/dl Target BrACs]). Two sets of analyses are conducted in the current work. The first used an independent sample (n = 90) to assess whether novel, age-contingent effects of acute alcohol reported by Boissoneault et al. (2014; n = 90) were replicable. The second was an analysis of sex effects, combining these samples (N = 180) to facilitate analyses precluded by insufficient power in our earlier work. All procedures (e.g., measures, inclusion/exclusion criteria, recruitment practices) were identical between the current work and Boissoneault et al. (2014). All study procedures were approved by the Medical Institutional Review Board at the University of Florida. All participants provided written informed consent and were compensated for their time.

Participants, screening procedures, and inclusion/exclusion criteria

Volunteers were recruited via radio and print advertisements. Respondents were informed of general inclusionary criteria via phone calls: (a) being 25–35 or 55–70 years of age, (b) having previous experience consuming alcohol, (c) having no history of problems with alcohol or other substances, (d) being a current nonsmoker with at least 10 years of abstinence, (e) being in good physical health, and (f) having no history of significant head injury or prolonged unconsciousness. Individuals meeting these criteria were invited to participate in a screening session to determine study eligibility.

Screening procedures included collection of demographic information and inventories of anxiety (Anxiety Inventory; Spielberger, 1983) and depressive symptomatology (Beck Depression Inventory [BDI-II] for individuals ages 25–35 years [Beck et al., 1996]; Geriatric Depression Scale [GDS] for individuals ages 55–70 years [Yesavage et al., 1982–1983]). Recent (6-month) alcohol consumption was assessed via quantity-frequency index (Cahalan et al., 1969). Women consuming one or fewer standard drinks per day and men consuming two or fewer drinks per day remained eligible for study participation. Trained research assistants administered a computerized diagnostic interview (Robins et al., 1995) assessing probabilistic Axis-1 diagnoses accord-

ing to criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994). Exclusionary criteria included lifetime diagnoses of any substance dependence (excluding nicotine) or psychotic disorder or current diagnosis of a major depressive disorder. Current or past medical histories including epilepsy, uncontrolled type 2 diabetes, uncontrolled hypertension, electroconvulsive therapy, HIV/AIDS, head trauma, or other histories challenging data interpretation were also exclusionary. Women who were pregnant or breastfeeding were disqualified. The use of common prescription or overthe-counter medications was allowed only when not contraindicated for use with alcohol. The use of antihypertensives, hormone replacement, or serotonin/norepinephrine reuptake inhibitors was allowed only in cases of stabilized use (≥3 months).

Experimental procedures and alcohol administration

Experimental procedures were initiated between 9:00 A.M. and 10:00 A.M. Participants were instructed to fast for at least 4 hours before their arrival and were provided a light breakfast (~220 kcal). Negative urine drug screens, breath alcohol measures, and, where relevant, pregnancy tests were required for continued eligibility. Recent use of medications was reviewed; recent use of medications contraindicated for use with alcohol, psychostimulants, or those with sedative properties (e.g., sleep aids) was exclusionary.

Alcohol administration procedures were adapted from Fillmore et al. (2000) and were consistent with our previous work. Within age and sex groups, participants were randomly assigned to one of three doses. Modified Widmark calculations (Watson et al., 1981) were used to estimate alcohol volumes required to achieve targeted peak BrACs of .00 (placebo), .04 (low), or .065 (moderate) g/dl. Estimates accounted for participant age, sex, height, and weight. Two hundred-proof medical-grade ethanol was added to 366 ml of caffeine-free, sugar-free, citrus soda (split across two isovolumetric beverages). To enhance placebo effectiveness via sensory cues, all container rims and beverage surfaces were misted with diluted ethanol. Beverages were consumed within 5 minutes (2 minutes/beverage; 1 minute break between beverages). To maintain double-blind procedures, drink preparation, delivery, and BrAC checks were performed by study staff who did not participate in testing procedures. BrAC results were obscured from participants and study staff responsible for testing. BrACs (Intoxilyzer, Model 400; CMI, Inc., Owensboro, KY) were measured throughout testing, at 10, 25, 60, 75, and 85 minutes after consumption; however, only those immediately preceding (25 minutes; pre-test) and following (60 minutes; post-test) the working memory task were analyzed. A standard measure of subjective intoxication (10-point Likert scale anchored from no intoxication to most intoxicated I have ever been; e.g., Peterson et al., 1990) was gathered during each BrAC check. A third beverage was delivered at 25 minutes after consumption. For most participants (>95%), this beverage contained no alcohol. To raise BrACs to target levels in participants with BrACs <50% of target (i.e., <.02 or <.0325 g/dl), this beverage contained half of the previously consumed dose.

Working memory task

The working memory task (Gazzaley et al., 2005) included presentation of two "face" stimuli and two "scene" stimuli per trial (i.e., four target stimuli per trial). As task performance relied on attending to only one of the two stimuli sets in any given trial, faces and scenes were selected as stimuli sets because of their discernibility. All visual stimuli were gray scale. Facial stimuli were evenly distributed between male and female faces; however, all face stimuli presented within any given trial were the same sex.

Each target stimulus was presented for 800 ms (200 ms interstimulus interval). All possible sequences of target stimuli presentation (e.g., Scene-Face-Face-Scene) were used, with equal pseudorandom distribution across the experiment. Target stimuli were followed by a 9,000-ms delay (fixation cross only), after which a probe image was presented (1,500 ms). Participants used a two-button response pad to indicate whether the probe matched any of the target stimuli ("Hit Trials") or did not match ("Correct Rejection Trials"). A 4,000-ms response window was initiated at probe presentation.

Each block of 20 trials was preceded by an instructional set. Participants were instructed to "remember scenes and ignore faces" (Scene Condition) or "remember faces and ignore scenes" (Face Condition). All probe images in the Scene Condition were scenes; all probes in the Face Condition were faces (and matched the sex of target stimuli). Fifty percent of trials were Hit Trials and 50% Correct Rejection Trials. Instructions for all conditions directed participants to respond "as quickly and accurately as possible."

The task required approximately 25 minutes to complete and was preceded and followed by BrAC checks. Accuracy and reaction time measures were collected and used to derive an efficiency measure (accuracy/reaction time for correct trials). Efficiency measures were derived for all combinations of instruction sets and probe types (e.g., Hit Trials in Scene Condition).

A Control Condition was included as a means of verifying performance validity and adherence to instructions. Participants were instructed to passively view the target stimuli and respond to a directional arrow (left or right response buttons) displayed in place of the probe. All other aspects of stimuli presentation were consistent with experimental conditions. Control trials were administered only after experimental trials had been completed. Preliminary analysis of control trials observed exceptionally high accuracy (ap-

TABLE 1. Descriptive measures by age (replication sample)

Variable	Younger (25–35 years) M (SD)	Older (55–70 years) M (SD)
Age, in years	27.2 (2.4)	62.6 (4.8)
Education, in years	16.6 (1.2)	16.2 (2.6)
Depressive symptoms (BDI/GDS) ^{a,b}	$2.3 (3.0)^a$	$1.9(2.3)^b$
Anxiety symptoms (AI) ^c	40.8 (5.8)	42.8 (7.2)
Standard drinks/day (average)	0.54 (0.34)	0.71 (0.61)

^aBeck Depression Inventory, Second Edition (Beck et al., 1996); ^bGeriatric Depression Scale (Yesavage et al., 1982–1983); ^cState Anxiety Index (Spielberger, 1983).

proaching 100%) across groups, suggesting participants attended to probe stimuli and instructional sets throughout the task. No exclusions for poor control condition performance were made.

Analysis strategy

Analyses were conducted using SAS Version 9.4 (SAS Institute, Inc., Cary, NC). As described above, two families of analyses were conducted. The primary dependent measure for both sets of analyses was efficiency, indexing speed/accuracy trade-offs (Sternberg, 1984; Townshend & Ashby, 1978). Efficiency has been used in previous works from our laboratory (e.g., Sklar et al., 2012) and others (e.g., Durazzo et al., 2012) and provided the primary performance metric in the Boissoneault et al. (2014) study. In addition to performance efficiency, both sets of analyses examined demographic/affective characteristics, BrACs, and subjective intoxication. To better appreciate the pattern of results across analyses and studies, effect size estimates are reported as partial eta squared or Cohen's d. Where appropriate, results and effect sizes are reported for nonsignificant findings to afford comparison with results reported by Boissoneault et al. (2014).

Replication analyses. Boissoneault et al. (2014) reported divergent effects of acute alcohol that were most apparent in efficiency measures and were observed regardless of instructional set. Thus, the current analysis focused on efficiency and collapsed across instructional sets. The primary analytical approach remained the same, including (2 [Age] × 3 [Dose]) analyses of variance (ANOVAs) conducted separately for each probe type (hit vs. correct rejection) and a priori comparisons of active to placebo doses within each age group.

Sex analyses. Repeated-measures (RM) ANOVAs (2 [Age] × 3 [Dose] × 2 [Sex] × 2 [Repeated: Instruction Set]) were used to explore potential interactions with sex in the combined sample. The instructional set was not collapsed in these analyses, as potential interactions with sex were not addressed in previous investigations (Boissoneault et al., 2014). Where interactions with sex were noted, analyses were decomposed by sex, instructional set, or both. A priori

comparisons of older and younger groups, within each dose, were conducted separately for men and women.

To clarify relationships in the original and replication data sets (Aim 1) and to add clarity to unanticipated results (Aim 2), we also conducted several post hoc analyses. The rationale and approach for these analyses are described below with regard to results from planned analyses.

Results

Replication analyses (Aim 1)

Participants. Replication analyses included 90 participants (45 older, 45 younger). Descriptive measures are presented in Table 1. Preliminary analyses detected no differences between dose groups. No age differences were detected for education, average alcohol consumption (standard drinks/day), or anxiety symptomatology.

BrACs and subjective intoxication. RM ANOVA (2 [Age] \times 2 [.04 vs .065 g/dl Dose] \times 2 [Repeated: Pre-Test vs. Post-Test]) detected no differences in BrACs by age group or any interactions with age. BrACs were lower at task completion than at task initiation, F(1, 54) = 7.38, p < .01. BrAC results by age were highly consistent with those reported in Boissoneault et al. (2014) and other studies from our laboratory (e.g., Price et al., 2018), thus, only BrACs by sex (reported below) were depicted graphically in the current work.

RM ANOVA for ratings of subjective intoxication detected no age effect or age by dose interaction. A within-subject effect of the measurement period was noted, F(1, 54) = 24.78, p < .01, with subjective intoxication declining across time. No within-subject interactions were observed.

Working memory performance efficiency. ANOVA (2 [Age] × 3 [Dose]) for hit efficiency detected a significant main effect of age group, F(1, 88) = 11.70, p < .01, $\eta_p^2 = .123$, with older adults evincing lower efficiency. No interaction was detected, F(2, 88) = 0.82, p = .44, $\eta_p^2 = .019$. Consistent with Boissoneault et al. (2014), t tests were performed comparing performance under each active dose to placebo within each age group. No differences were observed in either older (p = .52, d = 0.11; p = .62, d = 0.08, for .04 and .065 doses, respectively) or younger (p = .76, d = 0.11; p = .61, d = 0.18, respectively) groups.

ANOVA for correct rejection efficiency detected a significant main effect of age group, F(1, 89) = 7.73, p < .01, $\eta_p^2 = .084$, with lower efficiency among older adults. No interaction was observed, F(2, 89) = 1.33, p = .27, $\eta_p^2 = .031$. A priori comparisons revealed no differences relative to placebo in either older (p = .83, d = 0.08; p = .45, d = 0.28, for .04 and .065 doses, respectively) or younger (p = .54, d = 0.23; p = .41, d = 0.36, respectively) groups.

Post hoc analyses. Despite strong similarities between group means and the visual pattern of results between data sets, our replication analyses failed to reproduce interaction

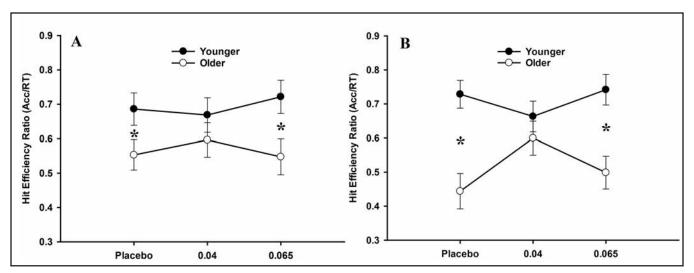


FIGURE 1. Hit efficiency $(M \pm SE)$ for replication (2A) and original (2B) samples. Comparisons in the original data set revealed significantly greater efficiency for hit trials among younger, relative to older, individuals at the placebo, t(29) = 4.15, p < .01, d = 1.58, and .065, t(28) = 3.71, p < .01, d = 1.50, but not .04, t(27) = 0.98, p = .34, d = 0.36, doses. A consistent pattern was observed in the replication sample, including differences at the placebo, t(32) = 2.51, p = .02, d = 0.87, and .065, t(25) = 2.43, p = .02, d = 0.96, but not .04, t(26) = 1.00, p = .32, d = 0.38, doses. Figures 2A and 2B depict these patterns in the replication and original samples, respectively. ACC/RT = accuracy/reaction time.

*p < .05.

results detected by the analysis strategy used by Boissoneault et al. (2014). To reconcile both sets of findings and clarify patterns across and within each data set, we conducted a set of post hoc comparisons. Within each data set, age groups were compared at each alcohol dose.

Comparisons in the original data set revealed significantly greater efficiency for hit trials among younger, relative to older, individuals at the placebo, t(29) = 4.15, p < .01, d = 1.58, and .065, t(28) = 3.71, p < .01, d = 1.50, but not .04, t(27) = 0.98, p = .34, d = 0.36, doses. A consistent pattern was observed in the replication sample, including differences at the placebo, t(32) = 2.51, p = .02, d = 0.87, and .065, t(25) = 2.43, p = .02, d = 0.96, but not .04, t(26) = 1.00, p = .32, d = 0.38, doses. Figures 1A and 1B depict these patterns in the replication and original samples, respectively.

In the original sample, correct rejection analyses indicated greater efficiency among younger, relative to older, participants at the .04, t(27) = 2.49, p = .02, d = 0.94, and .065, t(28) = 3.94, p < .01, d = 1.45, doses. A consistent pattern was observed in the replication sample at the .065, t(26) = 2.46, p = .02, d = 0.94, but not .04, t(26) = 0.62, p = .54, d = 0.23, dose. No age difference was observed under placebo conditions in either the original, t(29) = 0.66, p = .51, d = 0.24, or replication, t(32) = 1.58, p = .12, d = 0.55, samples. Figures 2A and 2B depict these patterns.

Sex analyses (Aim 2)

Participants. Sex analyses included 96 younger (47 women) and 84 older (44 women) volunteers. Descriptive measures are presented by sex and age in Table 2. Preliminary

analyses of key demographic/affective measures detected no differences between dose groups.

Greater average alcohol consumption was reported by men, F(1, 179) = 18.60, p < .01. An age by sex interaction was revealed for anxiety symptomatology, F(1, 179) = 9.05, p < .01, with older women reporting greater symptomatology than other groups (ps < .01), which did not differ. Education was equivalent across groups. No sex differences in depressive symptomatology were noted within either age group.

BrACs and subjective intoxication. RM ANOVA (2 [Sex] \times 2 [Age] \times 2 [.04 vs. .065 g/dl Dose] \times 2 [Repeated: Pre-Test vs. Post-Test]) detected no effects of, or interactions with, age or sex. BrACs were lower at task completion than at task initiation, F(1, 105) = 20.09, p < .01. BrAC curves by sex and dose are depicted in Figure 3.

RM ANOVA conducted on measures of subjective intoxication detected no effects of or interactions with sex or age. A within-subject effect of measurement period was noted, F(1, 105) = 24.21, p < .01, such that subjective intoxication was lower at post-test. No within-subject interactions were observed.

Working memory performance efficiency. The RM ANO-VA (2 [Sex] × 2 [Age] × 3 [Dose] × 2 [Repeated: Instruction Set]) for hit efficiency detected no main effect of or interactions with sex.

The RM ANOVA (2 [Sex] × 2 [Age] × 3 [Dose] × 2 [Repeated: Instruction Set]) for correct rejection efficiency revealed a four-way interaction, F(2, 178) = 4.15, p = .02, $\eta_p^2 = .047$. This interaction was explored with two complementary strategies. ANOVAs ([Sex] × [Age] × [Dose]) were conducted separately within each instructional set (i.e., "remember faces" and "remember scenes"). Subsequently, RM

TABLE 2. Descriptive measures by age and sex (all participants)

	Younger (25–35 years)		Older (55–70 years)	
Variable	Men M (SD)	Women M (SD)	Men M (SD)	Women M (SD)
Age, in years	28.0 (2.7)	27.2 (2.5)	61.8 (4.6)	61.7 (4.6)
Education, in years	16.4 (1.3)	17.0 (1.0)	16.4 (2.5)	16.2 (1.8)
Depressive symptoms (BDIa/GDSb)	$2.5(3.0)^a$	$2.5(2.7)^a$	$1.8 (2.3)^b$	$2.0(2.1)^{b}$
Anxiety symptoms (AI) ^c	40.6 (5.5)	40.5 (5.2)	40.7 (5.1)	45.9 (7.4)
Standard drinks/day (average)	0.72 (0.46)	0.46 (0.33)	0.80(0.65)	0.48 (0.35)

^aBeck Depression Inventory, Second Edition (Beck et al., 1996); ^bGeriatric Depression Scale (Yesavage et al., 1982–1983); ^cState Anxiety Index (Spielberger, 1983).

ANOVAs ([Age] \times [Dose] \times [Repeated: Instruction Set]) were conducted separately within each sex.

ANOVA conducted on the "remember scenes" condition revealed no sex effect or sex-contingent interactions. Analysis of the "remember faces" condition detected a trend toward a three-way interaction, F(2, 168) = 2.31, p = .10, $\eta_p^2 = .027$. This trend appeared driven by the greater magnitude of difference between older and younger women under .065 conditions, t(28) = 4.61, p < .01, d = 1.74, relative to those between men, t(26) = 1.94, p = .06, d = 0.76.

Among men, RM ANOVA revealed an age main effect, F(1, 88) = 11.64, p < .01, $\eta_p^2 = .086$, but no effect of instruction set or interaction with dose. Among women, interactions between age and dose, F(2, 89) = 5.05, p < .01, $\eta_p^2 = .106$, and between age, dose, and instruction set, F(2, 89) = 3.04, p = .05, $\eta_p^2 = .067$, were observed. Subsequent (2 [Age] × 3 [Dose]) ANOVAs were conducted separately for each instruction set. Analysis of the "remember scenes" condition revealed an age effect, with older women performing less efficiently, F(1, 89) = 9.55, p < .01, $\eta_p^2 = .095$.

However, this difference was detected only in the .065 g/dl dose group, t(28) = 2.44, p = .02, d = 0.89. Analysis of the "remember faces" condition revealed an interaction between dose and age, F(2, 89) = 6.14, p < .01, $\eta_p^2 = .127$, with younger women evincing more efficient performance than older women at .065 g/dl, t(28) = 4.61, p < .01, d = 1.68, but not the .04 or placebo doses.

Figures 4 and 5 depict the pattern of results for scene and face conditions, respectively, revealed by both analytical approaches.

Post hoc analyses. Analyses were conducted to clarify the substantial divergence in performance efficiency in response to face stimuli noted between older and younger women at the .065 dose.

ANOVAs (2 [Age] × 2 [Dose: Placebo vs. .065]) were conducted separately for the components of efficiency, accuracy, and reaction time. Accuracy analysis revealed no dose by age interaction (p = .43). Reaction time analysis revealed an interaction, F(1, 61) = 10.16, p < .01, $\eta_p^2 = .149$, that was consistent with efficiency results; older women responded

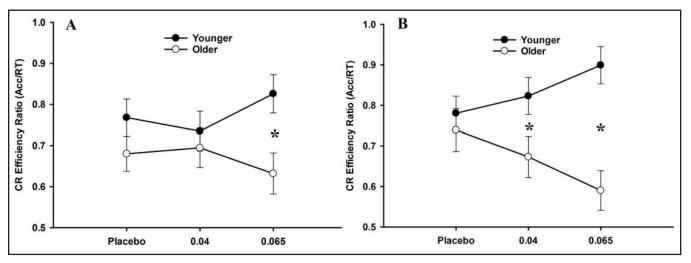


FIGURE 2. Correct rejection (CR) efficiency ($M \pm SE$) for replication (3A) and original (3B) samples. In the original sample, correct rejection analyses indicated greater efficiency among younger participants at the .04, t(27) = 2.49, p = .02, d = 0.94, and .065, t(28) = 3.94, p < .01, d = 1.45, doses. A consistent pattern was observed in the replication sample at the .065, t(26) = 2.46, p = .02, d = 0.94, but not .04, t(26) = 0.62, p = .54, d = 0.23, dose. No age difference was observed under placebo conditions in either the original, t(29) = 0.66, p = .51, d = 0.24, or replication, t(32) = 1.58, p = .12, d = 0.55, samples. Figures 3A and 3B depict these patterns in the replication and original samples, respectively. ACC/RT = accuracy/reaction time $t = t^2$

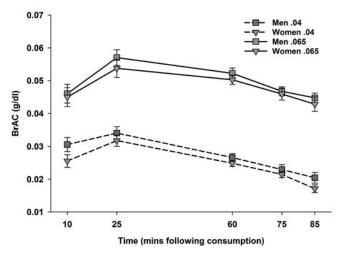


FIGURE 3. Breath alcohol concentrations (BrACs) ($M \pm SE$) by sex and dose. Repeated-measures analyses of variance detected no effects of, or interactions with, age or sex on BrACs. BrACs were lower at post-test (60 minutes) than pre-test (25 minutes), F(1, 105) = 20.09, p < .01. Mins = minutes.

more slowly, t(28) = 2.36, p = .025, d = 0.86, and younger women more rapidly, t(30) = 2.12, p = .04, d = 0.75, under .065 conditions relative to their respective placebo controls.

Although BrAC and subjective intoxication measures were equivalent between groups, these measures were incorporated in analysis of covariance (ANCOVA) models to ascertain their relationships with performance efficiency. Separate ANCOVA models included age group, each covariate, and group by covariate interaction terms. No main effect of post-task BrAC (p=.82) or interaction with age (p=.88) was detected. Analysis of post-task subjective intoxication revealed a strong interaction, F(1, 29) = 10.25, p < .01, $\eta_p^2 = .283$, such that the association between reported intoxication

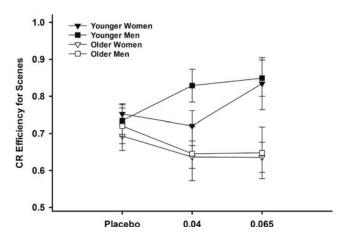


FIGURE 4. Correct rejection (CR) efficiency ($M \pm SE$) for men and women in "remember scenes" condition. Two-way analysis of variance, conducted separately among women, revealed an age effect, with older women performing less efficiently, F(1, 89) = 9.55, p < .01. Although performance among men is presented for comparison, analysis was confined to repeated-measures analysis of variance, as results indicated no interactions with instruction set.

and performance was positive among younger women (r = .48, p = .07) but negative among older women (r = -.69, p < .01).

Discussion

Replication (Aim 1)

Our replication analysis demonstrated age differences in performance efficiency for correct rejection trials at the .065 dose, consistent with relationships observed in the original data set. Consistent with Boissoneault et al. (2014), we also demonstrated that on hit trials an age main effect was apparent, but there was no significant age by alcohol interaction. In contrast with the earlier work, performance on hit trials was not improved among older adults at the .04 dose. Further, our analysis failed to replicate an age by dose interaction in correct rejection performance. Although the significance and directionality of age differences under the .065 and placebo conditions were consistent between studies, the strength of these effects varied. Magnitudes of difference between age groups were smaller under placebo conditions in the original data set (d = 0.24) relative to the replication sample (d = 0.55) but more pronounced under .065 conditions (d = 1.45 vs. d = 0.94), contributing to the discrepancy in interaction findings despite the similar patterns. Relatedly, these magnitude differences appeared to underlie discrepancies in within-age comparisons between placebo and active dose performance between studies, with the Boissoneault work detecting some within-age differences that were not observed in the current work.

Taken together, results from both studies support the conclusion that neurobehavioral effects resulting from moderate

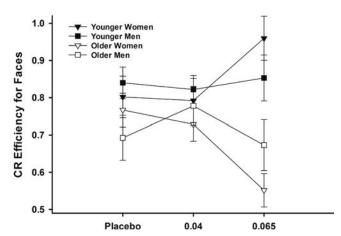


FIGURE 5. Correct rejection (CR) efficiency $(M \pm SE)$ for men and women in "remember faces" condition. Two-way analysis of variance, conducted separately among women, revealed an interaction between dose and age, F(2, 89) = 6.14, p < .01. Although performance among men is presented for comparison, analysis was confined to repeated-measures analysis of variance, as results indicated no interactions with instruction set.

alcohol consumption display age-contingent divergence in a manner sensitive to both task conditions and dose. This conclusion is consistent with our observations using electrophysiological (e.g., Lewis et al., 2013, 2016) and behavioral measures (e.g., Gilbertson et al., 2009; Sklar et al., 2012) across diverse tasks, including simulated driving (e.g., Price et al., 2018; Sklar et al. 2014). Although these results support the larger hypothesis of age-related vulnerability to alcohol effects, there remains a paucity of programmatic research directed to extending, clarifying, or challenging this interpretation.

Sex effects (Aim 2)

Analyses of correct rejection efficiency revealed an age-contingent divergence of performance among women administered the .065 dose. This interaction was particularly marked in responses to facial stimuli. Under these conditions, older women evinced the greatest performance decrements relative to other groups. In contrast, younger women displayed substantial performance advantages, with higher efficiency than other groups. We hypothesized that women in the current sample would be more sensitive to acute alcohol effects (see Miller et al., 2009, for a review) and that older women would show greater vulnerability. However, the dose-contingent performance advantages among younger women were surprising. We have previously observed some indications of alcohol-associated facilitation in working memory and attentional functions (Boissoneault et al., 2014; e.g., Lewis et al., 2013) but lacked the statistical power to determine whether such advantages were sex specific.

Although few studies have examined sex differences in the neurobehavioral effects of acute administration, the available work does not suggest sex-contingent advantages under moderate doses (e.g., Miller et al., 2009; Mills & Bisgrove, 1983). Thus, although recognizing the necessity of further investigation, we speculate that alcohol-associated performance enhancement among younger women, and decrements among older women, may be specific to task stimuli soliciting social/affective processing, such as the facial stimuli used in the current experiment. Notably, whereas faces are potent sources of affective information, our task stimuli were designed to contain no overt emotional expressions; all stimuli were neutral. Whether the observed interactions would be altered in a task using facial stimuli with emotional valence remains an empirical question for further study.

The current data provide a foundation for future inquiry but do not facilitate nuanced assessment of potential mechanisms. Post hoc analyses indicated that divergence in efficiency noted among women under .065 conditions was largely attributable to a marked divergence in reaction times. Older women responded more than 300 ms slower and younger women more than 200 ms faster relative to controls.

These data give rise to several plausible, but necessarily speculative, hypotheses.

Alcohol-associated alterations in inhibitory function may have differed by age, with younger women responding more impulsively and older women engaging greater inhibitory control relative to placebo groups. Consistent with this interpretation, we have noted facilitation of risk-associated driving behaviors (e.g., reduced braking in response to a potential threat) in younger adults, but attenuation of such behaviors (e.g., earlier and more pronounced braking) in older adults, under active dose conditions (Price et al., 2018). The age-specific relationships between subjective intoxication and performance are also consistent with this interpretation but offer only indirect support. Inclusion of state impulsivity measures in future work may provide greater clarification.

Relative to younger adults, older adults demonstrate decrements in face processing associated with differential facial search strategies, including greater focus on the lower face and mouth (e.g., Sullivan et al., 2007) and fewer fixations while scanning (e.g., Wong et al., 2005). Thus, one possibility for the observed age divergence is that the relative impact of alcohol on performance efficiency may vary by facial search strategy. Alcohol-associated performance advantages are often attributed to an "alcohol myopia" effect (Steele & Josephs, 1990). This enhancement of attention may advantage performance in individuals with optimal facial search strategies but disadvantage those without. The nature of the current data precludes a direct test of this hypothesis but highlights the utility of eye tracking in extensions of this work.

That a specific sensitivity to social stimuli among women may affect neurobehavioral performance following alcohol consumption is a novel finding. It is provocative that such an effect may be age contingent in its directionality, even in the absence of strong support implicating specific underlying processes. Although the persistence of these effects in contexts outside of the laboratory remains unknown, the commonality of alcohol consumption in situations requiring social processing suggests their functional relevance.

Limitations

In evaluating findings of the current study, several limitations bear consideration. First, although rigorous screening methods/criteria were applied to avoid inclusion of individuals with potentially confounding medical histories, elimination of all potential confounds was infeasible. Data for some risk factors contributing to neuropsychological decline, such as sleep quality and estrogen levels (Ratcliff & Van Dongen, 2009; Sherwin, 2012), were not collected.

Second, meaningful analyses regarding the potential influence of hormonal status on the observed age effects in women were limited. Data regarding the use of hormonal contraception and hormone replacement therapies were

collected. However, the disproportionate distribution in frequency of hormonal contraception across age groups (common among younger women, rare among older) and low frequency of hormone replacement (older women only, n=3) limited the potential utility of these measures in covariate analyses. Data regarding ovarian cycle/phases were not collected.

Third, because of concerns regarding participant safety, efforts to eliminate medical/psychiatric issues confounding data interpretation, and the nature of volunteer-based community sampling, participants in the current study were generally healthier than would be expected from a random sample of community members. These generalizability considerations apply similarly to affective measures and demographic characteristics of the sample. However, that alcohol-associated neurobehavioral vulnerabilities were noted in older adults despite these protective factors also bears consideration and may imply greater vulnerability in the general community.

Fourth, the current work focused on moderate drinkers and used National Institute on Alcohol Abuse and Alcoholism "low-risk" guidelines for weekly consumption as inclusion criteria. This approach was appropriate given the potential for interpretational issues associated with consumption levels exceeding these guidelines. However, we did not limit inclusion by drinking pattern. Therefore, although average consumption was limited, potential differences in drinking frequency or typically consumed quantity/occasion (e.g., Lewis et al., 2018) were not accounted for. In future studies, exclusion of or accounting for specific patterns of alcohol consumption (e.g., high occasional consumption without exceeding average limits) may be advantageous.

Fifth, although between-subjects designs confer several advantages to acute administration studies, the inherent limitations of this approach must be considered. In extending the current findings, within-subjects assessment may allow for greater control over several aforementioned limitations, including intersubject variability in drinking patterns.

Last, the data presented reflect only behavioral performance. The lack of data from additional modalities (e.g., eye tracking, neurophysiology) limits interpretation. The inclusion of multimodal methods in extensions of this work will enhance both the interpretation of results and elucidation of underlying mechanisms.

Conclusions

Taken together, these results provide additional support for the hypothesis that neurobehavioral effects of acute alcohol consumption are age dependent. Findings from our replication analysis reinforced earlier observations of this age-related susceptibility under .065 conditions and strengthened effect size estimations for this relationship but failed to disambiguate potential performance advantages in

older adults under .04 conditions. Sex analyses indicated that interactions between alcohol and age may be pronounced among women, particularly in contexts involving social/affective stimuli. Although our group has demonstrated the functional relevance of age-contingent alcohol effects in driving behavior (e.g., Price et al., 2018), further work is needed to ascertain potential impacts on social functioning and other daily-life measures critical to the health and wellbeing of aging adults.

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