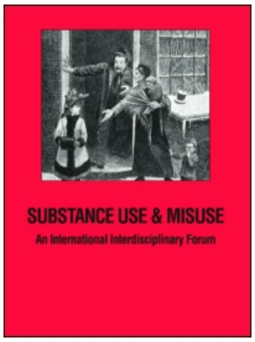

Substance Use & Misuse

ISSN: 1082-6084 (Print) 1532-2491 (Online) Journal homepage: http://www.tandfonline.com/loi/isum20

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SUBSTANCE USE & MISUSE
http://dx.doi.org/10.1080/10826084.2016.1245341

ORIGINAL ARTICLE

Gender Differences in Cognitive Functioning in Older Alcohol-Dependent Patients

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ABSTRACT

Background: Alcohol dependence is associated with impairments in cognition, especially in later life. Previous studies suggest that excessive drinking has more negative impact on cognition in women than in men. *Objectives*: In this study, differences in cognition between male and female older, alcohol-dependent patients were examined. *Method*: Older alcohol-dependent inpatients ($N = 164$, 62.2% men, mean age 62.6 ± 6.4) underwent neuropsychological tests of sensitivity to interference, mental flexibility, and visual processing. *Results*: No gender differences were found in age, educational level, estimated premorbid verbal intelligence, and sensitivity to interference. Duration of alcohol dependence was longer for men than for women. Men performed better than women on visual processing, and women better than men on mental flexibility. The superior mental flexibility of women remained significant after adjustment for duration of alcohol dependence. *Conclusions/Importance*: Older alcohol-dependent inpatients performed below average on cognitive tasks, which suggests that long-term excessive alcohol use negatively affects cognition. Our study does not demonstrate more severe cognitive impairment in women than in men.

KEYWORDS
Alcohol dependence; cognition; elderly; gender differences; inpatients

Alcohol dependence (AD) is associated with impairments in cognitive functioning, especially in later life. Of all patients with AD, 50% to 80% experience mild to severe cognitive impairment (Bates, Bowden, & Barry, 2002). The cognitive domains that are affected by severe chronic use of alcohol are diverse, and include among others cognitive flexibility, problem solving, decision making, working memory, response inhibition, attention, verbal fluency, and visual-spatial abilities (Bates, Buckman, & Nguyen, 2013; Fernández-Serrano, Perez-Garcia, Schmidt Rio-Valle, & Verdejo-Garcia, 2010; Loeber et al., 2009; Stavro, Pelletier, & Potvin, 2013). Most of these studies have been performed in adults aged 40–50 years. Studies in older alcohol-dependent patients are scarce, but have demonstrated particularly difficulties with executive skills (Munro, Saxton, & Butters, 2000) and cognitive flexibility (Wiseman, Souder, & O'Sullivan, 1997).

Numerous studies have revealed a relationship between long-term excessive alcohol consumption and atrophy of cortical brain tissue, in particular the frontal lobes, the limbic systems, and the cerebellum (Green et al., 2010; Momenan et al., 2012; Moselhy, George, & Kahn, 2001; Oscar-Berman & Marinković, 2007; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997; Sullivan & Pfefferbaum, 2005). In older alcohol-dependent patients, more severe structural abnormalities than in younger alcohol-dependent patients were found, even when the effects of normal aging and actual lifetime alcohol consumption were taken into account (Pfefferbaum et al., 1997).

The brain changes resulting from excessive alcohol use appear to be different between men and women (Agartz, Momenan, Rawlings, Kerich, & Hommer, 1999; Hommer, Momenan, Kaiser, & Rawlings, 2001; Pfefferbaum, Rosenbloom, Deshmukh, & Sullivan, 2001). Hommer and colleagues reported that women with AD had significantly smaller volumes of grey and white matter than women without AD. These differences, particularly in grey matter, were considerably larger than those found between men with and without AD (Hommer et al., 2001). Another neuroimaging study found greater reductions in hippocampal volumes in women with AD than in men with AD (Agartz et al., 1999). Mann et al. (2005) found comparable brain atrophy in men and women, despite a significantly shorter duration of AD in women. Conversely, Pfefferbaum et al. (2001) observed cortical atrophy in men with AD, but not in women with AD, after several months of sobriety. The authors attributed this to confounders such as smoking, or possibly to a more rapid recovery of cortical brain volume in women. Notwithstanding Pfefferbaum's results, most of these findings suggest that women are more susceptible to alcohol than men. This may be explained by the fact that after an equivalent dose of alcohol, on average, women have higher blood

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ethanol levels than men, because of a smaller body size (Jones & Jones, 1976; Lieber, 1997), a higher percentage of body fat and a lower percentage of body water than men per kilogram of body weight (Frezza et al., 1990; Lieber, 1997). In addition, the effect of alcohol consumption on brain and cognition may be different between men and women due to gender differences in the interaction between alcohol metabolism and hormonal status (Dufouil, Ducimetière, & Alpérovitch, 1997).

In addition to gender differences in the physical effects of alcohol, men and women also differ in drinking patterns. Women with AD report less lifetime drinking and a later age of onset than men (Agartz et al., 1999). This has been called "the telescoping effect" of excessive alcohol use in women: despite later onset and less alcohol consumption per occasion, women experience a more rapid progression of the negative consequences associated with excessive alcohol use than men (Mann et al., 2005; Piazza, Vrbka, & Yeager, 1989).

As it has been shown that neuropsychological scores of detoxified alcoholics are correlated with gray and white matter volumes in the brain (Chanraud et al., 2007), it is expected that, as a consequence of the brain tissue loss in AD, decline of cognitive functioning also differs between men and women. However, most research on cognitive functioning in alcohol-dependent persons has been done (mainly) in men, and studies that have made direct comparisons between men and women in cognitive functioning in alcohol-dependent persons are scarce. The first study to assess gender differences in problem solving ability, involving spatial relationships, in alcohol-dependent adults was performed by Acker (1986). Alcoholics of both genders (mean age of 42.6 ± 9.8 years) performed poorly compared with control subjects. In spite of the men reporting more years of drinking, the men's performance was equally poor as the women's performance, which supports the idea of a greater vulnerability of women to the cognitive effects of long-term excessive alcohol use.

A study in Russian treatment-seeking alcohol-dependent patients in their third week of treatment (mean age: 32.2 ± 5.1 years) showed that both alcohol-dependent men and women performed more poorly on a wide array of cognitive tests than healthy controls. However, female performance was more strongly impacted than male performance on tests of perceptual and visual planning and processing, working memory, and motor control, including sensitivity to interference (Stroop test) (Flannery et al., 2007). Alarcon, Nalpas, Pelletier, and Perney (2015) observed no gender differences in scores on the Montreal Cognitive Assessment (MoCA) in hospitalized alcohol-dependent patients aged 49.9 ± 9.2 years. In a sample of 143 male and female alcoholics in their thirties, Parsons (1994) did not find gender differences in performance on 16 neurocognitive tests in the verbal, visual-spatial, perceptual-motor, and semantic memory domains. No gender differences were found either when the same tests were administered to another sample of 90 alcoholics, and efficiency (accuracy divided by time needed to complete the test) was taken into account (Glenn & Parsons, 1992).

In older persons, gender differences in the association between alcohol consumption and cognitive function have only been studied in population-based samples. Some of these studies have demonstrated beneficial effects of alcohol on cognition, specifically in women (Britton, 2004; Dufouil et al., 1997; Yonker, Nilsson, Herlitz, & Anthenelli, 2005). However, these studies generally did not include persons who are alcohol-dependent or drinking excessively, e.g. the persons in the "heavy drinking" category of Yonker et al. drank on average 11.1 ± 4.2 alcoholic consumptions per week. One large population-based study of American older adults included a subgroup of participants who were chronic heavy drinkers or had a problem-drinking history. This study showed that heavy or problem drinking was neither associated with "fluid intelligence" (immediate free recall, delayed free recall, and working memory) in men, nor in women. However, it was associated with lower crystallized intelligence (acquired and generalized knowledge) in women, but not in men (Lyu & Lee, 2012).

With the current study, we aimed to further illuminate gender differences in cognitive functioning, in particular executive functioning, in older patients with AD. We sought to measure a range of cognitive abilities that are vulnerable to the effects of AD, with a limited number of tests. We focused on the following cognitive abilities: sensitivity to interference, mental flexibility, and visual processing. S*ensitivity to interference* was measured with the Stroop Color Word Test, a test sensitive for selective attention, automaticity, inhibitory processes, and executive control (Davidson, Zacks, & Williams, 2003), which is relevant in substance dependence. *Mental flexibility* was measured with the Trail Making Test (TMT; Tombaugh, 2004), which is a commonly used instrument in this field of research and provides information on visual search, scanning, speed of processing and executive functions such as divided attention and mental flexibility. Finally, we included a test of *visual processing*, to measure the ability to accurately process visual-spatial information.

Methods

Participants

This study included patients from an inpatient alcohol detoxification unit for older patients in The Hague, The

Netherlands, from April 2011 to February 2014. The inclusion criteria were: age 50 years or older and sufficient command of the Dutch language to understand the instructions of the cognitive tests in Dutch. Patients were included when they were abstinent from alcohol for at least 72 hours, to preclude the effect of alcohol intoxication. If the patients showed clinical signs of alcohol withdrawal, the assessment was postponed.

Procedure

At admission to the inpatient facility, an interview with the European version of the Addiction Severity Index (EuropASI; Kokkevi & Hartgers, 1995) was conducted by a certified nurse. After the patients were informed about the study and had provided informed consent, an appointment was made for administering the neuropsychological tests described below. These tests were administered by a graduate student of clinical neuropsychology, who had been trained in the standardized test procedure. All participants were tested within three weeks after detoxification, as this was for most patients the maximum stay at the detoxification unit.

Measures

Duration of alcohol dependence

Although research is scarce and findings are mixed, the duration of AD might influence the severity of the cognitive damage (Joos et al., 2013; Pishkin, Lovalb, & Bourne, 1985) and may also be related to gender. The data for this covariate were obtained from the following question from the EuropASI (Kokkevi & Hartgers, 1995): "how many years (in total in your life) have you regularly used 5 or more alcoholic drinks per day?." Drinking 5 or more alcoholic beverages a day shows considerable overlap with a diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000)(Saha, Stinson, & Grant, 2007).

As a proxy for *premorbid verbal intelligence* the Dutch Adult Reading Test (DART) was used (Schmand, Lindeboom, & Van Harskamp, 1992). This test has a high correlation with verbal intelligence in healthy controls and is relatively insensitive to cerebral deterioration in brain damaged, demented and psychotic patients (Schmand, Bakker, Saan, & Louman, 1991).

Educational level was measured on an ordinal scale from 1 (less than primary education) to 7 (university degree), according to Verhage (1964).

Sensitivity to interference was assessed with the Stroop Color Word Test (Stroop, 1935). This test consists of three cards in which color words need to be read or ink colors need to be named as quickly and accurately as possible. The sensitivity to interference refers to the difference in completion time between the third subtest (color word interference condition) and the second subtest (color condition). Percentile scores were used, corrected for age and educational level. Sensitivity to interference is considered a general measure of cognitive flexibility and impulse control (Davidson et al., 2003).

Mental flexibility was tested with the Trail Making Test (TMT; Tombaugh, 2004). The TMT provides information on visual search, scanning, speed of processing, and executive functions such as divided attention and mental flexibility. The Mental Flexibility score is derived from the performance of TMT-B relative to TMT-A. Percentile scores were used, corrected for age and educational level.

Visual processing was tested with the subtest Figure Recognition from the Dutch version of the Kaufman Short Neuropsychological Assessment Procedure (K-SNAP; Kaufman & Kaufman, 1994; Mulder, Dekker, & Dekker, 2005). This subtest assesses the ability to process visual information and closure. The patient is presented with 25 incomplete pictures of silhouettes of objects and visual scenes. The patient is asked to identify the picture and is given a 45 seconds time limit for answering. The patient gets one point for each correct answer with a maximum of 25 points. Testing is discontinued after 4 consecutive incorrect responses. The scores for the Figure Recognition test were obtained by transforming the summed raw scores into scaled scores (Kaufman & Kaufman, 1994).

Data analysis

First, descriptive statistics were calculated, and gender differences in demographic characteristics and cognitive performance were tested using Student's *t*-tests. Next, we checked whether there were gender-specific significant differences in the results of the cognitive tests, between patients with available data for duration of alcohol dependence and patients without available data for duration of alcohol dependence, with Student's *t*-tests in men and women. If no selection bias was apparent, the difference in mean scores between men and women on the cognitive tests were calculated, adjusted for duration of alcohol dependence by means of analyses of covariance (ANCOVA). For the analysis of gender differences in the three cognitive tests we applied a Benjamini-Hochberg correction for false discovery rate (Benjamini & Hochberg, 1995), with a critical value of 0.05, as recommended by Glickman, Rao, and Schultz (2014). P-values of ≤ 0.05 were considered significant for all other analyses. All analyses were performed using IBM SPSS

Table 1. Characteristics and cognitive functioning in older alcohol dependent men and women ($N = 164$).

Characteristic	Total Mean (SD) $N = 164$	Men Mean (SD) $n = 102$	Women Mean (SD) $n = 62$	t (df)	p-value*
Age (years)	62.6 (6.4)	62.6 (6.1)	62.6 (7.0)	0.04 (162)	0.97
Educational Level[1]	4.7 (1.5)	4.7 (1.6)	4.7 (1.3)	0.27 (162)	0.79
Duration of alcohol dependence (years)	18.2 (14.1)	20.6 (14.8)	14.2 (12.3)	2.46 (118)	0.02
Premorbid verbal IQ[2]	101.3 (13.0)	101.4 (13.9)	101.0 (11.5)	0.22 (152)	0.83
Sensitivity to interference[3]	37.7 (24.7)	37.3 (24.4)	38.4 (25.4)	-0.27 (145)	0.79
Mental flexibility[4]	32.0 (28.6)	28.0 (27.5)	38.7 (29.5)	-2.17 (139)	0.03
Visual processing[5]	8.8 (2.8)	9.2 (2.8)	8.2 (2.8)	2.18 (162)	0.03

*Student's *t*-tests
SD = standard deviation
[1]Educational Level according to Verhage (1964): range 1–7.
[2]Estimated premorbid verbal Intelligence Quotient (IQ): Dutch Adult Reading Test.
[3]Sensitivity to interference: Stroop Color Word Test. Percentiles, adjusted for age and educational level, compared to a healthy population.
[4]Mental flexibility: Trail Making Test (TMT). Percentiles, adjusted for age and educational level, compared to a healthy population.
[5]Visual processing: Figure Recognition subtest of the Kaufman Short Neuropsychological Assessment Procedure (K-SNAP). Standardized norm scores (M = 10, SD = 3), compared to a healthy population.

Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp.).

Results

A total of 164 inpatients (102 men, 62.2%)participated in the study. The mean age of the participants was 62.6 ± 6.4 years. Table 1 shows the characteristics of the study population, test scores on the cognitive measures and differences between men and women. On the premorbid verbal IQ test, 10 patients had missing data, 17 patients did not complete the Stroop test, and for 23 patients TMT data were missing. Data on duration of alcohol dependence were missing for 44 participants (27 men, 17 women).

No gender differences were found in age, educational level, and estimated premorbid verbal intelligence. The duration of alcohol dependence was on average 6.4 years longer for men than for women. The cognitive performance of this study sample was, given the percentiles, below average compared to healthy persons of the same age (Kaufman & Kaufman, 1994). In univariate analyses, no gender differences were found in sensitivity to interference (Stroop test). In mental flexibility (TMT), women performed significantly better than men. Men performed significantly better than women on visual processing (K-SNAP Figure recognition subtest). The gender differences in mental flexibility and visual processing remained significant with a Benjamini–Hochberg correction for multiple comparisons, with a critical value of 0.05.

Analysis of patients with and without available data on duration of alcohol dependence showed that women with missing data on duration of alcohol dependence performed worse on visual processing than women with complete data (t (60) = 2.19, $p = 0.03$). This was neither the case for the other two cognitive tasks, nor for men on any of the tasks (results not shown). Therefore, we could not analyze the difference between men and women in visual processing adjusted for duration of alcohol dependence.

In Table 2 the differences between men and women in sensitivity to interference and mental flexibility, with adjustment for duration of AD are described, for the subgroup of patients for whom data of duration of AD were available. After adjustment for duration of alcohol dependence the difference in mental flexibility remained significant, $F(1,104) = 7.02$, $p = 0.009$; women performed better than men.

Discussion

The aim of this study was to investigate whether male and female older, alcohol-dependent patients differ in sensitivity to interference, mental flexibility and visual processing. The men and women in the study sample were similar with regard to age, educational level and estimated premorbid verbal IQ. However, men had been drinking excessively (5 or more alcoholic drinks per day) for on average 6.4 years longer than women.

Table 2. Differences in cognition between men and women, adjusted for duration of alcohol dependence ($n = 120$).

Characteristic	All Mean (SD) $n = 120$	Men Mean (SD) $n = 75$	Women Mean (SD) $n = 45$	F (df)	p-value*
Sensitivity to interference[1]	39.2 (23.8)	38.5 (23.2)	40.2 (24.9)	0.65 (1,104)	0.42
Mental flexibility[2]	31.7 (28.8)	27.8 (27.7)	38.8 (29.7)	7.02 (1,104)	0.009

*ANCOVAs
[1]Sensitivity to interference: Stroop Color Word Test. Percentiles, adjusted for age and educational level, compared to a healthy population.
[2]Mental flexibility: Trail Making Test (TMT). Percentiles, adjusted for age and educational level, compared to a healthy population.

To our knowledge, no earlier studies have made a direct comparison of cognitive functioning between male and female older alcohol-dependent patients, therefore our results are not easily comparable to existing literature. However, based on the available epidemiological literature it was expected that men would perform better than women on all three cognitive tests.

No gender differences were found in sensitivity to interference as measured with the Stroop Color Word Test. Our data did not confirm the findings of Flannery et al. (2007), who found that women with AD experienced more sensitivity to interference in the Stroop task than men with AD and healthy controls. Van der Elst et al. (2006) found that healthy women were less sensitive to interference than men. If this were the case for our study sample before they became addicted, which we have not been able to verify, the effects of excessive alcohol use on sensitivity to interference may have been stronger in women than in men, resulting in a similar performance. A similar performance in men and women on cognitive tests was also found in several other studies, in younger alcohol-dependent patients (Acker, 1986; Alarcon, Nalpas, Pelletier, & Perney, 2015; Parsons, 1994).

Alcohol-dependent women performed better than men on mental flexibility, measured by the TMT, both unadjusted and after adjustment for duration of alcohol dependence. A recent study (Plotek et al., 2014) showed that healthy women performed better on the TMT than men, in contrast with an earlier study showing that performance on TMT A and B was associated with age and education, but not with gender, in a sample of healthy adults (Tombaugh, 2004). The results of our study could be explained by a better performance in women before the onset of alcohol dependence, and mental flexibility being equally impaired in men and women, which would cause women to keep their advantage. Another possibility is that the impairment in mental flexibility caused by excessive alcohol use is stronger in men than in women, which is not caused by longer duration of alcohol dependence but may nevertheless be caused by other (unmeasured) confounders, such as larger quantities of alcohol intake or a poorer diet in men with AD than in women with AD. These results could be supporting the conclusions of an earlier study that found more cortical atrophy in men with AD than in women with AD (Mann et al., 2005).

In our study, men performed better than women on the visual processing task. We would expect this effect to become even stronger after adjustment for duration of alcohol dependence; however, we were not able to analyze this due to selectively missing data. Several authors found that men performed better than women on a figure recognition task (Abramov, Gordon, Feldman, & Chavarga, 2012; Halpern & LaMay, 2000). However, a more recent study did not find gender-related differences in figure recognition (Lewis, Rees, & Lee, 2009).

Considering the performance level on the sensitivity to interference (Stroop), mental flexibility (TMT) and visual processing (Figure Recognition) tests, when corrected for age and education, both men and women performed below average compared to a healthy norm group. This corresponds with previous reports stating that drinking alcohol heavily for long periods of time is associated with impairments on tests of cognitive functioning (Bates et al., 2013; Fernández-Serrano et al., 2010; Loeber et al., 2009; Munro, Saxton, & Butters, 2000; Stavro et al., 2013; Wiseman, Souder, & O'Sullivan, 1997). Our results suggest that, irrespective of gender, the consequences of excessive alcohol consumption on cognition are detrimental.

Some limitations to this study should be noted. First, we do not know how the participants to our study performed on the cognitive tests before they became dependent on alcohol. We only have a proxy measure of their premorbid verbal IQ, which was similar between men and women. Including a comparison group of healthy older adults would not solve this problem, because the differences between our patients and healthy older adults are so large and cover so many aspects of life other than just the AD, that a sound comparison would not be possible. Second, "years of drinking 5 or more alcoholic drinks per day" is a proxy measure of duration of alcohol dependence and the validity of this measure is not exactly known. Self-report is vulnerable to recall-bias; the more time has passed, the more difficult it becomes to report this correctly, even more so for patients with AD. Third, the interactions between alcohol, aging, the brain and gender are complex. The effects of alcohol on the brain are diverse and are influenced by a lot of variables, which were not included in this study, e.g. comorbidity with other somatic or psychiatric disorders, genetic background and eating habits. These residual confounders may have influenced the results of this study. Fourth, because of the short concentration span of the older patients with AD we have only been able to administer a limited number of neuropsychological tests, which were selected based on their sensitivity to the detrimental effects of AD. It is possible that different cognitive tests would have yielded different results. Finally, since the study sample consisted of older AD inpatients, the conclusions cannot be generalized, neither to outpatients, nor to community-dwelling older alcohol-dependent persons.

In conclusion, our results do not confirm that a long period of alcohol dependence results in different and more severe cognitive impairment in women than in men. In fact, women outperformed men on the mental flexibility task. Further research in this area is suggested to shed more light on the detrimental cognitive effects of excessive alcohol use on the aging brain, ideally with longitudinal studies. This information may help to provide adequate, personalized education, prevention and treatment programs.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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