COGNITIVE AND BEHAVIOURAL ASPECTS

The Effects of Gender and a Co-occurring Depressive Disorder on Neurocognitive Functioning in Patients with Alcohol Dependence

I-Chao Liu¹, Chen-Huan Chiu²* and Tsung-Tsair Yang¹

¹Department of Psychiatry, Cardinal Tien Hospital and School of Medicine, Fu Jen Catholic University, No. 362 Zhongzheng Rd., Xindian City, Taipei County 231, Taiwan and ²Department of General Psychiatry, Taipei City Psychiatric Center, Taipei City Hospital and Taipei Medical University, No. 309 Songde Rd., Xinyi District, Taipei City 110, Taiwan

*Corresponding author: Department of General Psychiatry, Taipei City Psychiatric Center, Taipei City Hospital, No. 309 Songde Rd., Xinyi District, Taipei City 110, Taiwan; Tel.: +886-2-27263141 ext 1305; Fax: +886-02-27262194; E-mail: daf33@tpech.gov.tw

ABSTRACT — Aims: The present study aims to examine neuropsychological impairments by comorbidity and gender among patients with alcohol dependence. Methods: The study sample is comprised of 123 subjects who fulfilled a Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnosis of alcohol dependence from January 2006 to December 2007. Subjects were asked to complete the following psychological tests: the Barratt Impulsivity Scale (BIS), Wechsler Adult Intelligence Scale, Wechsler Memory Scale and Color Trails Test. We compared the results of neuropsychological assessments based on two types of classifications: people with comorbid depression and people without comorbidity; females and males. Results: The immediate visual memory and the BIS scores in patients with comorbid depression were significantly different from the scores in patients without comorbidity. In addition, females performed significantly poorer on the Working Memory Index than males and had a later age of regular drinking. Conclusions: Further investigation of the mechanism associated with the gender difference on cognition and exploration of the temporal relationship between alcohol dependence and depressive disorder on the cognitive aspect is needed.

INTRODUCTION

Several lines of evidence indicate that the brain is vulnerable to long-term alcohol exposure (Rourke and Löberg, 1996; Oscar-Berman and Evert, 1997; Harper et al., 2003). Patients with alcohol dependence, the individual’s cognitive impairments would significantly affect one’s ability to recover shortly or achieve treatment success (Rourke and Löberg, 1996). However, the extent of brain damage and the degree of cognitive impairment differ across individuals with alcohol dependence (Oscar-Berman and Marinkovic, 2003). This means that not all alcohol dependents are equally at risk of certain neurobehavioral deficits. Therefore, the identification of a vulnerable subgroup with impaired neurocognitive functioning is of importance for predicting the outcome of alcohol dependence.

Comorbid psychiatric disease among people with alcohol dependence is prevalent (Regier et al., 1990; Kessler et al., 1997; Driessen et al., 1998; Romeis et al., 1999; Schneider et al., 2001). The occurrence of comorbidity influences the success of preventive strategies as well as treatment responses (Baigent, 2005; Bischof et al., 2005). As demonstrated in the literature, people with alcohol use disorder and other psychiatric problems have a poorer response to treatment, more frequent relapses and more hospitalizations, leading to the challenge of searching for suitable therapeutic management (Burns et al., 2005). Because a co-existing psychiatric disease substantially contributes to the heterogeneity of the disease presentation and development, it is reasonable to hypothesize that psychiatric comorbidity may also be related to the neurocognitive impairments in subjects with alcohol dependence. However, the role of cognitive functions on the association of alcohol dependence and co-existing psychiatric disorders, especially depression, is little studied.

In addition to comorbidity, gender difference may be also associated with the clinical manifestations and the severity of neurocognitive impairment in alcohol dependence. A gender-related difference in alcohol dependence has been mentioned in prior research (Piazza et al., 1989; Weisner and Schmidt, 1992; Brady et al., 1993; Kessler et al., 1994; Grant et al., 2004). Women are found to have different clinical manifestations, including later alcohol exposure and drinking less per occasion, and are more likely to be abstinent than men. Differences in drinking patterns and alcohol metabolism have also been reported and further led to gender-specific discrepancies in neuropsychological presentations (Hesselbrock, 1996). Women are found to be vulnerable to brain damage from alcohol ingestion. Recent neuroimaging studies have confirmed this finding by demonstrating equivalent brain atrophy in men and women in spite of less alcohol consumption among female alcoholics (Mann et al., 2005).

Although clinical manifestations of alcohol dependence diverging by gender and comorbid conditions may relate to varying degrees of problems on neurocognitive functioning, the extent to which the neuropsychological performance is impaired in certain subgroups has yet to be investigated. In this study, we focus on gender factor and one of the major comorbid psychiatric disorders, the depressive disorder, in subjects with alcohol dependence. The cognitive functions in subgroups were examined and compared. We hypothesized that alcohol-dependent subjects with a co-occurring depressive disorder tend to have poorer cognitive function than alcohol-dependent cases without comorbidity. Moreover, women with alcohol dependence have poorer performance on specific cognitive functions corresponding to frontal lobe functions than alcohol-dependent men. In this study, we chose well-standardized neuropsychological instruments to detect subtle impairments in cognitive functioning among people with alcohol dependence.
METHODS

The subjects of this study had been admitted to a university-affiliated hospital from January 2006 to December 2007 and met the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnostic criteria for alcohol dependence. A diagnostic interview was adapted for making an initial psychiatric diagnosis by qualified psychiatrists. Those who had a DSM-IV diagnosis of schizophrenia, severe physical condition, other substance use disorders and past history of severe head injury such as intracranial hemorrhage were excluded from this study. A total of 123 inpatient participants comprised the sample of this 2-year study. To avoid the influence from withdrawal conditions, we obtained informed consent after at least a 1-week detoxification program. Moreover, 96.7% of participants have received sedatives and hypnotics during a detoxification period, but the use of antidepressants was postponed until the diagnosis of depressive disorder, if existent, was finally made. Indeed, at the time of the application of the neuropsychological assessment, no subjects took antidepressants. Moreover, all subjects were free of medication 1 day before the assessment. Two trained psychologists then collected individual neuropsychological information in addition to demographic data. The Mini-International Neuropsychiatric Interview was used to screen for additional psychiatric diagnoses, and the final diagnosis regarding lifetime DSM-IV major depressive disorder or dysthymic disorder was confirmed via diagnostic interviews by qualified psychiatrists.

Impulsivity was measured by a self-reporting scale, the Barratt Impulsiveness Scale-Eleven Edition (BIS-11). It is widely used to evaluate impulsive behavior reflecting a preference for immediate rewards and significant difficulty in resisting such rewards (Mitchell, 1999; Monterosso and Ainslie, 1999). The BIS-11 consists of 30 statements of personal characteristics, and subjects are requested to indicate the extent to which they apply to them using a four-point scale ranging from rarely/never (scored as 1) to always/always (scored as 4). The impulsiveness measure is the sum of the scores of these responses. The scale can be decomposed into three subscales measuring specific aspects of impulsivity: motor impulsivity, impulsive non-planning and attentional impulsivity. The BIS-11 has been used with a variety of populations (Stanford and Barratt, 1996; Kirby et al., 1999; Mitchell, 1999; Crean et al., 2000), and its reliability and validity have been confirmed (Carrillo-de-la-Pena et al., 1993; Patton et al., 1995; Fossati et al., 2002).

In addition to filling out the BIS (Bischof et al., 2005), subjects were assessed using the following well-standardized psychological tests: Wechsler Adult Intelligence Scale—Third Edition (WAIS-III), Wechsler Memory Scale—Third Edition (WMS-III) and Color Trails Test (CTT). WAIS-III was used to evaluate individuals’ intellectual level and Working Memory Index (WMI) was calculated in addition to verbal and performance intelligence quotients. The score on the WMI was derived from Arithmetic, Digit Span and Letter—Number Sequencing subscales on WAIS. Raw scores of CTT were transformed to standardized T scores, with a mean of 50 and a standard deviation of 10 as the norm. Subsets of the above instruments were taken into consideration: immediate and visual memory scores for WMS-III; first part and second part for CTT. The project has been reviewed and approved by the ethics committee of Cardinal Tien Hospital.

We dichotomized all subjects into two groups based on two variables, respectively: comorbidity and gender. For example, those who had a DSM-IV major depressive disorder or dysthymic disorder were the cases and the rest were comparison subjects. Then chi-square tests and t-tests were employed for the comparison of the distribution of each independent variable in both comorbid and non-comorbid groups. In univariate analyses, we first detected the potential significant factors associated with comorbidity. Since the significance from certain variables can mainly result from the influence of another factor, subsequent multivariate analysis was applied. The potential significant variables with a P-value of <0.1 were retained to fit in following multivariate statistical analyses. In our study, we defined comorbidity as a binary dependent variable and identified those factors that can significantly classify the comorbid group and the non-comorbid group. Multiple logistic regression analysis was thus applied to determine significant factors related to comorbidity. We repeated the same statistical procedure for the other dependent variable, gender, and identified those independent variables significantly related to gender. We also evaluated the impact of each significant factor on group differences. Adjusted odds ratios were estimated based on the final fitted models. We defined a P-value of <0.05 as the significant level.

RESULTS

Characteristics of alcohol-dependent participants

Alcohol consumption of one drink at least once a month for ≥6 months was defined as regular use in our study. The mean age of our sample at interview was 39.3 years (SD 0.83). The mean duration of becoming regular users was around 15 years in subjects with alcohol dependence based on the difference between age at regular use and age at interview (Table 1). With regard to educational attainment, 70% of the participants have 7–12 years of education. The proportion of subjects having 6 years of education was 11.4%; the proportion of subjects with >12 years of education was 17.9%. Around two-thirds of our sample was not working at interview. Approximately 30% of subjects were either single or divorced; the remaining 38.2% were married. A high proportion (63%) of our sample had physical conditions including cardiovascular diseases, neurological problems, diabetes mellitus and gastrointestinal problems.

We performed two types of comparisons for variables: females vs males, and having comorbid depression vs not having comorbid depression. Compared with the norm, all subjects with alcohol dependence had a poorer performance on all types of psychological assessments. However, the results were not significantly different from the norm.

Comparison by gender

In univariate analyses (Table 2), females were found to have a later mean age at regular drinking and less likely to be currently working compared with male alcohol dependents. As to the self-reporting impulsivity and neuropsychological tests, no significant group differences were revealed in the BIS score and performance on WMS. The score on WMI and two other
sub-scores on WAIS were found to have significantly different distributions in both groups. The female cases were likely to obtain a 10-point lower score. Females also needed more time to finish the two parts of the CTT.

Only two factors, age at regular drinking and WMI, retained their significance in the final multivariate model as shown in Table 4. Women tended to have a late age at regular drinking given the same performance on working memory as men. After controlling for age of regular drinking, females with alcohol dependence were more likely to have a poorer performance on working memory than males (odds ratio = 0.96, P-value = 0.02).

**Comparison by comorbidity**

About 58% of our hospital-based sample had a comorbid major depressive disorder or dysthymic disorder. As demonstrated in Table 3, four factors, currently working, the BIS score including all three subscales, the score on delayed visual memory and the score on immediate visual memory, were found to be significantly different between both groups. Subjects with comorbidity were less likely to be working at interview. The alcohol dependents with a co-existing depressive disorder tended to have a higher self-reported impulsive score and poorer performance on delayed visual memory and immediate visual memory on the WMS compared with those without comorbidity.

In the final fitted model as shown in Table 4, the score on immediate visual memory and the BIS scores in patients with comorbidity were significantly different from the scores in patients without a major depressive condition. After adjusting for the self-rated BIS score, alcohol dependents with a depress-

<table>
<thead>
<tr>
<th>Table 1. Characteristics of alcohol-dependent participants (N = 123)</th>
<th>Table 2. Comparisons by gender in alcoholics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td><strong>Female (N = 27)</strong></td>
</tr>
<tr>
<td>Age (in years)</td>
<td>39.6</td>
</tr>
<tr>
<td>Age at first drinking (in years)</td>
<td>17.5</td>
</tr>
<tr>
<td>Age at regular drinking (in years)</td>
<td>26.4</td>
</tr>
<tr>
<td>Currently working*</td>
<td>26.8%</td>
</tr>
<tr>
<td>Married</td>
<td>33.8%</td>
</tr>
<tr>
<td>Having a physical disease</td>
<td>63.4%</td>
</tr>
<tr>
<td>Self-report and neuropsychological tests</td>
<td></td>
</tr>
<tr>
<td>Barratt impulsivity Scale*</td>
<td>79.1</td>
</tr>
<tr>
<td>Attentional impulsivity*</td>
<td>20.1</td>
</tr>
<tr>
<td>Motor impulsivity*</td>
<td>28.8</td>
</tr>
<tr>
<td>Non-planning*</td>
<td>30.2</td>
</tr>
<tr>
<td>WAIS*</td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>85.0</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>79.6</td>
</tr>
<tr>
<td>Working Memory Index</td>
<td>89.4</td>
</tr>
<tr>
<td>WMS*</td>
<td></td>
</tr>
<tr>
<td>Immediate visual memory score*</td>
<td>79.7</td>
</tr>
<tr>
<td>Delayed visual memory score*</td>
<td>80.8</td>
</tr>
<tr>
<td>Color Trails Test</td>
<td></td>
</tr>
<tr>
<td>CTT-1</td>
<td>41.0</td>
</tr>
<tr>
<td>CTT-2</td>
<td>44.9</td>
</tr>
</tbody>
</table>

*P-value <0.10 for gender.
*Wechsler Adult Intelligent Scale.
*Wechsler Memory Scale.
sive comorbid disorder still had a significantly lower score on immediate visual memory (odds ratio = 0.98, P-value = 0.03). Those with a co-occurring depressive disorder were more likely to report impulsivity than those without comorbidity, with the adjustment of the immediate visual memory score.

**DISCUSSION**

Our findings show that alcohol dependents had on average low scores on all standardized neuropsychological instruments, which is consistent with previous studies showing a predominant deficit in neuropsychological functioning among alcoholics (Butters et al., 1977; Leber et al., 1981; Fabian et al., 1984; Donat, 1986). In addition, our study results confirmed our first hypothesis that alcoholics with a co-occurring depressive disorder demonstrate more neurocognitive deficits than alcoholics without comorbidity. Alcohol dependents with a depressive disorder were more impulsive and had a more impaired performance on immediate visual memory than patients without comorbidity.

In this study, the prevalence of a co-existing depressive condition was up to 58% of all subjects. This is apparently higher than previous reports because our sample was drawn from a hospital and a high proportion of comorbidity with depressive disorders may lead alcohol dependents to seek medical help. In the literature, it has been found that people with alcohol use disorder and comorbidity of affective disorders have an additive harmful effect on their cognition (van Gorp et al., 1998). The effect of depressed mood on neuropsychological functioning has been well documented (Snyder and Nussbaum, 1998), and it has been indicated that a past history of alcohol abuse is associated with an inferior performance on a measure of immediate visual memory. Prior studies have reported that subjects diagnosed with major depressive disorder scored significantly lower than controls on a visual memory task (Elliott et al., 1996; Shah et al., 1999). The additive effect from both depression and alcohol dependence on immediate visual memory was further confirmed in our study.

The main diagnostic characteristic of alcohol dependence is the inability to refrain from drinking in spite of being aware of adverse consequences. This represents a form of impulsivity, and impulsivity is mostly defined as action without planning or behavior that is prematurely executed and has maladaptive consequences (Barratt et al., 1999; Moeller et al., 2001). Gorenstein and Newman (1980) proposed that behavioral phenomena such as psychopathology, antisocial and impulsive traits, and alcoholism should be viewed as variable expression of a generalized disinhibitory complex (Gorenstein and Newman, 1980). Recently, substance dependence, such as alcohol dependence, has been considered part of the disinhibitory/externalizing disorder spectrum (Kendler et al., 2003).

In our study, an elevated level of impulsivity was found to be associated with comorbid depressive disorder among those who fulfilled the diagnosis of alcohol dependence.

The second hypothesis that female alcoholics tend to have poorer neurocognitive performance corresponding to frontal functioning than male alcohol dependents is also supported by our study results. On average, female cases have a poorer performance on working memory and a later age at regular drinking. Working memory is indicative of an individual’s ability to memorize new information, hold it in short-term memory, concentrate and manipulate that information to produce reasoning processes. Usually related to the frontal lobe, working memory is an important prerequisite of many cognitive abilities so that under-functioning will likely affect an individual’s ability to efficiently perform other mental operations. After controlling for age at regular use, we can still detect a poor working memory performance among women with alcohol dependence, indicating a gender-specific difference on cognition. This finding supports a proposed concept that alcohol consumption may be more detrimental to females than to males, and that there is a greater vulnerability of women to the adverse effects of alcohol (Peifferbaum et al., 2006).

With regard to the later onset of regular drinking among females, it suggests a distinctive pathogenesis for females and males. Although both biological and psychosocial factors are able to determine the formation of this disease, the magnitude of each factor’s contribution may differ by gender. We ought to be aware of the gender effects in observing disease development.

The between-subgroup discrepancy on neuropsychological performance may imply an underlying distinct mechanism leading to alcohol dependence. There are three possible explanations for the poorer neuropsychological performance in alcohol dependents with a depressive disorder than alcohol dependents without comorbidity. First, because people with alcohol dependence or a depressive disorder are at an increased risk for developing cognitive impairments, people with depression may experience additively harmful effects from heavy alcohol consumption on cognitive functioning. Second, people with alcohol dependence and accompanying cognitive impairments are likely to have a slow rate of recovery. As a consequence, the inability to cope with a persistent adverse psychosocial environment can be a risk for a depressive disorder. The cognitive function among alcohol dependents is further influenced by the occurrence of depression. Third, the finding can be accounted for by a predisposed genetic factor in the high-risk subgroup. A common genetic vulnerability may place people at risk for developing both diseases.

As to the gender factor, the role of gender in the relationship between neuropsychological impairments and alcohol dependence may be different from the role of co-existing depression. Heavy alcohol consumption may exert different actions in the cognitive functions and the development of disease in females compared with males. The deficit on working memory function may result from a female vulnerability to alcoholic toxic effects on the brain, but it is yet to be determined whether a gender-specific genetic predisposition is theoretically possible to cause this kind of cognitive deficit.

Several limitations should be noted when interpreting the results of this study. First, as mentioned above, we recruited the study sample from an inpatient setting; thus, the generalization of the study results is limited. One study had assessed the neuropsychological performance of community subjects with comorbid depression and alcohol use. They found a different level of performance on WAIS from ours (Hunt et al., 2009). Our study findings cannot be generalized to alcoholic outpatients or a community sample. Second, we did not include healthy controls in the study and compare the two subgroups according to the classification of all subjects with alcohol dependence. However, we applied well-standardized psychological instruments, and the norm on psychological performance is well established. Third, the sample of this present study received...
psychological assessment after the acute withdrawal period. Although previous studies have found that neuropsychological problems persist after the withdrawal period (Goldman, 1990; Rourke and Grant, 1999; Bates et al., 2002; Fein et al., 2006), the long-term cognitive performance of alcoholics cannot be directly derived based on the information we obtained.

A longitudinal study design may help to elucidate the causal relationship between the harmful effects of alcohol and neuropsychological deficits by gender. Exploration of the temporal relationship between alcohol dependence and co-occurring depressive disorder, in terms of the cognitive aspect, is warranted in future studies. In addition to the exploration of pathogenesis, the importance of assessing cognitive function among people with alcohol dependence is closely related to treatment, prognosis and relapse as mentioned above (Smith and McCrady, 1991; Rourke and Løberg, 1996; Sullivan et al., 2000; Fals-Stewart and Bates, 2003). Cognitive impairments have been shown to exert a considerable effect on patients’ psychosocial status. For alcohol dependent individuals, the individual’s ability to benefit from specific treatment programs is influenced by cognitive functions. Treatment modality can be chosen to be suitable for subjects with a certain type of cognitive impairment. The potential differences in cognition within this heterogeneous group should be taken into consideration for planning a successful treatment intervention and achieving a short recovery process. Finally, there is a need for familial studies of gene markers to determine if visual memory deficits, impulsivity or working memory is a heritable risk factor among subgroups for alcohol dependence.

**SOURCES OF SUPPORT**

This work was supported by grant DOH 95-TD-M-113-042 to I.C.L.

DOH: Department of Health, Executive Yuan, Republic of China

**Conflict of interest statement.** None declared.

**REFERENCES**


