COGNITIVE EFFECTS

Cognitive Components of Frontal Lobe Function in Alcoholics Classified According to Lesch’s Typology

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Abstract — Aims: This study examined the frontal lobe cognitive function and the mental state among patients with different types of alcohol dependence according to Lesch’s typology. Methods: The frontal assessment battery (FAB) and the mini-mental status examination (MMSE) were given to 170 patients with alcoholism from a Brazilian outpatient service classified by Lesch’s typology and to 40 non-alcoholic controls matched for age, gender, socio-demographic characteristics and education. Results: Of the alcoholic sample, 21.2% were classified as Type I, 29.4% as Type II, 28.8% as Type III and 20.6% as Type IV. Alcoholics showed significantly lower overall scores on the MMSE and the FAB as compared to non-alcoholic subjects. Type IV alcoholics had lower MMSE and FAB overall scores as compared to non-alcoholic controls and also to all other types of alcoholic subjects. However, Type II and III subjects with alcoholism also had lower overall FAB scores, but not overall MMSE scores, as compared to non-alcoholic controls. The FAB subsets of motor programming, sensitivity to interference and inhibitory control were significantly reduced in Types II, III and IV alcoholics as compared to non-alcoholic subjects, but only motor programming remained impaired in Type IV alcoholics with preserved mental function. Conclusions: Executive dysfunctions in alcohol dependence seem to vary depending upon the type of alcoholism. Therefore, the determination of clinical type of alcohol dependence by applying Lesch’s typology, along with brief mental state and frontal function examinations, is of clinical relevance in the examination of alcoholics and provides significant clues for more directed forms of alcohol dependence treatment.

INTRODUCTION

Alcoholism has long been considered a complex disease, given its biological, sociological and psychopathological components. A prospective long-term study carried out by Lesch et al. (1988) over 4–7 years with 444 patients has led to the development of a new typology of chronic alcoholism that is able to differentiate subgroups of patients with chronic alcoholism cross-sectionally, according to clinical, biochemical and neurophysiological factors (Lesch et al., 1990). The diagnosis according to this typology qualitatively differentiates patients in many spheres other than drinking behavior and demands corresponding, modified therapeutic strategies (Lesch et al., 1988, 1990).

Briefly in this typology, the Type I alcoholism is primarily characterized by the development of tolerance with the appearance of early heavy withdrawal symptoms (considered as a model of allergy) (Hillemacher and Bleich, 2008; Pombo and Lesch, 2009). Patients develop meta-alcoholic psychosis, like delirium tremens, and might suffer from withdrawal epileptic seizures. They tend to use alcohol to weaken withdrawal symptoms (Bönisch et al., 2006). Type II alcoholics show suicidal intentions, anxiety and pre-morbid conflicts (considered as a model of anxiety or conflict) (Pombo and Lesch, 2009). Alcohol seems to be used as a strategy against anxiety, and they frequently become aggressive when intoxicated (Walter et al., 2006). Type III alcoholics exhibit an aggressive and impulsive behavior with the existence of psychiatric co-morbidity (Pombo and Lesch, 2009). Alcohol seems to be used as a self-medication to treat an underlying affective disorder (alcohol as antidepressant) (Hillemacher and Bleich, 2008). Finally, Type IV alcoholics comprise patients with disturbance or cerebral damage before the conclusion of brain development (Walter et al., 2006), associated with behavioral disorders and serious social problems (Hillemacher and Bleich, 2008; Pombo and Lesch, 2009). Alcoholic beverages are also used as a means by which to self-medicate symptoms in this group (alcohol drinking as adaptation).

Frontal lobe dysfunctions are consistently described in chronic alcoholics (Ihara et al., 2000; Munro et al., 2000). Currently, the literature emphasizes the hypothesis of primary frontal lobe damage in alcoholics, even in chronic alcoholics who appear clinically ‘intact’, because they also present morphological abnormalities in the frontal lobes (Moselhy et al., 2001).

General measures of intelligence, especially those with a large verbal component, do not reveal performance deficits in alcoholics (Moselhy et al., 2001). However, the frontal deficits have been reported even in alcoholic subjects whose intelligence is average or even above average (Moselhy et al., 2001).

The cognitive components of the frontal lobe syndrome include deficits in spatial working memory, short-term memory, sustained attention over time, problem solving, decision-making, planning of future actions, behavioral inhibition and self-control, as well as a tendency to engage in repetitive behavior or perseveration, likely due to a difficulty in the ability to shift response sets (Moselhy et al., 2001). These cognitive dysfunctions are particularly disruptive for higher order cognitive abilities that enable individuals to engage successfully in independent goal-directed behavior and to operate in non-routine situations (i.e. novel, conflicting or complex tasks). That is to say, these impairments in cognition interrupt the ability to engage in executive functions (Godefroy, 2003). Deficits in language, motor control, creative thinking, artistic expression and emotional behavior are also seen in frontal syndromes (Moselhy et al., 2001).
All of these frontal lobe deficiencies have been described in patients with chronic alcoholism, a condition especially marked by an inability to abstain from alcohol, having direct implications for its treatment (Goldstein and Volkow, 2002). According to Moselhy et al. (2001), accumulating evidence shows that the cognitive frontal lobe deficits seen in alcoholic patients are an important predictor of outcomes following treatment. However, up to now, there are no studies focusing in which type of alcoholism the frontal functions are impaired or most impaired, or which are the executive functions that may be impaired in different types of alcoholism.

Moselhy et al. (2001) suggested that in everyday clinical practice, tests for frontal lobe damage in alcoholics are seldom used and, thus, lesions in this area easily may be overlooked. Additionally, the behavioral symptoms of frontal lobe dysfunction may be interpreted readily as part of the behavioral pattern of alcoholism (Moselhy et al., 2001).

Classical neuropsychological tests evaluating frontal function are usually very extensive and time consuming. Dubois et al. (2000) developed a frontal assessment battery (FAB), a brief instrument very sensitive to frontal lobe dysfunction (Dubois et al., 2000) that takes ~10 min to administer and can be applied easily at the bedside (Dubois et al., 2000; Appollonio et al., 2005). This battery consists of six subsets that screen global executive dysfunction, including conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control and environmental autonomy (Dubois et al., 2000).

A brief assessment of global cognitive function in both the inpatient and outpatient medical setting (Smith et al., 2006) can be readily achieved by the mini-mental status examination (MMSE) (Folstein et al., 1975). This instrument has been validated and extensively used in both clinical practice and research to screen and to estimate the severity of cognitive impairments, as well as to follow the course of cognitive changes. Its feasibility to be included as a part of screening protocols in substance abuse research was suggested by Smith et al. (2006).

Therefore, in order to investigate if different types of alcoholism also have differences in their cognitive functions, this study examined frontal lobe-specific cognitive function, employing the FAB, and general cognitive function, employing the MMSE, in different categories of alcohol dependence according to Lesch’s typology.

METHODS

Subjects

Between November 2006 and February 2007, alcohol-dependent outpatients referred to a specialized public service in the Medical School Hospital of the Federal University of Espírito Santo for alcohol dependence treatment were included in an open, non-randomized study. These patients were included sequentially in the order in which they received assistance. The control group comprised either non-alcoholic outpatients from other medical services of the same Medical School Hospital and of friends or relatives with characteristics similar to that of the alcoholic patients recruited in March of 2007.

After having been informed of all procedures and given written informed consent, 170 outpatients diagnosed with alcohol dependence by International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), and 40 subjects without a diagnosis of alcohol dependence were included in this study.

Ethical approval was provided by the Brazilian Institutional Review Board at the Federal University of Espírito Santo, Brazil, which was conducted in strict adherence to the Declaration of Helsinki and is in accord with ethical standards of the Committee on Human Experimentation of the Federal University of Espírito Santo, ES, Brazil, where this study was completed.

Socio-demographic characteristics and drinking behavior characteristics

Both control and alcoholic subjects were given a structured interview that gathered information concerning socio-demographic data and alcohol drinking characteristics. This interview was then followed by a global physical examination.

Procedures

Types of alcoholism according to Lesch’s typology. Alcoholic patients were classified according to the Lesch typology (Lesch et al., 1988, 1990) on the basis of Lesch’s decision tree (see Lesch et al., 1990), which details the basis for the diagnostic process in this model.

Mini-mental status examination (MMSE). The MMSE is administered in ~10 min and includes simple questions, such as the time and place of the test, as well as simple tasks, such as repeating lists of words, performing arithmetic, using and comprehending language, and engaging in basic motor skills. An adapted, Portuguese language version of the MMSE was used. As in its original version, the adapted, Portuguese version of the MMSE is an 11-item test with a maximum score of 30 that examines five areas of cognitive function: orientation, registration, attention and calculation, recall and language. The mean of the MMSE score from all subjects in each group or subgroup was used as the main parameter. However, as the MMSE is strongly influenced by age and educational level, an additional analysis was performed excluding subjects that scored under the mean MMSE for age and years of schooling categories found by Crum et al. (1993) in an extensive population-based analysis. In their study, they provided a mean MMSE score of 29 for those with at least 9 years of schooling between the age of 18 and 34 years, 28 between 35 and 69 years, and 27 between 70 and 79 years. For those with 5–8 years of schooling, the mean MMSE score was 27 for age between 18 and 29 years and also between 40–44 years and 50–54 years, 26 between 30 and 39 years and also between 55 and 69 years, and 25 for those aged between 70 and 79 years old. Finally, for those with 0–4 years of schooling, the mean MMSE score was 22 for those aged between 18 and 24 years and also between 55–59 and 65–74 years old, 25 for those aged between 25 and 34 years old, 23 for those aged between 35 and 54 years and also between 60 and 64 years old, and 21 for those aged between 75 and 79 years old.

Frontal function assessment (FAB). A frontal function examination was conducted via a brief tool exploring different domains of executive function, the FAB, which was elaborated by Dubois et al. (2000). The Dubois et al. (2000) designed battery consists of six subsets exploring the following domains:
conceptualization (e.g. subjects must conceptualize the links between two objects from the same category, for example, an apple and a banana), mental flexibility (e.g. subjects need to recall as many words as they can begin with a given letter in a 1-min trial), motor programming (e.g. subjects must execute a motor series in a correct order), sensitivity to interference (e.g. subjects must provide an opposite response to the examiner’s alternating signal), inhibitory control (e.g. subjects must inhibit a response that was previously given to the same stimulus) and environmental autonomy (e.g. subjects must inhibit the activation of patterns of behavior triggered by sensory stimulation, such as the prehension behavior when they see the examiner’s hand). Each of these subsets is scored from 0 (zero) to a maximum of 3. Therefore, the potential maximum total score of the FAB would be 18.

Statistical analysis
Data were presented by percentage or mean ± standard deviation (SD).

For parametric data, a two-sample unpaired t-test was used in all comparisons between the non-alcoholic control and alcoholic groups. A one-way analysis of variance (ANOVA) for independent measures, followed by a Fisher’s LSD (protected t-test), was employed in the comparisons among subgroups of alcoholics classified according to Lesch’s typology and the non-alcoholic control group. The chi-square test was employed for socio-demographic analysis between non-alcoholic control and alcohol-dependent group and among different types of alcoholism.

Additional multiple linear regression analyses were done between total FAB score and multiple variables, including types of alcoholism, MMSE, socio-demographic characteristics (i.e. age, gender, race, years of education, marital state, employment), alcohol drinking behavior (i.e. age at onset of alcohol use, amount of alcohol used, days of abstinence before the study or dependence severity), smoking, use of other drugs and other psychiatric diagnoses.

A two-tailed α level of 0.05 was used to determine statistical significance. GraphPad Prism 4.0 (GraphPad Software, Inc., San Diego, CA, USA) and the Statistical Package for the Social Sciences (SPSS) software (SPSS, Inc., Chicago, IL, USA) were used for statistical analysis and graphic presentations.

RESULTS

Socio-demographic and alcohol-drinking behavior characteristics
The socio-demographic characteristics of non-alcoholic control subjects (n = 40) were very similar to that of the alcohol-dependent subjects in the total sample (n = 170); these characteristics were similar among alcohol subjects classified according to Lesch’s typology (Table 1) as well. Of 170 alcoholic subjects, 36 (21.2%) were classified as Type I, 50 (29.4%) as Type II, 49 (28.8%) as Type III and 35 (20.6%) as Type IV (Table 1). There were no statistically significant differences in socio-demographic characteristics between control and alcohol subjects or among the different types of alcoholic patients (Table 1).

The mean age (± SD) of the non-alcoholic control group was 44.6 ± 8.7 years and that of the alcoholic group was 46.4 ± 9.7 years (Table 1). The alcoholic group primarily comprised males (87.1%), in a ratio of approximately 7:1 (Table 1). In order to keep the control group as similar as possible to the alcohol group, the proportion of males: females in the non-alcoholic group was approximately 7:1 as well. Of note, this proportion was slightly different in Type II and Type III alcoholics. The Type II subgroup was constituted entirely of male alcoholic patients (1 male: 0 female), whereas the Type III subgroup showed the highest proportion of female alcoholic patients (2.5 male:1 female).

Some drinking behavioral characteristics were similar among different types of alcoholics (Table 1). The mean age at onset of alcohol use was very similar among different alcoholics and also quite similar to the non-alcoholic subjects (Table 1). However, as expected, the mean daily amount of alcohol used by the non-alcoholic group was substantially smaller as compared to the alcoholic group (P < 0.0001) and from the subgroups of the different types of alcoholics (P < 0.001) (Table 1). It was also observed that Type III alcoholics had the largest mean daily amount of alcohol used, which was significantly different than that of Type II (P < 0.01) and Type IV (P < 0.05) alcoholics.

Mini-mental status examination (MMSE)

MMSE: total sample. The comparison between the non-alcoholic control and alcoholic groups showed that the alcoholic patients demonstrated a significantly lower mean of MMSE total score (P < 0.01) as compared to the control group (Figure 1A).

In the analysis comparing the subgroups of alcoholics classified according to Lesch’s typology, there was a statistically significant difference between the non-alcoholic control group and the subgroups of alcoholics (Types I, II, III and IV) (F(4, 205) = 19.79; P < 0.0001). Type IV alcoholics demonstrated a significantly lower mean MMSE total score (P < 0.01) as compared to the non-alcoholic control group and also to all of the other types of alcoholics (Figure 1B).

MMSE: cut-offs for age and years of schooling. When considering the mean MMSE score normalized for age and years of schooling categories by Crum et al. (1993) as cut-offs, 39.4% of alcoholic patients and 22.5% of non-alcoholics subjects were underscored. In a more specific analysis, 16.7%, 32.0%, 32.7% and 82.9% of Lesch’s type I, II, III and IV patients, respectively, scored under the Crum et al. (1993) MMSE cut-offs.

In the analysis excluding MMSE subjects scoring below the cut-offs, the mean MMSE total scores of non-alcoholic and alcoholic groups were not significantly different (Figure 1C). There were also no statistically significant differences in the comparison of the subgroups of alcoholics (Figure 1D), indicating that the cut-offs used to exclude below-scored MMSE performance normalized for age and years of schooling were effective at keeping subjects with no suggestive dementia under analysis.

Frontal assessment battery (FAB)

FAB total sample: general analysis. Figure 2A shows the percentage of non-alcoholic or alcoholic subjects in each FAB score. The majority of alcoholic subjects showed lower scores...
Table 1. Baseline socio-demographic and drinking behavioral characteristics of alcoholic and non-alcoholic control groups

<table>
<thead>
<tr>
<th>Lesch's type</th>
<th>Non-alcoholic controls</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Total alcoholics</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>40 (100)</td>
<td>36 (21.2)</td>
<td>50 (29.4)</td>
<td>49 (28.8)</td>
<td>35 (20.6)</td>
<td>170 (100)</td>
</tr>
<tr>
<td><strong>Demographic variables</strong></td>
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<tr>
<td>Gender: n (%)</td>
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</tr>
<tr>
<td>Male</td>
<td>35 (87.5)</td>
<td>33 (91.7)</td>
<td>50 (100)</td>
<td>35 (71.4)</td>
<td>30 (85.7)</td>
<td>148 (87.1)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (12.5)</td>
<td>3 (8.3)</td>
<td>–</td>
<td>2 (4.3)</td>
<td>5 (14.3)</td>
<td>22 (12.9)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>44.6 (8.7)</td>
<td>46.3 (11.0)</td>
<td>48.0 (9.0)</td>
<td>43.8 (9.0)</td>
<td>47.7 (9.9)</td>
<td>46.4 (9.7)</td>
</tr>
<tr>
<td>Range</td>
<td>29–63</td>
<td>20–70</td>
<td>30–74</td>
<td>24–62</td>
<td>33–76</td>
<td>20–76</td>
</tr>
<tr>
<td>Marital state (%)</td>
<td></td>
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<tr>
<td>Married</td>
<td>77.5</td>
<td>50.0</td>
<td>60.0</td>
<td>67.4</td>
<td>57.1</td>
<td>59.4</td>
</tr>
<tr>
<td>Divorced</td>
<td>12.5</td>
<td>27.8</td>
<td>32.0</td>
<td>24.5</td>
<td>14.3</td>
<td>25.3</td>
</tr>
<tr>
<td>Single</td>
<td>10.0</td>
<td>16.7</td>
<td>8.0</td>
<td>6.1</td>
<td>25.7</td>
<td>12.9</td>
</tr>
<tr>
<td>Widower</td>
<td>0</td>
<td>5.6</td>
<td>–</td>
<td>2.0</td>
<td>2.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Years of education (%)</td>
<td></td>
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<tr>
<td>Illiterate</td>
<td>0.0</td>
<td>5.7</td>
<td>4.0</td>
<td>8.2</td>
<td>5.7</td>
<td>5.9</td>
</tr>
<tr>
<td>1–4 years</td>
<td>40.0</td>
<td>45.7</td>
<td>48.0</td>
<td>36.7</td>
<td>62.9</td>
<td>47.3</td>
</tr>
<tr>
<td>5–8 years</td>
<td>22.5</td>
<td>34.3</td>
<td>28.0</td>
<td>30.6</td>
<td>28.6</td>
<td>30.2</td>
</tr>
<tr>
<td>&gt;9 years</td>
<td>37.5</td>
<td>14.3</td>
<td>20.0</td>
<td>24.5</td>
<td>2.9</td>
<td>16.6</td>
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<tr>
<td><strong>Employment (%)</strong></td>
<td></td>
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<tr>
<td>Formal job</td>
<td>38.5</td>
<td>16.7</td>
<td>18.0</td>
<td>22.0</td>
<td>23.5</td>
<td>19.9</td>
</tr>
<tr>
<td>Temporary job</td>
<td>2.6</td>
<td>13.9</td>
<td>10.0</td>
<td>4.9</td>
<td>5.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Informal job</td>
<td>33.6</td>
<td>47.2</td>
<td>26.0</td>
<td>24.4</td>
<td>20.6</td>
<td>29.2</td>
</tr>
<tr>
<td>Unemployed</td>
<td>7.7</td>
<td>13.9</td>
<td>28.0</td>
<td>24.4</td>
<td>35.3</td>
<td>25.5</td>
</tr>
<tr>
<td>Insured</td>
<td>5.1</td>
<td>2.8</td>
<td>4.0</td>
<td>14.6</td>
<td>5.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Retired</td>
<td>12.8</td>
<td>5.6</td>
<td>14.0</td>
<td>9.8</td>
<td>8.8</td>
<td>9.9</td>
</tr>
<tr>
<td><strong>Measurements of alcohol drinking behavior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of alcohol use, mean (SD)</td>
<td>15.7 (5.9)</td>
<td>14.7 (4.0)</td>
<td>15.3 (4.7)</td>
<td>14.9 (5.4)</td>
<td>14.7 (4.0)</td>
<td>14.9 (4.6)</td>
</tr>
<tr>
<td>Amount of alcohol used (g/day), mean (SD)</td>
<td>9.9 (11.4)</td>
<td>368.9** (272.5)</td>
<td>299.8** (246.9)</td>
<td>478.9** +/++ (404.6)</td>
<td>344.0** (242.8)</td>
<td>372.5*** (314.2)</td>
</tr>
<tr>
<td>Days of abstinence before the study, mean (SD)</td>
<td>–</td>
<td>241.3 (457.5)</td>
<td>136.3 (312.2)</td>
<td>162.0 (395.8)</td>
<td>269.6 (570.7)</td>
<td>193.4 (33.0)</td>
</tr>
<tr>
<td>Dependence severity (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mild</td>
<td>–</td>
<td>–</td>
<td>6.0</td>
<td>–</td>
<td>2.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>–</td>
<td>2.8</td>
<td>56.0</td>
<td>24.5</td>
<td>17.1</td>
<td>27.6</td>
</tr>
<tr>
<td>Severe</td>
<td>–</td>
<td>972</td>
<td>38.0</td>
<td>75.5</td>
<td>80.0</td>
<td>70.0</td>
</tr>
</tbody>
</table>

**P < 0.001 (Fisher’s LSD protected t-test). ****P < 0.0001 (unpaired t-test) as compared to the non-alcoholic control group. + P < 0.05 as compared to Lesch’s Type IV. ++ P < 0.01 as compared to Lesch’s Type II.

as compared to non-alcoholic controls, shifting the graphic pattern slightly to the left.

In the analysis considering the different types of alcoholism, the graphic patterns of Lesch’s types I, II and III were very similar to the non-alcoholic subjects (Figure 2B). Lesch’s type IV alcoholics, however, showed a clear shifting to the left (Figure 2C), with almost all subjects demonstrating substantially lower scores as compared to non-alcoholic subjects. Of this subgroup, the maximum score was 12.

**FAB total sample: comparisons among groups.** Alcoholic patients had significantly lower mean FAB overall scores ($P < 0.0001$) as compared to the non-alcoholic control subjects (Figure 3A). When considering different types of alcoholism (Figure 3B), statistically significant differences were found among groups ($F(4, 205) = 14.51; P < 0.0001$). Type IV alcoholics showed a significantly lower mean FAB total score ($P < 0.01$) as compared to non-alcoholic controls and also to other types (I, II or III) (Figure 3B). However, Type II and III alcoholics also showed lower mean FAB total scores ($P < 0.01$) as compared to non-alcoholic subjects (Figure 3B).

**FAB total sample: multiple linear regression analysis.** The multiple linear regression analysis of the frontal lobe function in alcoholic patients showed the existence of predictive variables for FAB performance ($r = 0.71, F(14, 354) = 6.49, P < 0.0001$). The type of alcoholism ($P = 0.01$) and performance on the MMSE ($P = 0.001$) were predictive of FAB performance; specifically, Lesch’s type IV alcoholism and lower scores on the MMSE were related to lower FAB scores. No other variables, including socio-demographic characteristics (i.e. age, gender, race, years of education, marital state, employment), alcohol drinking behavior (i.e. age at onset of alcohol use, amount of alcohol used, days of abstinence before the study or dependence severity) or other characteristics investigated (i.e., smoking, use of other drugs, and other diagnoses), were predictive for frontal function performance.

**FAB total sample: analysis of subsets.** Because particular aspects of frontal function are affected in alcoholic patients, an analysis of each subset of the FAB between the non-alcoholic control and the alcoholic subjects, as well as among controls and the different types of alcoholics, is presented in Table 2.

**Conceptualization.** In the general analysis between alcoholics and non-alcoholics, there was not a significant difference; however, a statistically significant difference was found in the comparisons between the non-alcoholic control and the
Frontal Function in Different Types of Alcoholism

Fig. 1. Mean (±SD) of the mini-mental status examination (MMSE) scores by the non-alcoholic control group or the alcoholic patients (A and C), and by alcoholics classified according to Lesch’s typology (B and D). (C and D) An additional analysis excluding subjects underscored for age and years of schooling, according to the norms defined by Crum et al. (1993). **P < 0.01 as compared to the non-alcoholic control group; +++P < 0.01 as compared to Lesch’s Types I, II and III.

Table 2. Mean (±SD) scores obtained in subsets of the frontal assessment battery (FAB) of alcoholic (total sample or classified according to Lesch’s typology) and non-alcoholic control groups

<table>
<thead>
<tr>
<th>Lesch’s type</th>
<th>Non-alcoholic controls</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Total alcoholics</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>36</td>
<td>50</td>
<td>49</td>
<td>35</td>
<td>170</td>
</tr>
<tr>
<td>Conceptualization</td>
<td>0.88 ± 1.02</td>
<td>1.06 ± 1.19</td>
<td>0.70 ± 0.97</td>
<td>0.86 ± 1.02</td>
<td>0.26 ± 0.56**</td>
<td>0.74 ± 1.00</td>
</tr>
<tr>
<td>Mental flexibility</td>
<td>2.05 ± 0.90</td>
<td>2.28 ± 0.94</td>
<td>2.00 ± 0.97</td>
<td>2.14 ± 0.94</td>
<td>1.23 ± 0.94**</td>
<td>1.94 ± 1.00</td>
</tr>
<tr>
<td>Motor programming</td>
<td>2.52 ± 0.88</td>
<td>2.33 ± 0.76</td>
<td>1.94 ± 1.02**</td>
<td>1.82 ± 1.05**</td>
<td>1.71 ± 0.96**/+</td>
<td>1.94 ± 1.00**</td>
</tr>
<tr>
<td>Sensitivity to interference</td>
<td>2.65 ± 0.62</td>
<td>2.08 ± 1.03**</td>
<td>1.98 ± 1.08**</td>
<td>1.98 ± 1.05**</td>
<td>1.17 ± 1.10**/+</td>
<td>1.84 ± 1.11**</td>
</tr>
<tr>
<td>Inhibitory control</td>
<td>1.68 ± 1.23</td>
<td>1.36 ± 1.18</td>
<td>1.26 ± 1.23</td>
<td>1.12 ± 1.18*</td>
<td>0.46 ± 0.82**/+</td>
<td>1.08 ± 1.17**</td>
</tr>
<tr>
<td>Environmental autonomy</td>
<td>2.85 ± 0.53</td>
<td>2.83 ± 0.56</td>
<td>2.74 ± 0.72</td>
<td>2.92 ± 0.34</td>
<td>2.74 ± 0.74</td>
<td>2.81 ± 0.61</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01 and ***p < 0.001 as compared to the non-alcoholic control group; +++p < 0.01 as compared to Lesch’s Type I for motor programming, and to Lesch’s Types I, II and III for sensitivity to interference or inhibitory control.

subgroups of alcoholics (F(4, 205) = 3.42; P = 0.01). Type IV alcoholics had significantly lower mean scores (P < 0.01) as compared to the non-alcoholic controls and the subgroups of alcoholics (Table 2).

Mental flexibility. For mental flexibility, the general analysis between alcoholics and non-alcoholics was not statistically significant, but a statistically significant difference was found in the comparisons among the non-alcoholic control and the subgroups of alcoholics (F(4, 205) = 6.90; P < 0.0001). Type IV alcoholics showed significantly lower mean scores (P < 0.01) as compared to the non-alcoholic control and also to the subgroups of alcoholics (Table 2).

Motor programming. The motor programming subset was significantly lower (P < 0.001) in alcoholic patients as compared to non-alcoholic controls (Table 2). The comparison among non-alcoholic controls and alcoholic
The mean scores for Type IV alcoholics were also significantly lower \((P < 0.001)\) in alcoholic patients as compared to non-alcoholic controls (Table 2). The comparison among non-alcoholic controls and alcoholic subgroups also showed statistically significant differences \((F(4, 205) = 10.41; P < 0.001)\). Type I \((P < 0.05)\), II, III and IV \((P < 0.01)\) alcoholics showed significantly lower mean scores as compared to the non-alcoholic control group. Mean scores of Type IV alcoholics were also significantly lower \((P < 0.01)\) as compared to Type I, II and III alcoholics (Table 2).

**Inhibitory control.** The inhibitory control subset was also significantly lower \((P < 0.01)\) in alcoholic patients as compared to non-alcoholic controls (Table 2). There was a statistically significant difference among the control group and subgroups of alcoholics \((F(4, 205) = 5.63; P = 0.0003)\). Type III \((P < 0.05)\) and IV \((P < 0.01)\) alcoholics showed lower mean scores as compared to the non-alcoholic control group. The mean scores of the Type IV subgroup were also significantly lower \((P < 0.01)\) as compared to Type I, II and III alcoholics (Table 2).

**Environmental autonomy.** This environmental autonomy subset was not different between alcoholic and non-alcoholic subjects or between the non-alcoholic control and the subgroups of alcoholic patients.

**FAB: MMSE’s cut-offs for age and years of schooling.** Because low MMSE performance was highly predictive of the impaired frontal lobe function in alcoholic patients, an additional analysis of FAB performance (Figure 3C and D) excluding MMSE below-scored subjects was done, for the non-alcoholic control, the group of alcoholics and the subgroups of alcoholics.

In this analysis, the mean FAB total score of alcoholic patients was no longer statistically different from the non-alcoholic control (Figure 3C). However, when considering the different types of alcoholism, there was a statistically significant difference among groups \((F(4, 129) = 3.31; P = 0.01)\). The Type IV subgroup still showed significantly lower mean FAB total scores as compared to non-alcoholic subjects and to the other subtypes of alcoholics \((P < 0.01)\) (Figure 3D).

Thus, alcoholic patients, particularly from Lesch’s type IV group, showed significantly impaired frontal lobe function even after including only the participants that had MMSE scores above the cut-offs for age and years of schooling.

Considering the subsets of the FAB, scores for sensitivity for interference and motor programming were significantly lower in alcoholic patients \((P < 0.05)\) as compared to the non-alcoholic controls. The mean scores for motor programming were significantly lower \((P < 0.05)\) in Type III and IV alcoholics as compared to the non-alcoholic control.

**DISCUSSION**

In the present study, 21.2% of alcoholics from a Brazilian outpatient service were classified as Type I, 29.4% as Type II, 28.8% as Type III and 20.6% as Type IV, considering the criteria established by Lesch *et al.* (1990).
The distribution of patients in each type of alcoholism was somewhat different from that found by Lesch and Walter (1996) in a sample of 260 outpatients from a research center in Vienna, Austria. They reported a larger proportion of Type I alcoholics, 36.2%, a smaller proportion of Type II and III alcoholics, 23.5% and 22.3%, respectively, but a very similar proportion of Type IV alcoholics, 18.1% (Lesch and Walter, 1996).

These differences in the distribution of types of alcoholism seem to depend on the socio-demographic characteristics of a population and also on the specific circumstances of that population. Using the same criteria, different distributions have been reported by the same group of researchers, examining a different population at a different time.

For example, from the same research center in Austria, Wöber et al. (1998) found prevalence rates of 20.7%, 25.6%, 31.7% and 21.9% for Type I, II, III and IV alcoholics in a sample of 82 alcoholic patients. From this same research center, Walter et al. (2006) found an almost completely different distribution of alcoholics from that observed 10 years before. They observed a high proportion of Lesch Type II alcoholics (55.3%), and small proportions of Lesch’s Types I (11.3%) and IV (11.3%). The proportion of Type III alcoholics observed was 22%.

In Germany, Hillemacher et al. (2006), in a study of 192 alcoholic outpatients, classified 19.3% as Type I, 49% as Type II, 19.7% as Type III and 12% as Type IV. From the same service in Germany, Bönisch et al. (2006) found that out of a sample of 167 alcoholic patients, 15.5% were Type I, 38.9% were Type II, 34.7% were Type III and 10.8% were Type IV.

These differences in the distribution of alcoholic types are likely due to the fact that Lesch’s classification system considers a series of features including parental factors, drinking behavior, biochemical characteristics, psychiatric factors, neurological disorders, as well as the physical, psychological and social development of the patient (Lesch et al., 1988, 1990; Walter et al., 2006), all of which certainly vary among different groups of alcoholics examined in different regions and populations. Therefore, correct classification must carefully follow the diagnostic process of chronic alcoholism for the typology of Lesch’s types, outlined in Lesch’s Decision Tree (Lesch et al., 1990). Once accurately determined by this classification system, even if in different proportions, the characteristics of each type of alcoholic may be compared across different populations and times of observation.

In our study, Type III alcoholics showed higher daily amounts of alcohol ingestion compared to the other types of alcoholics.
One behavioral characteristic of this type of alcoholic is that alcohol seems to be consumed as a means by which to self-medicate depression; additionally this group tends to exhibit self-destructive tendencies (Lesch and Walter, 1996; Walter et al., 2006). Therefore, the higher consumption of alcohol may be related to this particular characteristic in this type of alcoholic. However, the other characteristics of alcohol ingestion examined in this study, such as age at onset of alcohol use and days of abstinence before the study, were not different among types of alcoholics, suggesting that the pattern of alcohol use may not be crucial in determining the type of alcoholism.

In a general analysis, alcoholic patients showed significantly lower mean total scores on the MMSE. Type IV alcoholic patients demonstrated significant impairment in MMSE performance as compared to the non-alcoholic controls and the other subtypes of alcoholism. Considering cut-offs for age and years of schooling normalized by Crum et al. (1993), a large proportion of alcoholic patients were below scored (39.4%). Of this below-scored group, a large majority were Type IV alcoholics (82.9%), suggesting that a large number of alcoholics have impaired mental functioning, notably the Type IV subgroup of alcoholics. After excluding all below-scored subjects, the remaining subjects in each group showed equivalent mean scores on the MMSE.

Considering all alcoholic patients and non-alcoholic control subjects, the general analysis of frontal function by the FAB showed that most alcoholic patients had lower scores when compared to non-alcoholic subjects. This pattern of decreased FAB performance among alcoholics was clearly evident in Type IV subjects. This type of alcoholics showed significantly lower FAB total scores as compared to non-alcoholic subjects and to other types of alcoholics. However, Types II and III also showed significant impairments in FAB total performance.

However, considering only the subjects above the cut-offs for age and years of schooling normalized by Crum et al. (1993) for MMSE performance, only type IV continued to demonstrate a significant decrease in the FAB total performance.

The executive frontal lobe function that was most impaired was the sensitivity to interference. In the general analysis, this subset was significantly lower in alcoholic patients; in the comparison among the different subtypes of alcoholism, all types were significantly impaired as compared to non-alcoholic controls and this impairment was more severe in Type IV alcoholics. When considering only subjects above the cut-offs for MMSE performance, this function was still impaired in alcoholic patients in general, but there were no differences among the different types of alcoholics.

The sensitivity to interference or behavioral self-regulation may be measured by tasks in which verbal commands conflict with sensory information (Dubois et al., 2000). This response can be measured by giving conflicting instructions. For example, an examiner might ask the subject to provide an opposite response to the examiner’s alternating signal (e.g. tapping once when the examiner taps twice). In that way the subject has to follow the verbal command instead of what they see (Dubois et al., 2000). Usually, patients with a frontal lobe lesion fail to obey the verbal command and tend to execute echopractic movements, imitating the examiner (Dubois et al., 2000). As this function was impaired in alcoholics, it may suggest that alcoholics are prone to repeat movements by imitation.

The second most impaired executive function was the motor programming function. It was significantly lower in the total sample of alcoholic patients and was significantly impaired in type II, III and particularly IV alcoholics as compared to non-alcoholic subjects. When considering only subjects above the cut-offs for MMSE performance, this function remained impaired in alcoholic patients in general, and more specifically in alcoholic types III and IV.

Motor programming is required for temporal organization and the maintenance and execution of successive actions (Dubois et al., 2000). This function can be examined by asking the subject to execute motor series in specific orders, such as Luria’s (1966) ‘fist-edge-palm’ task used in the FAB. This task assesses the ability to learn novel motor sequences and to engage in purposeful motor output (Suchy and Kraybill, 2007). Therefore, alcoholics with motor programming dysfunction are presumably impaired in their ability to learn new tasks and to engage in successive actions and consequently may show ineffective goal-directed behavior.

The third frontal function that was impaired in alcoholic patients was inhibitory control. Again, it was alcoholic types III and IV that showed lower scores of this cognitive function. This function, however, was no longer impaired in alcoholics and types of alcoholics when we considered subjects with MMSE scores above the cut-offs for age and schooling.

The inhibitory control or go-no-go paradigm can be assessed by asking the subjects to inhibit a response that was previously given to the same stimulus, e.g. not tapping when the examiner taps twice (Dubois et al., 2000), and not once as was previously asked when examining the sensitivity to interference. This task elicits a false motor response and allows a clinician to determine how much a subject is able to inhibit inappropriate responses, that is, the ability to control impulsiveness (Dubois et al., 2000).

As inhibitory control was impaired in alcoholics, these patients may show inappropriate and impulsive behavior.

The impairment of the frontal functions of sensitivity to interference (i.e. a tendency to show response behavior triggered by environmental stimuli), motor programming (i.e. difficulty in learning new motor responses and impaired goal-directed behavior) and inhibitory control (i.e. inappropriate and impulsive behavior) may underlie the compulsive behavior toward alcohol use seen in this population. Considering the high sensitivity to interference, any stimulus that has been associated with alcohol use would trigger the response to consume alcohol. Additionally, the weak goal-directed behavior and the lack of inhibitory control would account for the loss of control when using alcohol, which characterizes alcohol addiction and relapse.

Although there were no significant differences between alcoholic patients and non-alcoholic subjects, Type IV alcoholics showed significantly lower scores on conceptualization and mental flexibility when compared to the non-alcoholic control group. However, these functions were not affected in subjects with mean total MMSE scores above the cut-offs. These results suggest that conceptualization and mental flexibility may not depend exclusively on frontal functions and that these functions may be related to a more general cognitive function.

Alcohol-related brain damage with impairments in the frontal executive function has been largely demonstrated in the late stages of alcoholism (Cielieski et al., 1995; Garrido and Fernández-Guinea, 2004). This is the first time, however,
that executive frontal lobe functions have been examined in the context of different types of alcoholism.

In our sample, type IV alcoholics showed impairments in their executive frontal and general cognitive function. Even in those with a preserved mental function, the executive frontal function was still significantly compromised, notably in the motor programming subset. These results clearly indicate that, in addition to all of the characteristics considered by Lesch to distinguish the different types of alcoholism, and also the genetic differences of Lesch subtypes observed by Bönisch et al. (2006), alcoholics also differ in their cognitive function. Thus, in the treatment of these individuals, the limitations that these conditions impose must be considered.

Therefore, the determination of the clinical type of alcohol dependence by applying Lesch’s typology, along with the brief mental status and especially frontal function examinations, is of clinical relevance in the examination of alcoholics and provides significant clues for a more focused treatment of different types of alcohol dependence.

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REFERENCES


