



## Executive Functions in Adult Offspring of Alcohol-Dependent Probands: Toward a Cognitive Endophenotype?

Fabien Gierski, Bérengère Hubsch, Nicolas Stefaniak, Farid Benzerouk, Christine Cuervo-Lombard, Céline Béra-Potelle, Renaud F. Cohen, Jean-Pierre Kahn, Frédéric Limosin

### ► To cite this version:

Fabien Gierski, Bérengère Hubsch, Nicolas Stefaniak, Farid Benzerouk, Christine Cuervo-Lombard, et al.. Executive Functions in Adult Offspring of Alcohol-Dependent Probands: Toward a Cognitive Endophenotype?. *Alcoholism: Clinical and Experimental Research*, 2013, 37 (Suppl 1), pp.E356-E363. 10.1111/j.1530-0277.2012.01903.x . hal-02167780

**HAL Id: hal-02167780**

**<https://hal.univ-reims.fr/hal-02167780>**

Submitted on 28 Oct 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Executive Functions in Adult Offspring of Alcohol Dependent Probands: Toward a Cognitive Endophenotype ?

Fabien Gierski, PhD <sup>a,b,\*</sup>, Bérengère Hubsch, MD <sup>a</sup>, Nicolas Stefaniak, PhD <sup>b</sup>, Farid Benzerouk, MD <sup>a</sup>, Christine Cuervo-Lombard, PhD <sup>a</sup>, Céline Bera-Potelle, MD <sup>a</sup>, Renaud Cohen, MSc Psy <sup>c</sup>, Jean-Pierre Kahn, MD PhD <sup>c</sup>, Frédéric Limosin, MD PhD <sup>d, e, f</sup>

<sup>a</sup> Department of Psychiatry, Reims University Hospital, Reims, France

<sup>b</sup> C2S Laboratory (EA 6291), Reims Champagne-Ardenne University, Reims, France

<sup>c</sup> Department of Psychiatry and Clinical Psychology, Nancy University Hospital, Vandoeuvre-lès-Nancy, France

<sup>d</sup> Department of Psychiatry, Corentin-Celton Hospital, Assistance Publique-Hôpitaux de Paris, Issy-les-Moulineaux, France

<sup>e</sup> Paris Descartes University, Sorbonne Paris Cité

<sup>f</sup> INSERM U894, Psychiatry & Neurosciences Centre, Paris, France

*Corresponding author:*

Dr Fabien Gierski

Université de Reims Champagne-Ardenne, Laboratoire C2S (EA6291)

Maison de la Recherche - 57, rue Pierre Taittinger

51096 Reims Cedex, France.

Tel: +333.26.91.36.34.

Fax: +333.26.91.37.19.

Email: fabien.gierski@univ-reims.fr

**Abstract:** 237 words (max 250)

**Text:** 4342 words (max 4500)

**Figures:** 0    **Tables:** 3

**Supplementary tables:** 2

**Acknowledgements:** Funding for this study was provided by a Projet Hospitalier de Recherche Clinique grant (No.: PHRC-IR-2006-11). We thank Drs Kadri, Miron, Rigaud, Santolalla, and Werner, for their support with recruitment; Sarah Barrière and Sylvie Leleu for their help throughout the study; Stéphanie Caillies, Kathleen Smith and anonymous reviewers for their helpful comments on the manuscript.

## **ABSTRACT**

**Background:** Executive function (EF) impairment in alcohol dependence (AD) has been related to the toxic effects of alcohol on frontal lobes. However, this impairment could be partially present before the onset of the disease and might constitute a vulnerability factor. Although a considerable body of research has investigated executive functioning among AD patients, much less attention has been directed toward high-risk individuals. Most studies were carried out among children or adolescents, and very few were conducted in adults. The aim of the present study was to examine EF in a group of adult offspring of AD individuals.

**Methods:** One hundred and fifty-five non-alcoholic adults with (FHP) or without (FHN) family history of AD were included in the study. All participants were screened for past and current psychiatric diagnoses, and alcohol, tobacco and other substance use. They were compared on self-rated impulsiveness using the Barratt Impulsiveness Scale (BIS-11) and EF using a neuropsychological test battery.

**Results:** Group comparison revealed that FHP participants had significantly higher BIS-11 scores than the FHN participants, while neuropsychological examination revealed lower EF scores for FHP participants. Hierarchical regression analysis revealed that the number of AD family members was a predictor of EF results whereas impulsiveness was not.

**Conclusions:** Non-alcoholic adult offspring of AD individuals showed increased impulsiveness and decreased EF suggesting weakness of two distinct neurobehavioral decision systems. Findings support evidence that EF weaknesses may qualify as a suitable endophenotype candidate for AD.

**Keywords:** Executive functions, impulsiveness, first-degree relatives, alcoholism, endophenotypes

## **Introduction**

Alcohol dependence (AD) involves both environmental and genetic vulnerability factors. Although it has a rather high degree of heritability (estimated range between 40% and 60%), vulnerability to alcohol dependence is broadly considered as a complex polygenic phenotype (Begleiter and Porjesz, 1999). To clarify the risk factors involved in AD, attempts have been made to identify endophenotypes in AD patients and their relatives (Andrew and Fein, 2010; Singh and Basu, 2009). Endophenotypes (or intermediate phenotypes) are defined as heritable traits associated with an increased risk for developing a disorder (Gottesman and Gould, 2003). They must be found in probands and their unaffected relatives at a higher rate than in the general population (Leboyer et al., 1998).

In alcoholism, brain electrophysiological abnormalities have been extensively investigated over the last four decades with the use of event-related potentials or more recently event-related oscillation and are undoubtedly the most studied endophenotype. Such research has documented a reduction in the P3 amplitude component (P3-AR) among currently-abstinent AD individuals (Andrew and Fein, 2010; Fein and Chang, 2006; Porjesz and Rangaswamy, 2007; Rangaswamy and Porjesz, 2008), their at-risk first-degree relatives (Hesselbrock et al., 2001; Kamarajan et al., 2006; Rangaswamy et al., 2007; Singh and Basu, 2009), and non-alcoholic adolescent twin pairs who became discordant for alcoholism as adults (Carlson et al., 2004; Perlman et al., 2009).

In contrast, there have been few if any studies of cognitive endophenotypes in alcoholism. Nevertheless, several authors consider that cognitive functions and specifically executive functions (EF) are among the most promising endophenotype candidates for many psychiatric disorders (Bertisch et al., 2009; Cavedini et al., 2010; Gau and Shang, 2010; Owens et al.,

2011; Robbins et al., 2012; Schulze et al., 2011; Viswanath et al., 2009) including addictions (Hester et al., 2010).

Executive functions consist of a set of highly heritable cognitive processes (Friedman et al., 2008), frequently associated to the frontal lobes, that guide complex behavior over time through planning, decision-making, and response control (Zinn et al., 2004). Accumulating evidence suggests that EF can be divided into separable processes that share some underlying commonality. Miyake et al. (2000), found evidence supporting the existence of the unity and the diversity of three distinct albeit interrelated executive processes: inhibition, set shifting and updating. According to these authors, inhibition is the ability to deliberately inhibit dominant, automatic, or prepotent responses when necessary. Set shifting is the ability to disengage from an irrelevant task or mental set and subsequently engage actively in a relevant task or mental set. Updating is the ability to actively maintain information in working memory and to integrate new and relevant information into that set by replacing old, no longer relevant information, with newer and more relevant information. Results from neuroimaging studies are likely to support this model given that those three processes, although associated with relatively distinct prefrontal and parietal brain areas, have also shown common activated areas (Collette et al., 2005; McNab et al., 2008).

While data concerning updating processes in AD individuals seem controversial (Hildebrandt et al., 2004; Pitel et al., 2007; 2009), impairment in the two other processes has been widely documented. Currently-abstinent AD individuals exhibit impaired abilities for performing neuropsychological tests designed to assess inhibition and set shifting processes, such as the Wisconsin Card Sorting Test (WCST), the Stroop Color Word Test and the Trail Making Test (Davies et al., 2005; Moriyama et al., 2002; Oscar-Berman et al., 2009; Pitel et al., 2007; 2009; Ratti et al., 2002; Sullivan et al., 2000; Tedstone and Coyle, 2004; Zinn et al., 2004).

1 Nevertheless, these results might reflect a cumulative effect of genetic liability coupled with  
2 the direct toxicity of alcohol on brain tissues and are not sufficient to hypothesize the  
3 existence of a cognitive endophenotype in AD. Furthermore, in contrast to a large number of  
4 electrophysiological studies, very much less attention has been given to EF among non-  
5 alcoholic first-degree relatives of AD individuals, and the results of those studies are  
6 inconclusive. For instance, Drejer et al. (1985), reported that adolescent sons of alcoholic  
7 fathers performed worse on tests of categorising, organisation and planning than did those of  
8 non-alcoholic fathers. Ozkaragoz et al. (1997), found that 10- to 14-year-old sons of alcoholic  
9 individuals performed significantly worse on attentional and general intellectual tasks than did  
10 sons of social drinkers. Poon et al. (2000), reported lower IQ, weaker planning and attentional  
11 abilities, and more difficulties in school achievement among 6- to 9-year-old sons of alcoholic  
12 fathers; as well, sons of alcoholic fathers with coactive antisocial personality disorder  
13 performed worse than sons of alcoholic fathers without coactive antisocial personality  
14 disorder. Corral et al. (1999), reported that offspring (age 7-15 years) of AD parents with a  
15 high family history of AD performed worse on the WCST than did offspring of parents with  
16 either a negative or low familial density of AD; these results were confirmed in a three-year  
17 follow-up (Corral et al., 2003). More recently, it has been reported that offspring (age 7-17  
18 years) of alcoholic parents performed worse than did matched controls on the Stroop test,  
19 which measures inhibition, and on subtests of the Wechsler Intelligence Scale for Children,  
20 which measures academic performance (Diaz et al., 2008). In contrast, Gillen and  
21 Hesselbrock (1992), did not find any neuropsychological impairment in a group of male  
22 adults with a family history of alcoholism. These authors suggested that cognitive disabilities  
23 found among offspring of AD individuals in other studies may have been related to a failure  
24 to consider personal history of antisocial personality disorder. However, in a prospective

study on boys (3- to 14-year-olds) with varied familial risks for developing alcoholism, Nigg et al. (2004), showed weaker EF abilities in families with alcoholism without antisocial comorbidity than in families with alcoholism and antisocial comorbidity.

Much of the research on EF reported above involved non-adult offspring of AD; however, executive functions are mainly mediated by the frontal lobes, which are not physically and functionally mature before the end of adolescence (Giedd et al., 1999; Tamm et al., 2002; Toga et al., 2006). Moreover, in some studies groups were not comparable concerning general intellectual abilities, which might have interacted with EF task performance (Friedman et al., 2006). The aim of the present study was to address these issues. We investigated whether a group of adult non-alcoholic offspring of AD individuals would perform EF tests less efficiently than a group of participants without family history of AD. We decided to focus on inhibition and set shifting processes for which results among AD individuals are consistent, and because these processes are more likely to play a role in addiction (Bickel et al., in press; Ham and Parsons, 2000; Young et al., 2009). We also explored the relation between familial density of alcoholism and EF performance.

## **Material and Methods**

### *Participants*

A total of 100 healthy non-alcoholic adults who had at least one first-degree biological AD relative (family history positive, FHP) were screened to participate in the study. They were matched for age, gender, and years of education with an equal number of healthy non-

1 alcoholic volunteers who had no family history of alcoholism or substance dependence in any  
2 first- or second-degree relative (family history negative, FHN). Participants were recruited  
3 from among respondents to advertisements and flyers placed in and around the university  
4 hospitals. Based on the telephone screening results, we preselected individuals for the FHP  
5 group who appeared to have at least one first-degree relative with alcohol-related problems.  
6 Individuals who reported that they had no first- or second-degree relatives with alcohol-  
7 related problems were preselected for the FHN group.

8 The experimental design was submitted to the local ethical committee, which approved the  
9 study. Participants freely gave their written informed consent prior to the study. They received  
10 €60 to compensate for their participation in the study, which included clinical and  
11 neuropsychological examinations and blood sample collection for DNA analyses (the results  
12 of which will be reported separately).

#### 14 *Procedure*

15 *Clinical Assessment.* All participants were interviewed face to face by a trained clinician.  
16 Current and lifetime psychiatric diagnoses and drinking history were assessed using a semi-  
17 structured interview: the Diagnostic Interview for Genetic Studies (DIGS), which includes  
18 screening for substances and alcohol misuse and dependence, the CAGE questionnaire, and a  
19 question about the largest number of drinks ever consumed in a 24-hour period (Berney et al.,  
20 2002; Nurnberger et al., 1994). Nicotine dependence was assessed using the Fagerström Test  
21 for Nicotine Dependence (FTND; Heatherton et al., 1991). We also calculated the total  
22 number of pack-years by multiplying the self-reported number of packs per day by the  
23 number of years of regular cigarette smoking. Familial history of alcohol and substances



consumption was assessed by the Family Informant Schedule and Criteria (FISC; Mannuzza et al., 1985). Impulsiveness was assessed using the Barratt Impulsiveness Scale-11 (BIS-11; Patton et al., 1995; Stanford et al., 2009). This 30-item self-report questionnaire, designed to measure behavioural and cognitive aspects of impulsiveness, generates a total score of general impulsiveness obtained by summing three subtest scores: motor (acting without thinking), attentional (an inability to focus attention or concentrate), and non-planning (lack of forethought).

*Neuropsychological Assessment.* Each participant was assessed in a single session by a qualified psychologist blind to group allocation. General intellectual ability (IQ) was assessed using Raven's Progressive Matrices (Raven et al., 2003). The executive functions of set shifting and inhibition processes were assessed as follows:

1. *Wisconsin Card Sorting Test* (Heaton et al., 1993): this test requires participants to match cards by colour, shape, and number to four key cards. We used the 64 Card-computerized version of the task. Participants are not told how to sort the cards, but must determine the correct category from the computer feedback. After 10 consecutive correct responses the sorting rule changes and participants must sort according to the new rule. Participants were scored on the number of achieved categories, the number of non-preserved errors, and the number of perseverative errors; the latter is a measure of set shifting ability.

2. *Stroop Color Word test* (Stroop, 1935): participants are asked to name as quickly and as accurately as possible the ink color of rows of X's (Color condition), to read color words (Word condition), and to name the ink color of incongruous color words (Color-Word condition). The Stroop task involves speed of information processing (Color and Word

conditions) and the ability to inhibit a prepotent response tendency (Color-Word condition).

The time to correctly perform each condition was recorded. Following Golden (1976), we also calculated an interference score, which takes overall slowing into account.

3. *Trail Making Test* (TMT; Reitan and Wolfson, 1985): this test is composed of two parts.

In part A, participants are required to connect a series of 25 circles containing numbers

randomly arranged in a spatial array. This part requires attention, mental tracking, and visual

search. In part B, participants are asked to alternate between connecting a series of circles

containing numbers in increasing order and connecting a series of circles containing letters in

alphabetic order. This part requires the additional process of set shifting as participants must

alternate between number use and letter use. The dependent measure was the completion time

(in seconds) for each part. The completion time difference between part B and A was also

calculated in order to provide a relatively pure indicator of set shifting (Sanchez-Cubillo et al.,

2009).

4. *Arithmetic Switching Task* (AST; Emerson and Miyake, 2003; Miyake et al., 2000): this

test consists of three lists of 30 two-digit numbers, a separate list for each condition. In the

Add condition, the task was to add 3 to each number and write down the answers. In the

Subtract condition, the task was to subtract 3 from each number. In the Add-subtract

condition, the task was to alternate between adding and subtracting (i.e., add 3 to the first

number, subtract 3 from the second number, and so on). The order of conditions was

randomized. The participants were instructed to complete each list as quickly and as

accurately as possible, starting at the top of the list and finishing at the bottom. This task

involves arithmetic skills and speed of information processing in each condition;

additionally, the add/subtract condition requires the process of set shifting between the two

operations. The dependent measure was the completion time (in seconds) for each condition.

1 We also calculated a switch cost measure, which represents the average time needed to switch  
2 from one operation to the other, independent of the time to perform the basic arithmetic  
3 operations. This measure was calculated by subtracting the mean completion time for the two  
4 blocked lists from the completion time for the alternating list.

5  
6 *Selection of the sample.* For reasons related to planned genetic analyses, only Caucasian  
7 participants were included in the study. Participants with current or past major medical,  
8 neurological (including head injury), or psychiatric disorders (including alcohol/substance  
9 dependence or abuse), and/or participants who were taking concurrent psychotropic  
10 medications were excluded from the study. However, past histories (at least 6 months) of  
11 mood or anxiety disorders, as well as concurrent externalising disorders (such as antisocial  
12 personality disorder or attention deficit hyperactivity disorder) were not exclusion criteria.  
13 Among the 100 FHP participants, 55 had an AD father, 18 had an AD mother, 14 had both  
14 parents AD, and 13 had no AD parents but did have AD siblings. Only first-degree relatives  
15 of AD father were included in the analysis to prevent a potential confound from the effects of  
16 heavy alcohol or drug use during pregnancy, and to have a homogenous group of relatives.  
17 Among those 55 FHP participants in the final sample, forty (72.72%) had only an AD father,  
18 13 (23.64%) had an AD father and one AD sibling, and two (3.64%) had an AD father and  
19 two AD siblings; the mean number of first-degree AD relatives was 1.31 ( $S.D = 0.54$ ). As  
20 mentioned above, there were 100 FHN participants in the control group.

21  
22 *Statistical Analysis.* Data collection and processing were performed using SPSS® version 19  
23 for Windows. Comparisons of demographic, clinical and neuropsychological variables were  
24 performed using Student's two-sample t-tests or Pearson's Chi-square tests where

appropriate. Scores yielded by the neuropsychological battery reflecting relatively pure executive functions were subjected to a factor analysis using the principal components analysis (PCA) method in an attempt to extract from them a more refined and, therefore, a more valid EF indicator. After having checked with the Kaiser–Meyer–Olkin measure of sampling adequacy, and Bartlett's test of sphericity, that the adequacy of the correlation matrix was sufficient for performing the PCA, criteria adopted for factor loading included eigenvalues greater than 1 rated and the scree plot analysis. An executive factor score was obtained according to the extracted factor weighting and original variables values. Generated factor scores were then compared using Student's two-sample t-tests. Finally, the relationships between socio-demographic and clinical characteristics, and the executive factor score, were examined with Pearson's correlation coefficients, and a hierarchical multiple regression was performed in order to determine which variables predicted the executive factor score.

## Results

### *Demographics and clinical questionnaires*

Table 1 summarises the demographic and clinical characteristics of the groups. Mean age (range: 18–59 for FHP and 18–59 for FHN), mean education level (range: 8–20 years for FHP and 8–15 years for FHN), and gender ratios were comparable between the groups. General intellectual abilities, assessed by Raven's Matrices, were also comparable.

-----  
Insert Table 1 about here  
-----

Data from the DIGS indicated that FHP participants exhibited greater lifetime prevalence rates for major depression episodes (MDE) and anxiety disorders than did FHN participants. The mean number of MDE in the FHP group was also higher than in the FHN group. The lifetime rates of suicide attempts and the number of suicide attempts were also higher for the FHP group, but these differences did not reach statistical significance. None of the participants in either group were diagnosed with attention deficit hyperactivity disorder, but two participants of the FHP group (3.60%) were diagnosed with antisocial personality disorder. Concerning drinking variables, CAGE scores were comparable between the two groups, with a maximum score of 1 in each group. The lifetime prevalence rates of past drunkenness were also comparable. The maximum amount of alcohol consumption in a 24-hour period among participants who reported having been drunk at least once ( $n = 26$  for FHP;  $n = 40$  for FHN), was close to significance level, with FHN reporting a higher amount of alcohol consumption; the highest reported maximum consumption in each group was 12 units of alcohol in the FHP group and 40 units in the FHN group. The distribution of smoking status and the Fagerström maximum score (past or present smoking:  $n = 32$  for FHP;  $n = 39$  for FHN) were also close to significance level, while the mean pack-year was significantly higher for FHP participants. Ranges varied between 0.25 and 42 in the FHP group and 0.42 and 46 in the FHN group.

Self-rated impulsiveness, assessed by the BIS-11, was significantly higher overall in the FHP than in the FHN group; FHP participants showed higher BIS-11 total, motor, attentional and non-planning scores.

#### *Neuropsychological Assessment*

Table 2 summarizes EF performance according to family history of alcoholism. Group comparisons revealed significant differences for the number of achieved categories and perseverative errors on the WCST, for completion times on each of part B and part B-A on the TMT, and for Add/subtract completion time on the AST. For each of these tasks, performance of the FHP group was worse than performance of the FHN group. In contrast, variables which are more likely to reflect speed of information processing such as the Stroop-Word, the TMT-A and the AST-Add condition completion times were not significantly different between groups.

-----

Insert Table 2 about here

-----

Variables that reflected "purer" measures of EF (*i.e.*, the WCST number of perseverative errors, the Stroop interference score, the TMT B-A completion time, and the AST switch time) were subjected to an exploratory factor analysis using the PCA method. The optimal solution is presented in Supplementary Table 1 with the factor loading for each variable. The executive factor had an eigenvalue of 1.99 and accounted for 49.91 % of the variance. To facilitate interpretation, the derived executive factor scores were inverted (multiplication by -1) so that all high scores were indicative of a better executive performance.

1 In order to compare executive abilities between the groups, we performed a two-tailed  $t$  test  
2 on the factor scores with Group (2 levels: FHP vs. FHN) as between-participant variable. This  
3 analysis revealed a significant effect of Group [ $t(153) = 2.81$  ;  $p = 0.006$ ].

4 The relationships between socio-demographic and clinical characteristics and the executive  
5 factor scores were examined with Pearson's correlation coefficients (Supplementary Table 2).

6 Results showed that the executive factor scores were negatively correlated with age, number  
7 of AD relatives and pack-year, and positively correlated with education level and IQ.

8 Finally, we performed a hierarchical multiple regression in order to determine whether the  
9 number of AD relatives would explain the executive factor scores after controlling for  
10 variables known to have an impact on executive functioning and all other variables on which  
11 the groups differed. These variables were entered in five steps which were forced in order to  
12 ensure that the number of AD relatives was the last variable entered in the model. Background  
13 variables (age, education level and IQ) were entered in step one, the number of past MDE and  
14 lifetime anxiety disorders in step two, pack-year in step three, BIS-11 total score in step four,  
15 and the number of AD relatives in step five. To test for multicollinearity, we examined the  
16 tolerance values. With all predictors entered, the tolerance ranged from 0.69 to 0.95,  
17 indicating that there was no issue, as only tolerance values below 0.20 are potentially  
18 problematic (Menard, 2010). The results are shown in Table 3.

19 -----

20 Insert Table 3 about here

21 -----

22 After controlling for background variables, we found a significant contribution of the  
23 psychiatric disorder history, but no significant contribution of smoking history and

1 impulsiveness variables. The number of AD relatives significantly improved the final model.  
2 The standardised beta coefficient of this variable indicated a negative effect of family history  
3 of alcoholism on executive performance.  
4

## 5 **Discussion**

6 Many reports have suggested that EF impairments are a core feature of AD. These  
7 impairments may reflect the combined effects of genetic liability and direct alcohol toxicity  
8 on the frontal lobes. In contrast, few studies have examined executive functions in unaffected  
9 offspring of AD individuals and those few were mainly conducted among sons or early  
10 adolescents. However, given that frontal lobes are not functionally mature before the end of  
11 adolescence, we decided to explore executive functioning in a sample of unaffected adult  
12 offspring.

13 Compared to the FHN group, our sample of adult FHP offspring performed worse on  
14 executive tests involving inhibition and set shifting processes. They also exhibited higher self-  
15 rated impulsiveness as assessed with the BIS-11. These results were not due to group-specific  
16 differences in educational level, general intellectual abilities or speed of information  
17 processing. Given that several other factors such as past psychiatric lifetime diagnoses,  
18 alcohol/substance consumption, and smoking could have a deleterious effect on executive  
19 functions (Douglas and Porter, 2009; Eysenck et al., 2007; Glass et al., 2009; Richards et al.,  
20 2003; van Holst and Schilt, 2011), we attempted to control for the effect of these potential  
21 confounding variables. Consistent with findings from previous studies (Diaz et al., 2008; Hill  
22 et al., 2010; Raucher-Chene et al., in press), we found that the prevalence rate of past lifetime  
23 psychiatric diagnoses was higher among FHP. We also found that FHP were more likely to



1 smoke than FHN were, and presented higher rates of cigarette consumption; these results are  
2 consistent with a finding in the literature that AD individuals have a higher sensitivity to  
3 nicotine dependence (Le Strat et al., 2010). On the other hand, drinking consumption history  
4 suggested that FHN participants were more likely to drink higher amounts of alcohol in a  
5 single session. A possible explanation of the present results is that FHP individuals  
6 voluntarily regulate their consumption. Results of regression analysis indicated that although  
7 we found a significant influence of psychiatric diagnoses history, other variables such as  
8 smoking history or self-reported impulsiveness did not significantly contribute to EF  
9 performance; and above all, when the influence of those variables was controlled, the familial  
10 density of alcoholism continued to explain the EF abilities.

11 In agreement with Kamarajan et al.'s (2004) model, which postulates that disturbances in  
12 prefrontal network systems are involved in AD, our findings suggest that impulsivity and EF  
13 impairment may be important factors underlying the pathogenesis of AD. Accordingly, recent  
14 studies using functional neuroimaging among adolescent and young adult AD offspring  
15 (Cservenka and Nagel, 2012; Heitzeg et al., 2010; Silveri et al., 2011) revealed a significant  
16 influence of AD family history status on brain activation during inhibition or decision-making  
17 tasks, suggesting a pre-existing abnormality in functions depending on frontal lobe in youths  
18 at risk for alcohol use disorders. However, it is important to emphasize that, in our study, the  
19 EF factor was not correlated with self-reported impulsiveness. Nevertheless, the recent review  
20 of addiction literature by Bickel et al. (in press) suggests that, while both behavioural  
21 impulsivity and executive function are related to addiction, each reflects different processes  
22 and has different neural substrates. These authors suggest that there are two neurobehavioral  
23 decision systems: an impulsive decision system embodied in the limbic and paralimbic brain  
24 regions, and an executive decision system embodied in areas of the prefrontal cortices. Our

1 results support the view that the two systems are distinct; even though adult offspring of AD  
2 individuals demonstrated both higher self-rated impulsiveness and weaker EF performance  
3 compared to controls, we found no relation between these factors.

4 Limitations of the study mainly stem from the screening method for inclusion and the  
5 characteristics of the samples. AD in first-degree family members was assessed only through  
6 interviews with the FHP offspring. It is possible that some of the family members of the FHP  
7 group would not fully meet the criteria for AD if they had been interviewed face to face by  
8 the clinicians. On the other hand, some relatives of the FHN group could have been AD.  
9 However, we used a standardised and well-validated semi-structured interview, the FISC  
10 (Mannuzza et al., 1985). Another potential limitation concerns the choice of the cognitive  
11 tasks. Cognitive tasks were chosen on the basis that, according to the literature, they assess  
12 processes of inhibition and set shifting. However, genetic studies conducted with  
13 monozygotic or dizygotic twins indicate that some of these tests differ with respect to  
14 heritability. Whereas the TMT has been reported to have good heritability (Owens et al.,  
15 2011), the Stroop Test has moderate heritability (Taylor, 2007), and the WCST, appears to  
16 have low heritability (Anokhin et al., 2003; Chou et al., 2010; Kremen et al., 2007; Taylor,  
17 2007). Therefore, it is possible that the use of tests with more heritability might have  
18 increased the power of our results. Nevertheless, findings reported by Anokhin et al. (2010)  
19 suggest that a gender effect exists for the genetic and environmental influences on WCST  
20 performance, and that the heritability of this test is higher for women. In fact, our sample was  
21 mostly composed of women. This is another potential limitation; our results should be  
22 confirmed in a more balanced sex-ratio sample. Finally, we acknowledge that, since P3-AR  
23 can be associated with pathologies other than alcoholism, weak EF is not specifically  
24 associated with having first-degree AD relatives. Indeed, EF weaknesses have been found in

1 unaffected relatives of patients with bipolar disorder, schizophrenia, autism, and obsessive-  
2 compulsive disorder (Cavedini et al., 2010; Delorme et al., 2007; Hill et al., 2008; Zalla et al.,  
3 2004), and might reflect an overall vulnerability factor.

4 In conclusion, our findings support evidence that EF weaknesses may correspond to a  
5 cognitive endophenotype and could be useful in the identification of etiopathogenic factors  
6 involved in AD. As well, our results suggest that clinical examinations and research on mood  
7 and anxiety disorders should take the family history status of AD into account, as AD  
8 offspring have higher rates of these disorders. Further studies applying genetic and  
9 neuroimaging techniques are warranted, to specify candidate polymorphisms and to  
10 substantiate the cerebral structures associated with the EF cognitive endophenotype of AD.

## **References**

- Andrew C, Fein G (2010) Event-related oscillations versus event-related potentials in a P300 task as biomarkers for alcoholism. *Alcohol Clin Exp Res* 34(4):669-680.
- Anokhin AP, Golosheykin S, Grant JD, Heath AC (2010) Developmental and genetic influences on prefrontal function in adolescents: a longitudinal twin study of WCST performance. *Neurosci Lett* 472(2):119-122.
- Anokhin AP, Heath AC, Ralano A (2003) Genetic influences on frontal brain function: WCST performance in twins. *Neuroreport* 14(15):1975-1978.
- Begleiter H, Porjesz B (1999) What is inherited in the predisposition toward alcoholism? A proposed model. *Alcohol Clin Exp Res* 23(7):1125-1135.
- Berney A, Preisig M, Matthey ML, Ferrero F, Fenton BT (2002) Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of alcohol and drug diagnoses. *Drug Alcohol Depend* 65(2):149-158.
- Bertisch H, Mesen-Fainardi A, Martin MV, Perez-Vargas V, Vargas-Rodriguez T, Delgado G, Delgado C, Llach M, LaPrade B, Byerley W, Bunney WE, Vawter MP, DeLisi LE (2009) Neuropsychological performance as endophenotypes in extended schizophrenia families from the Central Valley of Costa Rica. *Psychiatr Genet* 19(1):45-52.
- Bickel WK, Jarmolowicz DP, Mueller ET, Gatchalian KM, McClure SM (in press) Are executive function and impulsivity antipodes? A conceptual reconstruction with special reference to addiction. *Psychopharmacology*. Epub 2012 Mar 24.

- 1 Carlson SR, Iacono WG, McGue M (2004) P300 amplitude in nonalcoholic adolescent twin  
2 pairs who become discordant for alcoholism as adults. *Psychophysiology* 41(6):841-844.
- 3 Cavedini P, Zorzi C, Piccinni M, Cavallini MC, Bellodi L (2010) Executive dysfunctions in  
4 obsessive-compulsive patients and unaffected relatives: searching for a new intermediate  
5 phenotype. *Biol Psychiatry* 67(12):1178-1184.
- 6 Chou LN, Kuo PH, Lin CC, Chen WJ (2010) Genetic and environmental influences on the  
7 Wisconsin Card Sorting Test performance in healthy adolescents: a twin/sibling study.  
8 *Behav Genet* 40(1):22-30.
- 9 Collette F, Van der Linden M, Laureys S, Delfiore G, Degueldre C, Luxen A, Salmon E  
10 (2005) Exploring the unity and diversity of the neural substrates of executive functioning.  
11 *Hum Brain Mapp* 25(4):409-423.
- 12 Corral M, Holguin SR, Cadaveira F (2003) Neuropsychological characteristics of young  
13 children from high-density alcoholism families: a three-year follow-up. *J Stud Alcohol*  
14 64(2):195-199.
- 15 Corral MM, Holguin SR, Cadaveira F (1999) Neuropsychological characteristics in children  
16 of alcoholics: familial density. *J Stud Alcohol* 60(4):509-513.
- 17 Cservenka A, Nagel BJ (2012) Risky decision-making: An fMRI study of youth at high risk  
18 for alcoholism. *Alcohol Clin Exp Res* 36(4):604-615.
- 19 Davies SJ, Pandit SA, Feeney A, Stevenson BJ, Kerwin RW, Nutt DJ, Marshall EJ,  
20 Boddington S, Lingford-Hughes A (2005) Is there cognitive impairment in clinically  
21 'healthy' abstinent alcohol dependence? *Alcohol Alcohol* 40(6):498-503.

- 1 Delorme R, Gousse V, Roy I, Trandafir A, Mathieu F, Mouren-Simeoni MC, Betancur C,  
2 Leboyer M (2007) Shared executive dysfunctions in unaffected relatives of patients with  
3 autism and obsessive-compulsive disorder. *Eur Psychiatry* 22(1):32-38.
- 4 Diaz R, Gual A, Garcia M, Arnau J, Pascual F, Canuelo B, Rubio G, de Dios Y, Fernandez-  
5 Eire MC, Valdes R, Garbayo I (2008) Children of alcoholics in Spain: from risk to  
6 pathology. Results from the ALFIL program. *Soc Psychiatry Psychiatr Epidemiol* 43(1):1-  
7 10.
- 8 Douglas KM, Porter RJ (2009) Longitudinal assessment of neuropsychological function in  
9 major depression. *Aust N Z J Psychiatry* 43(12):1105-1117.
- 10 Drejer K, Theilgaard A, Teasdale TW, Schulsinger F, Goodwin DW (1985) A prospective  
11 study of young men at high risk for alcoholism: neuropsychological assessment. *Alcohol*  
12 *Clin Exp Res* 9(6):498-502.
- 13 Emerson MJ, Miyake A (2003) The role of inner speech in task switching: A dual-task  
14 investigation. *J Mem Lang* 48(1):148-168.
- 15 Eysenck MW, Derakshan N, Santos R, Calvo MG (2007) Anxiety and cognitive performance:  
16 attentional control theory. *Emotion* 7(2):336-353.
- 17 Fein G, Chang M (2006) Visual P300s in long-term abstinent chronic alcoholics. *Alcohol*  
18 *Clin Exp Res* 30(12):2000-2007.
- 19 Friedman NP, Miyake A, Corley RP, Young SE, Defries JC, Hewitt JK (2006) Not all  
20 executive functions are related to intelligence. *Psychol Sci* 17(2):172-179.

- 1 Friedman NP, Miyake A, Young SE, Defries JC, Corley RP, Hewitt JK (2008) Individual  
2 differences in executive functions are almost entirely genetic in origin. *J Exp Psychol Gen*  
3 137(2):201-225.
- 4 Gau SS, Shang CY (2010) Executive functions as endophenotypes in ADHD: evidence from  
5 the Cambridge Neuropsychological Test Battery (CANTAB). *J Child Psychol Psychiatry*  
6 51(7):838-849.
- 7 Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans  
8 AC, Rapoport JL (1999) Brain development during childhood and adolescence: a  
9 longitudinal MRI study. *Nat Neurosci* 2(10):861-863.
- 10 Gillen R, Hesselbrock V (1992) Cognitive Functioning, ASP, and Family History of  
11 Alcoholism in Young Men at Risk for Alcoholism. *Alcohol Clin Exp Res* 16(2):206-214.
- 12 Glass JM, Buu A, Adams KM, Nigg JT, Puttler LI, Jester JM, Zucker RA (2009) Effects of  
13 alcoholism severity and smoking on executive neurocognitive function. *Addiction*  
14 104(1):38-48.
- 15 Golden CJ (1976) Identification of brain disorders by the Stroop color and word test. *J Clin*  
16 *Psychol* 32(3):654-658.
- 17 Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and  
18 strategic intentions. *Am J Psychiatry* 160(4):636-645.
- 19 Ham HP, Parsons OA (2000) Predicting cognitive performance in alcoholics and  
20 nonalcoholics: specification of affective, childhood behavior disorders, and antisocial  
21 variables. *Appl Neuropsychol* 7(2):90-95.

- 1   Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991) The Fagerstrom Test for  
2    Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*  
3    86(9):1119-1127.
- 4   Heaton RK, Chelune G, Talley J, Kay G, Curtiss G (1993) Wisconsin Card Sorting Test  
5    manual-Computer version. FL: Psychological Assessment Resources, Odessa.
- 6   Heitzeg MM, Nigg JT, Yau WY, Zucker RA, Zubieta JK (2010) Striatal dysfunction marks  
7    preexisting risk and medial prefrontal dysfunction is related to problem drinking in  
8    children of alcoholics. *Biol Psychiatry* 68(3):287-295.
- 9   Hesselbrock V, Begleiter H, Porjesz B, O'Connor S, Bauer L (2001) P300 event-related  
10   potential amplitude as an endophenotype of alcoholism--evidence from the collaborative  
11   study on the genetics of alcoholism. *J Biomed Sci* 8(1):77-82.
- 12   Hester R, Lubman DI, Yucel M (2010) The role of executive control in human drug addiction.  
13   *Curr Top Behav Neurosci* 3:301-318.
- 14   Hildebrandt H, Brokate B, Eling P, Lanz M (2004) Response shifting and inhibition, but not  
15    working memory, are impaired after long-term heavy alcohol consumption.  
16    *Neuropsychology* 18(2):203-211.
- 17   Hill SK, Harris MS, Herbener ES, Pavuluri M, Sweeney JA (2008) Neurocognitive allied  
18    phenotypes for schizophrenia and bipolar disorder. *Schizophr Bull* 34(4):743-759.
- 19   Hill SY, Tessner KD, McDermott MD (2010) Psychopathology in offspring from families of  
20    alcohol dependent female probands: A prospective study. *J Psychiatr Res* 45(3):285-294.



- 1 Kamarajan C, Porjesz B, Jones K, Chorlian D, Padmanabhapillai A, Rangaswamy M, Stimus  
2 A, Begleiter H (2006) Event-related oscillations in offspring of alcoholics: neurocognitive  
3 disinhibition as a risk for alcoholism. *Biol Psychiatry* 59(7):625-634.
- 4 Kamarajan C, Porjesz B, Jones KA, Choi K, Chorlian DB, Padmanabhapillai A, Rangaswamy  
5 M, Stimus AT, Begleiter H (2004) The role of brain oscillations as functional correlates of  
6 cognitive systems: a study of frontal inhibitory control in alcoholism. *Int J Psychophysiol*  
7 51(2):155-180.
- 8 Kremen WS, Eisen SA, Tsuang MT, Lyons MJ (2007) Is the Wisconsin Card Sorting Test a  
9 useful neurocognitive endophenotype? *Am J Med Genet B Neuropsychiatr Genet*  
10 144B(4):403-406.
- 11 Le Strat Y, Ramoz N, Gorwood P (2010) In alcohol-dependent drinkers, what does the  
12 presence of nicotine dependence tell us about psychiatric and addictive disorders  
13 comorbidity? *Alcohol Alcohol* 45(2):167-172.
- 14 Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvent R, Pauls D, Mallet J (1998) Psychiatric  
15 genetics: search for phenotypes. *Trends Neurosci* 21(3):102-105.
- 16 Mannuzza S, Fyer AJ, Endicott J, Klein DF (1985) Family informant schedule and criteria  
17 (FISC). New York State Psychiatric Institute, New York Anxiety Disorders Clinic.
- 18 McNab F, Leroux G, Strand F, Thorell L, Bergman S, Klingberg T (2008) Common and  
19 unique components of inhibition and working memory: an fMRI, within-subjects  
20 investigation. *Neuropsychologia* 46(11):2668-2682.

- 1 Menard SW (2010) Logistic regression: from introductory to advanced concepts and  
2 applications. . SAGE Publications ed Thousand Oaks, CA.
- 3 Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD (2000) The unity  
4 and diversity of executive functions and their contributions to complex "Frontal Lobe"  
5 tasks: a latent variable analysis. *Cognit Psychol* 41(1):49-100.
- 6 Moriyama Y, Mimura M, Kato M, Yoshino A, Hara T, Kashima H, Kato A, Watanabe A  
7 (2002) Executive Dysfunction and Clinical Outcome in Chronic Alcoholics. *Alcohol Clin*  
8 *Exp Res* 26(8):1239-1244.
- 9 Nigg JT, Glass JM, Wong MM, Poon E, Jester JM, Fitzgerald HE, Puttler LI, Adams KM,  
10 Zucker RA (2004) Neuropsychological executive functioning in children at elevated risk  
11 for alcoholism: findings in early adolescence. *J Abnorm Psychol* 113(2):302-314.
- 12 Nurnberger JI, Jr., Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-  
13 Friedman J, Severe JB, Malaspina D, Reich T (1994) Diagnostic interview for genetic  
14 studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen*  
15 *Psychiatry* 51(11):849-859.
- 16 Oscar-Berman M, Valmas MM, Sawyer KS, Kirkley SM, Gansler DA, Merritt D, Couture A  
17 (2009) Frontal brain dysfunction in alcoholism with and without antisocial personality  
18 disorder. *Neuropsychiatr Dis Treat* 5:309-326.
- 19 Owens SF, Rijdsdijk F, Picchioni MM, Stahl D, Nenadic I, Murray RM, Toulopoulou T (2011)  
20 Genetic overlap between schizophrenia and selective components of executive function.  
21 *Schizophr Res* 127(1-3):181-187.

- 1 Ozkaragoz T, Satz P, Noble EP (1997) Neuropsychological functioning in sons of active  
2 alcoholic, recovering alcoholic, and social drinking fathers. *Alcohol* 14(1):31-37.
- 3 Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt impulsiveness scale.  
4 *J Clin Psychol* 51(6):768-774.
- 5 Perlman G, Johnson W, Iacono WG (2009) The heritability of P300 amplitude in 18-year-olds  
6 is robust to adolescent alcohol use. *Psychophysiology* 46(5):962-969.
- 7 Pitel AL, Beaunieux H, Witkowski T, Vabret F, Guillery-Girard B, Quinette P, Desgranges B,  
8 Eustache F (2007) Genuine Episodic Memory Deficits and Executive Dysfunctions in  
9 Alcoholic Subjects Early in Abstinence. *Alcohol Clin Exp Res* 31(7):1169-1178.
- 10 Pitel AL, Rivier J, Beaunieux H, Vabret F, Desgranges B, Eustache F (2009) Changes in the  
11 episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-  
12 month period. *Alcohol Clin Exp Res* 33(3):490-498.
- 13 Poon E, Ellis DA, Fitzgerald HE, Zucker RA (2000) Intellectual, cognitive, and academic  
14 performance among sons of alcoholics, during the early school years: differences related to  
15 subtypes of familial alcoholism. *Alcohol Clin Exp Res* 24(7):1020-1027.
- 16 Porjesz B, Rangaswamy M (2007) Neurophysiological endophenotypes, CNS disinhibition,  
17 and risk for alcohol dependence and related disorders. *ScientificWorldJournal* 7:131-141.
- 18 Rangaswamy M, Jones KA, Porjesz B, Chorlian DB, Padmanabhapillai A, Kamarajan C,  
19 Kuperman S, Rohrbaugh J, O'Connor SJ, Bauer LO, Schuckit MA, Begleiter H (2007)  
20 Delta and theta oscillations as risk markers in adolescent offspring of alcoholics. *Int J*  
21 *Psychophysiol* 63(1):3-15.

- 1 Rangaswamy M, Porjesz B (2008) Uncovering genes for cognitive (dys)function and  
2 predisposition for alcoholism spectrum disorders: a review of human brain oscillations as  
3 effective endophenotypes. *Brain Res* 1235:153-171.
- 4 Ratti MT, Bo P, Giardini A, Soragna D (2002) Chronic alcoholism and the frontal lobe: which  
5 executive functions are impaired? *Acta Neurol Scand* 105(4):276-281.
- 6 Raucher-Chene D, Gierski F, Hubsch B, Cuervo-Lombard CV, Bera-Potelle C, Cohen R,  
7 Kahn JP, Kaladjian A, Limosin F (in press) Depression, anxiety and personality  
8 dimensions in female first-degree relatives of alcohol-dependent probands. *Arch Womens*  
9 *Ment Health*. Epub 2012 Mar 13.
- 10 Raven J, Raven JC, Court JH (2003) Manual for Raven's Progressive Matrices and  
11 Vocabulary Scales. Harcourt Assessment. ed, San Antonio, TX.
- 12 Reitan RM, Wolfson D (1985) The Halstead-Reitan Neuropsychological Test Battery.  
13 Neuropsychology Press, Tucson, AZ.
- 14 Richards M, Jarvis MJ, Thompson N, Wadsworth ME (2003) Cigarette smoking and  
15 cognitive decline in midlife: evidence from a prospective birth cohort study. *Am J Public*  
16 *Health* 93(6):994-998.
- 17 Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD (2012) Neurocognitive  
18 endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends*  
19 *Cogn Sci* 16(1):81-91.
- 20 Sanchez-Cubillo I, Perianez JA, Adrover-Roig D, Rodriguez-Sanchez JM, Rios-Lago M,  
21 Tirapu J, Barcelo F (2009) Construct validity of the Trail Making Test: role of task-

switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc* 15(3):438-450.

Schulze KK, Walshe M, Stahl D, Hall MH, Kravariti E, Morris R, Marshall N, McDonald C, Murray RM, Bramon E (2011) Executive functioning in familial bipolar I disorder patients and their unaffected relatives. *Bipolar Disord* 13(2):208-216.

Silveri MM, Rogowska J, McCaffrey A, Yurgelun-Todd DA (2011) Adolescents at risk for alcohol abuse demonstrate altered frontal lobe activation during Stroop performance. *Alcohol Clin Exp Res* 35(2):218-228.

Singh SM, Basu D (2009) The P300 event-related potential and its possible role as an endophenotype for studying substance use disorders: a review. *Addict Biol* 14(3):298-309.

Stanford MS, Mathias CW, Dougherty DM, Lake SL, Anderson NE, Patton JH (2009) Fifty years of the Barratt Impulsiveness Scale: An update and review. *Pers Individ Dif* 47(5):385-395.

Stroop JR (1935) Studies of interference in serial verbal reactions. *J Exp Psychol* 18:643-662.

Sullivan EV, Rosenbloom MJ, Pfefferbaum A (2000) Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcohol Clin Exp Res* 24(5):611-621.

Tamm L, Menon V, Reiss AL (2002) Maturation of brain function associated with response inhibition. *J Am Acad Child Adolesc Psychiatry* 41(10):1231-1238.

Taylor J (2007) Heritability of Wisconsin Card Sorting Test (WCST) and Stroop Color-Word Test performance in normal individuals: implications for the search for endophenotypes. *Twin Res Hum Genet* 10(6):829-834.

- 1 Tedstone D, Coyle K (2004) Cognitive impairments in sober alcoholics: performance on  
2 selective and divided attention tasks. *Drug Alcohol Depend* 75(3):277-286.
- 3 Toga AW, Thompson PM, Sowell ER (2006) Mapping brain maturation. 29(3):148-159.
- 4 van Holst RJ, Schilt T (2011) Drug-related decrease in neuropsychological functions of  
5 abstinent drug users. *Curr Drug Abuse Rev* 4(1):42-56.
- 6 Viswanath B, Janardhan Reddy YC, Kumar KJ, Kandavel T, Chandrashekar CR (2009)  
7 Cognitive endophenotypes in OCD: a study of unaffected siblings of probands with  
8 familial OCD. *Prog Neuropsychopharmacol Biol Psychiatry* 33(4):610-615.
- 9 Young SE, Friedman NP, Miyake A, Willcutt EG, Corley RP, Haberstick BC, Hewitt JK  
10 (2009) Behavioral disinhibition: liability for externalizing spectrum disorders and its  
11 genetic and environmental relation to response inhibition across adolescence. *J Abnorm*  
12 *Psychol* 118(1):117-130.
- 13 Zalla T, Joyce C, Szoke A, Schurhoff F, Pillon B, Komano O, Perez-Diaz F, Bellivier F, Alter  
14 C, Dubois B, Rouillon F, Houde O, Leboyer M (2004) Executive dysfunctions as potential  
15 markers of familial vulnerability to bipolar disorder and schizophrenia. *Psychiatry Res*  
16 121(3):207-217.
- 17 Zinn S, Stein R, Swartzwelder HS (2004) Executive Functioning Early in Abstinence From  
18 Alcohol. *Alcohol Clin Exp Res* 28(9):1338-1346.

## Table Legends

### Table 1

IQ = intelligence quotient; MDE = major depressive episodes; Max-alcohol = lifetime maximum amount of alcohol consumption in a 24-hour period (in units); BIS = Barratt impulsiveness scale; <sup>a</sup> FHP:  $n = 26$  and FHN:  $n = 41$ ; <sup>b</sup> FHP:  $n = 32$  and FHN:  $n = 39$ ; data show means (standard deviations), unless otherwise noted.

### Table 2

WCST = Wisconsin Card Sorting Test; BIS = Barratt impulsiveness scale; Values are given as mean (standard deviation).

### Table 3

IQ = intelligence quotient; MDE = major depressive episodes; BIS = Barratt impulsiveness scale; AD = alcohol-dependent.

### Supplementary Table 1

WCST = Wisconsin Card Sorting Test.

### Supplementary Table 2

\*\*\*  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  $p < 0.05$ ; IQ = intelligence quotient; MDE = major depressive episodes; Max-alcohol = lifetime maximum amount of alcohol consumption in a 24-hour period (in units); AD = alcohol-dependent; BIS = Barratt impulsiveness scale; <sup>a</sup>  $n = 67$ ; <sup>b</sup>  $n = 71$ .

## TABLES

**Table 1.** Socio-demographic and clinical characteristics according to positive or negative family history (FH) of alcoholism.

<i>Variable</i>	<i>FH Positive n = 55</i>	<i>FH Negative n = 100</i>	<i>t or <math>\chi^2</math></i>	<i>p value</i>
Age	35.40 (12.05)	34.40 (11.10)	0.52	0.60
Gender				
% Female	74.50	72.00		
% Male	25.50	28.00	0.12	0.73
Education level	13.05 (2.59)	13.38 (1.95)	- 0.88	0.38
Raven's matrices IQ	107.51 (13.16)	107.59 (12.08)	- 0.04	0.97
Psychiatric diagnoses				
% Lifetime MDE	23.60	6.00	10.26	0.001
% Lifetime suicide attempts	9.10	3.00	2.69	0.10
% Lifetime anxiety disorders	21.80	6.00	8.65	0.003
Number of past MDE	0.24 (0.43)	0.06 (0.24)	3.29	0.001
Number of suicide attempts	0.09 (0.29)	0.04 (0.24)	1.16	0.24
Drinking history				
CAGE score	0.04 (0.19)	0.04 (0.19)	- 0.11	0.91
% Lifetime past drunkenness	47.30	41.00	0.57	0.45
Max-alcohol <sup>a</sup>	7.77 (5.76)	11.13 (8.42)	- 1.79	0.08
Smoking history				
% Current smokers	34.50	22.00		
% Former smokers	23.64	17.00		
% Non-smokers	41.86	61.00	5.33	0.07
Fagerström maximum score <sup>b</sup>	4.53 (2.34)	3.67 (2.01)	1.67	0.10
Pack-year	6.25 (9.91)	2.74 (6.22)	2.69	0.01
BIS-11				
Total	61.96 (9.02)	57.09 (7.57)	3.57	0.001
Motor	22.02 (4.11)	20.52 (3.01)	2.58	0.01
Attentional	16.16 (4.19)	14.08 (2.95)	3.59	0.001
Non-planning	24.62 (6.83)	22.48 (3.85)	2.48	0.01



**Table 2.** Performance on tests of executive functions according to positive or negative family history (FH) of alcoholism.

<i>Variable</i>	<i>FH Positive</i> <i>n = 55</i>	<i>FH Negative</i> <i>n = 100</i>	<i>t</i>	<i>p value</i>
WCST				
Categories	5.42 (1.46)	5.77 (0.74)	- 1.99	0.05
Non perseverative errors	10.33 (9.79)	8.90 (8.44)	0.91	0.34
Perseverative errors	12.33 (12.48)	8.85 (5.42)	2.41	0.02
Stroop test				
Word (sec)	40.08 (5.74)	39.58 (5.27)	0.54	0.59
Color (sec)	58.13 (10.20)	55.89 (6.99)	1.61	0.11
Color-Word (sec)	97.37 (25.93)	91.44 (19.11)	1.62	0.11
Interference (sec)	73.77 (25.00)	68.36 (18.18)	1.55	0.12
Trail Making Test				
Part A (sec)	29.67 (8.97)	29.53 (9.03)	0.09	0.92
Part B (sec)	70.16 (34.68)	60.90 (17.03)	2.23	0.03
B-A (sec)	40.49 (33.60)	31.37 (14.40)	2.35	0.02
Arithmetic Switching task				
Add (sec)	57.93 (19.26)	54.61 (16.91)	1.11	0.27
Subtract (sec)	78.98 (44.11)	68.89 (26.04)	1.79	0.07
Add/subtract (sec)	92.62 (38.96)	81.51 (30.39)	1.96	0.05
Switch-cost (sec)	24.16 (20.79)	19.76 (16.72)	1.44	0.15

**Table 3.** Hierarchical multiple regression analysis predicting the executive factor.

<i>Predictor variables</i>	<i>R<sup>2</sup></i>	<i>R<sup>2</sup> change</i>	<i>F change (df)</i>	<i>Sig. F change</i>	<i>Standardised coefficients (with all variables entered)</i>		
					<i>Beta</i>	<i>t</i>	<i>Sig. beta</i>
Step 1 Background variables	0.324		23.814 (3,149)	< 0.001			
Age					- 0.329	- 4.454	0.001
Education level					0.219	2.850	0.005
Raven's Matrices IQ					0.222	3.159	0.002
Step 2 Psychiatric disorder history	0.354	0.030	3.370 (2,147)	0.037			
Number of MDE					- 0.106	- 1.592	0.114
Lifetime anxiety disorders					- 0.096	- 1.299	0.196
Step 3 Smoking history	0.356	0.002	0.537 (1,146)	0.465			
Pack-year					0.105	1.346	0.181
Step 4 Impulsiveness	0.357	0.001	0.198 (1,145)	0.657			
BIS-11 total score					0.003	0.049	0.961
Step 5 Family history of alcoholism	0.393	0.036	8.631 (1,144)	0.004			
Number of AD relatives					- 0.216	-2.938	0.004

**Supplementary Table 1.** Factorial analysis of executives scores for the whole sample ( $n = 155$ ).

	<i>Executive Factor</i>	<i>Communalities</i>
WCST Perseverative errors	0.79	0.63
Stroop Interference	0.83	0.52
Trail Making Test B-A	0.72	0.68
Arithmetic Switching Task - Switch cost	0.40	0.16

**Supplementary Table 2.** Correlations between the executive factor and demographic and clinical data in the whole sample ( $n = 155$ ).

<i>Variable</i>	<i>Executive Factor</i>
Age	- 0.43***
Education level	0.45***
Raven's matrices IQ	0.29***
Psychiatric diagnoses	
Number of past MDE	- 0.14
Number of suicide attempts	0.06
Drinking history	
CAGE score	0.10
Max-alcohol <sup>a</sup>	0.17
Number of AD relatives	- 0.34***
Smoking history	
Fagerström score <sup>b</sup>	0.09
Pack-year	- 0.16*
BIS-11	
Total	- 0.08
Motor	- 0.04
Attentional	- 0.02
Non-planning	- 0.09