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

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1 **ABSTRACT**

2 **Background:** Executive function (EF) impairment in alcohol dependence (AD) has been
3 related to the toxic effects of alcohol on frontal lobes. However, this impairment could be
4 partially present before the onset of the disease and might constitute a vulnerability factor.

5 Although a considerable body of research has investigated executive functioning among AD
6 patients, much less attention has been directed toward high-risk individuals. Most studies
7 were carried out among children or adolescents, and very few were conducted in adults. The
8 aim of the present study was to examine EF in a group of adult offspring of AD individuals.

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

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

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

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

1 **Introduction**

2 Alcohol dependence (AD) involves both environmental and genetic vulnerability factors.
3 Although it has a rather high degree of heritability (estimated range between 40% and 60%),
4 vulnerability to alcohol dependence is broadly considered as a complex polygenic phenotype
5 (Begleiter and Porjesz, 1999). To clarify the risk factors involved in AD, attempts have been
6 made to identify endophenotypes in AD patients and their relatives (Andrew and Fein, 2010;
7 Singh and Basu, 2009). Endophenotypes (or intermediate phenotypes) are defined as heritable
8 traits associated with an increased risk for developing a disorder (Gottesman and Gould,
9 2003). They must be found in probands and their unaffected relatives at a higher rate than in
10 the general population (Leboyer et al., 1998).

11 In alcoholism, brain electrophysiological abnormalities have been extensively investigated
12 over the last four decades with the use of event-related potentials or more recently event-
13 related oscillation and are undoubtedly the most studied endophenotype. Such research has
14 documented a reduction in the P3 amplitude component (P3-AR) among currently-abstinent
15 AD individuals (Andrew and Fein, 2010; Fein and Chang, 2006; Porjesz and Rangaswamy,
16 2007; Rangaswamy and Porjesz, 2008), their at-risk first-degree relatives (Hesselbrock et al.,
17 2001; Kamarajan et al., 2006; Rangaswamy et al., 2007; Singh and Basu, 2009), and non-
18 alcoholic adolescent twin pairs who became discordant for alcoholism as adults (Carlson et
19 al., 2004; Perlman et al., 2009).

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

1 2011; Robbins et al., 2012; Schulze et al., 2011; Viswanath et al., 2009) including addictions
2 (Hester et al., 2010).

3 Executive functions consist of a set of highly heritable cognitive processes (Friedman et al.,
4 2008), frequently associated to the frontal lobes, that guide complex behavior over time
5 through planning, decision-making, and response control (Zinn et al., 2004). Accumulating
6 evidence suggests that EF can be divided into separable processes that share some underlying
7 commonality. Miyake et al. (2000), found evidence supporting the existence of the unity and
8 the diversity of three distinct albeit interrelated executive processes: inhibition, set shifting
9 and updating. According to these authors, inhibition is the ability to deliberately inhibit
10 dominant, automatic, or prepotent responses when necessary. Set shifting is the ability to
11 disengage from an irrelevant task or mental set and subsequently engage actively in a relevant
12 task or mental set. Updating is the ability to actively maintain information in working
13 memory and to integrate new and relevant information into that set by replacing old, no
14 longer relevant information, with newer and more relevant information. Results from
15 neuroimaging studies are likely to support this model given that those three processes,
16 although associated with relatively distinct prefrontal and parietal brain areas, have also
17 shown common activated areas (Collette et al., 2005; McNab et al., 2008).

18 While data concerning updating processes in AD individuals seem controversial (Hildebrandt
19 et al., 2004; Pitel et al., 2007; 2009), impairment in the two other processes has been widely
20 documented. Currently-abstinent AD individuals exhibit impaired abilities for performing
21 neuropsychological tests designed to assess inhibition and set shifting processes, such as the
22 Wisconsin Card Sorting Test (WCST), the Stroop Color Word Test and the Trail Making Test
23 (Davies et al., 2005; Moriyama et al., 2002; Oscar-Berman et al., 2009; Pitel et al., 2007;
24 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

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

4
5 Much of the research on EF reported above involved non-adult offspring of AD; however,
6 executive functions are mainly mediated by the frontal lobes, which are not physically and
7 functionally mature before the end of adolescence (Giedd et al., 1999; Tamm et al., 2002;
8 Toga et al., 2006). Moreover, in some studies groups were not comparable concerning general
9 intellectual abilities, which might have interacted with EF task performance (Friedman et al.,
10 2006). The aim of the present study was to address these issues. We investigated whether a
11 group of adult non-alcoholic offspring of AD individuals would perform EF tests less
12 efficiently than a group of participants without family history of AD. We decided to focus on
13 inhibition and set shifting processes for which results among AD individuals are consistent,
14 and because these processes are more likely to play a role in addiction (Bickel et al., in press;
15 Ham and Parsons, 2000; Young et al., 2009). We also explored the relation between familial
16 density of alcoholism and EF performance.

18 **Material and Methods**

19 *Participants*

20 A total of 100 healthy non-alcoholic adults who had at least one first-degree biological AD
21 relative (family history positive, FHP) were screened to participate in the study. They were
22 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).

13

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

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

8

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 2009).

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

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

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

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

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

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

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

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

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

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

24 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

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

14

15 **Results**

16 *Demographics and clinical questionnaires*

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

21

22

1 -----

2 Insert Table 1 about here

3 -----

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

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

5 *Neuropsychological Assessment*

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

14 -----

15 Insert Table 2 about here

16 -----

17 Variables that reflected "purer" measures of EF (*i.e.*, the WCST number of perseverative
18 errors, the Stroop interference score, the TMT B-A completion time, and the AST switch
19 time) were subjected to an exploratory factor analysis using the PCA method. The optimal
20 solution is presented in Supplementary Table 1 with the factor loading for each variable. The
21 executive factor had an eigenvalue of 1.99 and accounted for 49.91 % of the variance. To
22 facilitate interpretation, the derived executive factor scores were inverted (multiplication by -
23 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.

11

12

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19

1 **Table Legends**

2 **Table 1**

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

7
8 **Table 2**

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

11
12 **Table 3**

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

15
16 **Supplementary Table 1**

17 WCST = Wisconsin Card Sorting Test.

18
19 **Supplementary Table 2**

20 *** $p < 0.001$; ** $p < 0.1$; * $p < 0.5$; IQ = intelligence quotient; MDE = major depressive
21 episodes; Max-alcohol = lifetime maximum amount of alcohol consumption in a 24-hour
22 period (in units); AD = alcohol-dependent; BIS = Barratt impulsiveness scale; ^a $n = 67$; ^b
23 $n = 71$.

TABLES

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

<i>Variable</i>	<i>FH Positive</i> <i>n = 55</i>	<i>FH Negative</i> <i>n = 100</i>	<i>t or χ^2</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 ^a	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 ^b	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>R²</i>	<i>R² 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 ^a	0.17
Number of AD relatives	- 0.34***
Smoking history	
Fagerström score ^b	0.09
Pack-year	- 0.16*
BIS-11	
Total	- 0.08
Motor	- 0.04
Attentional	- 0.02
Non-planning	- 0.09