Startle-Response Based Tasks and Laboratory Measures of Impulsivity in Abstinent Alcoholic Patients

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Abstract

Aims: It is well known that impulsivity is a risk factor for the development of Addictive Disorders, and more specifically Alcohol Use Disorders (AUD). Recently, the Startle-Response Based Tasks (SRBT) and its different forms of plasticity have been found to be impaired in the alcoholic population. This is the first study to explore the correlation between impulsivity laboratory tasks and the SRBT test, in order to determine whether impulsivity and startle response (SR) could be related and in turn, explain their association with Alcohol Dependence (AD).

Methods: Subjects: 40 men, who met DSM-IV criteria for AD and had been abstinent for at least one month. Impulsivity was assessed using three laboratory tests: Continuous Performance Test (CPT), Stop-Signal Task (SST) and Differential Reinforcement for Low-Rate Responding (DRL6). Patients also underwent the SR test. They were compared to 40 matched controls.

Results: Impulsivity laboratory measures tasks (SST and commissions of the CPT) correlated positively with the magnitude of SR (P<0.05) and with habituation (P<0.05). Scores on DRL6 correlated negatively with the magnitude of SR (P<0.05). This was not found in the control group.

Conclusions: The fact that impulsivity laboratory measures and the SR are correlated in patients but not in controls, could imply the existence of a common link for these two measures in alcoholic patients. Our findings support the hypothesis of the existence of two different vulnerability pathways for the development of AUD: anxiety and disinhibitory behaviour.

INTRODUCTION

A risk factor associated with the development of alcohol use disorders (AUD) is impulsivity. Recently, other neurophysiological paradigms, such as the Startle-Response Based Tasks (SRBT) and its different forms of plasticity, have been proposed as vulnerability markers for the development of alcoholism (Grillon et al., 1997; Marin et al., 2012).

Impulsivity can be defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli regardless of the negative consequences of these reactions for the impulsive subject or for
others (Dickman, 1993; Potenza, 2007). Two laboratory paradigms have been described associated with impulsivity (Avila and Parcet, 2001). The first relates behavourial inhibition and refers to the ability of a subject to appropriately inhibit thoughts or actions. The second considers the degree to which immediate rewarding consequences have more control over an individual's behaviour than consequences that are delayed. Different operant behavioural tasks have been used to measure these two main dimensions of impulsivity. On one hand, the Continuous Performance Test (CPT; Conners, 1995) and Go/No-Go tasks, such as the Stop-Signal Task (SST; Logan, 1994) and the Information Sampling Task (Clark et al., 2006) assess the behavioural disinhibition dimension of impulsivity. On the other hand, the Card-Playing Task (Siegel, 1978), the Risk-Taking Task (Lane and Cherneck, 2000) and the Differential Reinforcement for Low-Rate Responding (DRL; McClure and Gordon, 1984) have been used to measure the delay reward dimension of impulsivity.

There is extensive literature linking impulsivity to AUD (Congdon and Canli, 2005; Rubio et al., 2007, 2008; Verdejo-García et al., 2008). It has also been reported that heavy alcohol use can trigger impulsive behaviours (Jentsch and Taylor, 1999; Goldenstein and Volkow, 2002). Early-onset alcoholism has been described as being more frequently associated with higher levels of impulsivity, sensation seeking traits, aggressiveness and inability to delay reward (Dom et al., 2006a, b, c). If we consider each dimension of impulsivity separately, it has been found that: (a) the behavioural inhibition dimension of impulsivity is related to an increased risk of alcohol dependence (AD) at follow-up (Rubio et al., 2008), lower drinking refusal self-efficacy (Gullo et al., 2010) and a greater association with a family history of alcoholism (Lovallo et al., 2006; Saunders et al., 2008); whereas (b) the delay of the reward dimension of impulsivity is associated with the risk of heavy drinking and early onset of alcohol consumption (Rubio et al., 2008), higher positive alcohol expectancies (Gullo et al., 2010), stronger physiological responses to alcohol, greater craving and stronger conditioning and approach motivation in response to alcohol cues (Glauser et al., 2000; Franken, 2002; Brunelle et al., 2004).

In summary, where laboratory measures of impulsivity have been used, alcohol-dependent subjects and heavy drinkers exhibit: (a) a significant impairment in performance in the CPT (Bjork et al., 2004; Rubio et al., 2007, 2008); (b) impairments in the SST (Duka et al., 2003; Bjork et al., 2004; Mitchell et al., 2005; Goudriaan et al., 2006; Rubio et al., 2007, 2008; Rose and Duka, 2008; Glass et al., 2009; Lawrence et al., 2009); (c) increased rates of risky responses in a Risk-Taking Task (Bjork et al., 2004); and (d) preference for small-immediate rewards in reward delay tasks (Richards et al., 1999; Duka et al., 2003; Bjork et al., 2004; Mitchell et al., 2005; Dom et al., 2006a,b,c; Rubio et al., 2007, 2008).

On the other hand, modulation of the startle reflex, which essentially measures the amplitude of the eye blink, is a well-replicated phenomenon that is recently gaining importance in addiction research (Donohue et al., 2007). Startle reflex is a defensive response to a sudden burst of white noise. It can also be elicited by tactile and visual intense stimuli. The acoustic startle response (SR) is mediated by a relatively simple neuronal circuit located in the lower brainstem (Koch, 1999). It is easily measured in humans by recording its most consistent and persistent component, the amplitude of the eye blink (Landis and Hunt, 1939). The SR has been used as a measure of behavioural reactivity to external stimuli (Morgan et al., 1993). There are different SRBT showing different forms of plasticity: pre-pulse inhibition (PPI), startle habituation (SH), fear conditioning and pleasure-attenuation. All these SRBT forms and the magnitude of the SR have been found to be affected by alcohol consumption and in AUD (Grillon et al., 1997; Hutchison et al., 1997; Keedwell et al., 2001).

In alcoholic populations, the majority of studies that have been carried out with SRBT have used the affective modulation of the SR (Lang et al., 1990). According to the affective modulation of the SR, the magnitude of the SR increases during states of negative affectivity or anxiety (Davis, 1986), whereas it attenuates in a pleasant emotional context (Lang et al., 1990). It has been found that alcohol-dependent subjects exhibit an attenuation of the SR during the presentation of alcohol-associated stimuli, compared with emotionally negative and neutral stimuli, suggesting that alcohol-related stimuli may retain their appetitive qualities during alcohol abstinence (Mucha et al., 2000; Grusser et al., 2002). The affective modulation of the SR has been correlated with different clinical parameters such as craving (Heinz et al. 2003; Rubio et al., 2006; Koenke et al. 2008), risk to relapse (Löber et al., 2007), early abstinence (Saladin et al., 2002), family history of alcoholism (Miranda et al., 2002) or Antisocial Personality Disorder (Miranda et al., 2003).

However, recently research has focussed on the SR test itself. Regarding the magnitude of the SR, research related to AUD has provided varied results, with some studies demonstrating a reduction in the magnitude of the SR in heavy drinkers (Hutchison et al., 2003), in abstinent alcohol-dependent men (Marin et al., 2012) and after alcohol intake in healthy subjects (Grillon et al., 1994; Hutchison et al., 1997); and others showing an increase of the magnitude of the SR during Alcohol Withdrawal Syndrome (AWS) (Howard and Ford, 1992; Krystal et al., 1997; Schellekens et al., 2012), especially after 2 or more detoxifications (Krystal et al., 1997), in early-onset alcohol-dependent patients (Schellekens et al., 2012), and a decrease to a lesser degree compared to other clinical populations after exposure to alcohol in young men who have a parental history of alcoholism (Grillon et al., 2000). Studies based on PPI—which refers to the ability of innocuous sensory events presented before a startle-eliciting stimulus to inhibit or reduce the startle reflex (Braff et al., 1992) and which has been described as an operational measure of sensorimotor gating (Swerdlow et al., 2006)—show that it is impaired in heavy drinkers (Hutchison et al., 2003), in alcohol-dependent abstinent men (Marin et al., 2012), during AWS (Keedwell et al., 2001), in children and young adults with a family history of alcoholism (Grillon et al., 1997, 2000) and with exposure to alcohol in healthy subjects (Hutchison et al., 1997). When habituation has been studied, it has been shown that there is a decrease in children with a family history of alcoholism (Grillon et al., 1997).

To our knowledge, there has been little research exploring the correlation between SRBT, the SR and its different forms of plasticity and laboratory measures of impulsivity. Two studies have found evidence that extrovert individuals, characterized by sensation seeking and impulsivity, show reduced startle reactivity (Blumenthal et al., 1995, 2001). In addition, LaRowe et al. (2006) have found, by using personality questionnaires (Eysenck Personality Questionnaire, Tellegen’s Multidimensional Personality Questionnaire) and scales (Sensation Seeking Scale) in healthy volunteers, that faster habituation may be associated with a tendency toward impulsivity and behavioural disinhibition.

The aim of the present study was to explore the correlation between laboratory measures of impulsivity and the startle-response paradigms in the alcoholic population, in order to shed light on a possible common origin of both as risk factors for the development of AUD. Our hypotheses were the following: (a) According to the results of our previous study (Marin et al., 2012), alcohol-dependent patients will exhibit a lower magnitude of the SR, a lesser percentage of the PPI.
and a lower habituation compared to healthy controls; (b) Magnitude of the SR could correlate either positively or negatively with measures of impulsivity, depending on the type of impulsivity considered (poor inhibitory control vs delay of reward); (c) PPI will correlate negatively with measures of impulsivity, so that alcohol-dependent patients with lower percentages of PPI will have higher levels of impulsivity; and (d) SH will correlate positively with measures of impulsivity, so that alcohol-dependent patients with a faster habituation will show higher levels of impulsivity, as previous studies have demonstrated.

**METHODS**

**Patients**

Patients were consecutively recruited from the Outpatient Alcohol Programme of the teaching hospital ‘Hospital 12 de Octubre’ in Madrid, Spain, from January 2008 to September 2009. The final sample comprised 40 abstinent alcoholic men, who proceeded from the sample of our previous study (Marin et al., 2012).

Inclusion criteria were the following: men, aged between 18 and 65 years who had met DSM-IV criteria for AD (APA, 2000) and who were abstinent from alcohol for at least one month. Females were not included because gender differences in the performance of the startle test could constitute a confounding variable. In fact, it has already been found that women exhibit less SR compared with men and show less PPI (Koller et al., 2001) and there are also variations according to the menstrual cycle (Aasen et al., 2005; Kumari et al., 2008). Moreover, several studies have also reported differences between males and females in impulsivity levels, and in how impulsivity modulates the use of substances and the development of a Substance Use Disorder (SUD) (Winhusen and Lewis, 2012; Kong et al., 2013; Perry et al., 2013).

Patients were excluded if they were under 18 or over 65 years of age, had a systemic or neurological disease (including epilepsy) that could interfere with coping strategies, a hearing or visual impairment which could interfere with the performance of the experiment, an associated neuropsychological deficit, an IQ of under 70, met criteria for any of the major psychiatric disorders such as schizophrenia and other psychotic disorders, affective disorders, obsessive compulsive disorder and anxiety disorders, or a score higher than 15 in the Hospital Anxiety and Depression (HAD) scale (Zung and Smith, 1983) as this indicates a greater likelihood of stress responses. Participants were also excluded if they had consumed alcohol in the last month. In addition, participants with a past history of withdrawal seizures or delirium tremens were excluded. Due to the difficulties in recruiting patients with just AD, a history of SUDs and occasional intake of cannabis were not considered as exclusion criteria. However, patients with chronic cannabis consumption or any current consumption of drugs such as cocaine or heroin were excluded, as these drugs have been associated with modifications of the SR and PPI (Scholes and Martin-Iverson, 2009; Corcoran et al., 2011; Walter et al., 2011), and they worsen the performance of executive functioning, and more specifically inhibition control (Solowij and Pesa, 2010; van Holst and Schilt, 2011; Madow-Gürpide et al., 2011). Because most of our patients were undergoing pharmacological treatment at the time when they were tested—with benzodiazepines, anticonvulsant agents, antidpressants, naltrexone and/or disulfiram—such therapies were not considered a reason for exclusion. However, these agents tended to be prescribed in low doses, usually with a tapering schedule until discontinuation. Only patients prescribed antipsychotic were excluded, because these agents are known to influence SRs and PPI (Martinez-Gras et al., 2009; Kishi et al., 2010).

Of the 60 patients that were included in our first study, only 40 completed the impulsivity laboratory tasks and were included in the final sample of our current study: 5 patients (12%) refused continuing assessment, 5 patients (12%) were excluded because they were unable to complete impulsivity tasks and 10 patients (24%) were excluded due to problems in the recording of the scores of the test.

The final sample comprised 40 men fulfilling current DSM-IV criteria for AD (APA, 2000) who had been abstinent from alcohol for at least 1 month.

**Controls**

The controls, 37 volunteer healthy males (mean age 40.39, SD 8.38) matched for sex, age and years of education, had been used in our previous study (Marin et al., 2012). They underwent the startle test and laboratory impulsivity tasks. Exclusion criteria for the control group were: a systemic, neurological or psychiatric disorder, an IQ of under 70, a hearing or visual impairment that could interfere with the conduct of the test, meeting criteria for a major psychiatric disorder such as schizophrenia and other psychotic disorders, affective disorders, obsessive compulsive disorder and anxiety disorders, a history of psychiatric disease in first-degree relatives [because impairments in the SR and PPI have been found in subjects with a positive family history of a psychiatric disease, even though they themselves have not developed the disorder (Grillon et al., 1997, 2000; Zimmermann et al., 2004)], current use of psychotropic medication, and a drug abuse/dependence disorder.

The clinical and demographic characteristics of patients and controls are summarized in Table 1.

**Procedure**

All participants were screened with a portable audiometer (AudioScope 3. Welch Allyn WA®) for hearing disabilities that could interfere with the conduct of the startle-response experiment and an eye examination was performed to identify visual impairments that could interfere with the laboratory measurement of impulsivity.

Questionnaires completed on initiation of the alcoholism treatment programme at our unit were available for all the patients. After the collection of demographic, social and clinical variables, the patients completed the Structured Clinical Interview for DSM-IV and the Patient Questionnaire (SCID PQ) for the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-P and SCID-II; Firsts et al., 1993, 1997) with a psychiatrist. The HAD scale was also used to detect severe anxiety and depressive states that could interfere with the results of the study. To assess IQ the second and third scale of the Cattell Test were used (Cattell and Cattell, 1994).

To prevent interference from nicotine consumption-abstinence, smokers were told to smoke during the morning on which the test was to be conducted (to prevent nicotine withdrawal) but to smoke the last cigarette no later than 1 h before the test (to prevent acute effects of nicotine on neuropsychological capacities) (Dawkins et al., 2007; Domier et al., 2007; Potter and Newhouse, 2008). They were also instructed to abstain from all food and liquids other than water for 4 h prior to the experimental session. A breath alcohol test was used to verify alcohol abstinence and a urine drug test to check for illicit drug consumption.

Patients were firstly tested with the ASR paradigm in a room run by the Psychiatry Department of our hospital that is specially prepared for this test and is protected against interference from external factors such as environmental noise or non-neutral visual stimulation. After a period of time that lasted between 30 min and 1 h, patients completed
Table 1. Demographic and clinical characteristics of patients and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 40)</th>
<th>Controls (n = 37)</th>
<th>t (77)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.73 ± 9.8</td>
<td>40.39 ± 8.38</td>
<td>-2.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age of alcohol use initiation (years)</td>
<td>13.18 ± 3.41</td>
<td>18.89 ± 2.81</td>
<td>7.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at which AD criteria were met (years)</td>
<td>33.54 ± 8.30</td>
<td>0 ± 0</td>
<td>-24.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous detoxifications (n)</td>
<td>2.08 ± 4.11</td>
<td>0 ± 0</td>
<td>-3.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time of abstinence (months)</td>
<td>37.08 ± 51.21</td>
<td>0 ± 0</td>
<td>-4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol intake (grams/day)</td>
<td>220.00 ± 201.22</td>
<td>12.43 ± 9.76</td>
<td>-6.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nicotine dependence (%)</td>
<td>22 ± 62.5%</td>
<td>11 ± 29.7%</td>
<td>13.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cannabis abuse (%)</td>
<td>1 ± 2.5%</td>
<td>0 ± 0%</td>
<td>6.01</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

The startle reflex was elicited and recorded with a commercial computerized human startle-response monitoring system (CIBERTEC S.A). Acoustic startle pulses (pulses and prepulses) were presented binaurally through headphones. Four types of startle stimuli were used: a pulse-alone stimulus of 110 dB white noise presented for 45 ms and three prepulse 25 ms stimuli of 80 dB white noise presented 30 ms, 60 ms and 120 ms before the pulse. Stimuli were presented against a continuous background noise of 65 dB. The inter-stimulus interval was 20 ms ± 2. Patients were told that brief loud startling sounds would be delivered through the headphones and were asked to keep their eyes open during the test and to avoid moving.

The eye blink component of the SR was measured by recording electromyographic (EMG) activity of the orbicularis oculi muscle directly beneath the right eye using two miniature silver/silver chloride disk electrodes. The ground electrode was placed on the forehead. Impedance level was kept below 5 kOhms. The startle system recorded EMG activity for 250 ms from the onset of the startle stimulus. EMG activity was band-pass filtered (low- and high-pass filters of 5 kHz and 1 Hz, respectively), with a 50-Hz notch filter used to eliminate 50-Hz interference. We used a sampling rate of 1000 Hz and a temporal window for startle measurement of 1 s after the startle. Electromyographic data were stored off-line in the analytical programme of the response monitoring system.

The methodology used in the startle session was consistent with previous studies (Braff et al., 1992; Martinez-Gras et al., 2009). The session began with a 5-min acclimatization period to reduce initial reactivity and familiarize participants with the test. The four kinds of startle stimuli previously described were presented in a pseudorandom order such that patients would be unable to anticipate the next trial. The experiment consisted of three blocks: (a) 5 pulse-alone trials; (b) 32 pulse-alone and prepulse-pulse trials with a 30 ms, 60 ms and 120 ms prepulse-to-pulse interval; and (c) 5 pulse-alone trials. A total of 42 trials were conducted in each experiment and the inter-trial interval averaged 15 s (range: 10–25 s). It lasted 15 min.

Continuous performance test

The CPT was firstly developed by Rosvold et al. (1956) to assess sustained attention and vigilance in brain damaged patients. Also, failure in this test has been explained as the result of impulsivity, recklessness and anxiety problems (Halperin et al., 1991; Ballard, 1996). In the last few years several computerized versions of the CPT have been developed to assess attention and impulsivity (Klee and Garfinkel, 1983). The AX version of the CPT (Conners, 1995) contains the letters A, B, F, G, H, J, K, N, T, V, and X. The letters are white on a black background and are displayed on the screen for 200 ms with a fixed inter-stimulus interval of 1000 ms.

The task lasts 10 min and is made up of three consecutive phases of 200 letters each. Subjects are asked to press the space bar when the letter ‘X’ appears preceded by the letter ‘A’. This occurs with a frequency of 10%. Also the letter ‘X’ not preceded by a letter ‘A’ is shown with a frequency of 10% and the letter ‘A’ appears with a frequency of 20%. Before the test starts subjects carry out two initial practice blocks lasting 1 min each, to guarantee that the task has been understood. Failure to press the space bar when the sequence ‘AX’ appears is an ‘omission error’. Pressing the space bar at any other time is a ‘commission error’. ‘Commission errors’ can be classified as: commissions A, X, A-other and other. Reaction time is the latency between the onset of the sequence ‘AX’ and the subject’s response.

The stop-signal task

The SST is a valid and reliable measure of the inhibition processes (Logan, 1994). It is based on the execution of a double concurrent task: the go task and the stop task. The go task consists of determining as fast as possible whether the stimulus presented is the letter ‘X’ or the letter ‘O’ by responding pressing two different keys on the computer. It has 280 trials presented in 5 consecutive blocks. In some trials, after ‘X’ and ‘O’ have appeared on the screen, a green spot with a diameter of 2.5 cm (the stop signal) is presented above these letters for 150 msec. This indicates that the subject must inhibit the execution of the go task and refrain from pressing the key on the computer.

In the present study ‘X’ and ‘O’ were presented in the centre of the screen for 1,000 ms. These letters were preceded by a 500 ms fixation point, also presented in the centre of the screen. The stop signal was presented initially 250 ms after the main stimulus (Logan et al., 1997), and the subsequent adjustment depends on the execution of the task: if the subject inhibits the response, the stop signal will be

Neuropsychological assessment

Impulsivity was assessed with three different laboratory measures: the CPT and the SST were used to test inhibitory control, and the Differential Reinforcement for Low-Rate Responding (DRL6) was used to test the delay of reward.

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presented 50 ms later, if not, it will be shown 50 ms before. The main parameter considered in this task is the Time Reaction to the Stop signal (RTSS), which refers to the time needed to inhibit Go-responses in 50% of the cases. Long RTSS intervals suggest a poor inhibition (Logan, 1994).

The differential reinforcement for low-rate responding
Differential reinforcement for low-rate responding assesses the subject’s ability to refrain from responding prematurely and provides an objective measure of impulse control (McClure and Gordon, 1984; Gordon and Mettelman, 1988). The subject is instructed to press the space bar of the computer, ‘wait a while’ and then press the key again. If the subject refrains from responding for at least 6 s he receives a reward point. If the subject responds before the interval has elapsed, the timer resets and no reward point is given. The subject does not know the time established by the machine to win a reward point. Both the number of correct responses and the total number of responses are recorded. Impulse control is measured through an efficiency ratio, which is the number of correct responses divided by the total number of responses. However, the number of correct responses (or rewards) can also be used to assess impulse control.

Startle variables
The startle variables considered for our study were (a) startle responsivity, defined as the magnitude of the SR after the presentation of the pulse-alone stimulus; (b) PPI, computed as the percentage decrement in startle amplitude in the presence vs the absence of the prepulse and calculated as the difference of the average SR magnitude in pulse-alone trials minus the magnitude of the average SR in prepulse trials divided by the magnitude in the pulse-alone trials (% PPI = [pulse − prepulse]/pulse × 100); and (c) SH, measured as the decrease in the SR throughout the session and calculated as the difference of the average SR magnitude of pulse-alone trials between the first and last block.

Neuropsychological variables
Dependent variables selected in the CPT were: (a) omissions AX, (b) commissions A; and (c) commissions X. Omission errors are considered as an inattention index and commission errors as an impulsivity index. The variable considered in the SST was: (a) Reaction Time to the Stop Signal (RTSS). Finally, dependent variables included from the DRLR-6 were: (a) correct answers or rewards, and (b) efficiency ratio.

Statistical analysis
The statistical analyses were performed using descriptive statistics for the demographic variables. In the descriptive statistics, qualitative variables were described as absolute frequencies and relative percentages for each category, whereas quantitative variables were calculated using means and SDs. Repeated measures analyses of variance (ANOVA) were used to explore the differences between controls and patients in the dependent variables (SR and impulsivity parameters), with the magnitude of the SR, PPI and habituation, on one hand, and omissions and commissions of the CPT, stop signal reaction time (SSRT) of the SST and rewards and efficiency of the DRL6, on the other hand, as the within-subject factors, and the two different groups (patients and controls) as the between-subjects factor. We used the variable of age as covariate, in order to control the potential effect of this parameter on the performance of the impulsivity tasks and the SR test. We have also run Pearson’s Partial Correlations, using age as a covariate, to assess the correlation between variables from the SR test and laboratory measures of impulsivity. Data were processed with the statistical computer programme SPSS (version 15.0).

RESULTS
Comparison between patients and controls in the SR test and impulsivity tasks
Means for impulsivity and startle measures are shown in Table 2.

Regarding SR variables, ANOVA revealed a significant global effect for the group condition (F(6,70) = 15.28, P = 0.001). Bonferroni post-hoc analysis determined that patients, compared to controls, showed lower magnitudes of the SR in the second block (P = 0.042). There was a trend towards significance in the third block (P = 0.065).

Regarding impulsivity variables, ANOVA revealed a significant global effect for the group condition (F(6,70) = 32.34, P = 0.001). Bonferroni post-hoc analysis demonstrated that patients, compared to controls, made more omission errors in the CPT task (P = 0.009), had longer SSRT in the SST (P = 0.004) and obtained less rewards (P = 0.04) and a lower efficiency in the DRL-6 task (P = 0.000).

Differences between means of post-hoc analysis are included in Table 2.

Correlations between SR and impulsivity measures in the patient group
Results related to correlation analyses in the patient group are summarized in Table 3.

Correlation between the inhibitory control paradigm of impulsivity and magnitude of the SR
Magnitude of the SR in the first block had a significant positive correlation (P < 0.05) with SSRT of the SST and a significant positive correlation (P < 0.01) with X Commissions of the CPT (P < 0.01). No significant differences were found between the magnitude of the SR and the RTSS of the SST.

Correlation between the delay reward paradigm of impulsivity and magnitude of the SR
Rewards of DRLR correlated negatively with the magnitude of the SR in the three blocks (P < 0.05).

Correlation between inhibitory control paradigm of impulsivity and SH
We found that X Commissions of the CPT correlated positively with the habituation of the SR (P < 0.01). We also found a significant positive correlation between the SSRT of the SST and SH (P < 0.05). No significant differences were found between the SH and the RTSS of the SST.

Correlation between impulsivity measures and PPI
No significant correlation was demonstrated between impulsivity measures and PPI.

Correlations between SR and impulsivity measures in the control group
In the control group, in contrast with the patient group, no significant correlations were found between impulsivity measures and parameters of the SR (Commissions X of the CPT and magnitude of the SR in the
Table 2. Measures of startle-response variables and laboratory paradigms of impulsivity

<table>
<thead>
<tr>
<th>Startle variables</th>
<th>Cases Mean (SD)</th>
<th>Controls Mean (SD)</th>
<th>F</th>
<th>P value</th>
<th>Difference between means</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA (1–5)</td>
<td>0.29 (0.22)</td>
<td>0.44 (0.54)</td>
<td>F(70.6) = 2.78</td>
<td>P = 0.041</td>
<td>0.15</td>
<td>P = 0.10</td>
</tr>
<tr>
<td>PA (6–37)</td>
<td>0.19 (0.16)</td>
<td>0.39 (0.57)</td>
<td>P = 0.042*</td>
<td>0.09</td>
<td>P = 0.065</td>
<td></td>
</tr>
<tr>
<td>PA (38–42)</td>
<td>0.17 (0.13)</td>
<td>0.35 (0.57)</td>
<td>0.18</td>
<td>0.082</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI 30</td>
<td>5.04 (31.35)</td>
<td>22.35 (18.1)</td>
<td>17.31</td>
<td>P = 0.005*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI 60</td>
<td>11.53 (32.15)</td>
<td>23.6 (27.64)</td>
<td>12.07</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI 120</td>
<td>23.71 (34.64)</td>
<td>26.62 (36.48)</td>
<td>2.91</td>
<td>P = 0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Habituation</td>
<td>0.12 (0.18)</td>
<td>0.09 (0.19)</td>
<td>0.03</td>
<td>0.01</td>
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</table>

Impulsivity variables

| Omissions AX      | 1.87 (3.52)    | 0.27 (0.56)       | P = 0.09* | 1.6     | P = 0.47 |
| Commissions A     | 0.18 (0.55)    | 0.11 (0.31)       | 0.07       | 0.29 |
| Commissions X     | 0.85 (3.99)    | 0.16 (0.37)       | 0.76       | 0.04* |
| SSRT              | 215.41 (90.77) | 170.03 (57.05)    | 50.31       | 0.01 |
| Rewards           | 49.42 (9.36)   | 60.12 (8.47)      | 10.7       | 0.04* |
| Efficiency        | 67.56 (19.71)  | 90.25 (9.76)      | 22.69       | P < 0.001* |

PA (1–5) = magnitude of the SR in Block 1; PA (6–37) = magnitude of the SR in Block 2; PA (38–42) = magnitude of the SR in Block 3; PPI 30 = PPI when the prepulse-to-pulse interval is 30 ms; PPI 60 = PPI when the prepulse-to-pulse interval is 60 ms; PPI 120 = PPI when the prepulse-to-pulse interval is 120 ms.

SSRT, Stop Signal reaction Time.

*P < 0.05.

Table 3. Correlation of SR parameters and impulsivity task parameters

<table>
<thead>
<tr>
<th>PA (1–5)</th>
<th>PA (6–37)</th>
<th>PA (38–42)</th>
<th>%PPI30</th>
<th>%PPI60</th>
<th>%PPI120</th>
<th>Hab</th>
<th>CPTomi</th>
<th>CPTcomA</th>
<th>CPTcomX</th>
<th>StopSSRT</th>
<th>DRL6rec</th>
<th>DRL6eff</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.71**</td>
<td>0.56**</td>
<td>0.41*</td>
<td>0.33*</td>
<td>0.5**</td>
<td>0.68**</td>
<td>-0.1</td>
<td>0.07</td>
<td>0.45**</td>
<td>-0.25</td>
<td>-0.37*</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>0.28</td>
<td>0.39*</td>
<td>0.26</td>
<td>0.26</td>
<td>-0.2</td>
<td>-0.11</td>
<td>0.02</td>
<td>0.03</td>
<td>0.11</td>
<td>-0.05</td>
<td>-0.02</td>
<td>-0.09</td>
<td></td>
</tr>
<tr>
<td>0.28</td>
<td>0.26</td>
<td>0.26</td>
<td>-0.2</td>
<td>-0.11</td>
<td>-0.02</td>
<td>0.11</td>
<td>0.06</td>
<td>-0.03</td>
<td>-0.02</td>
<td>-0.02</td>
<td>-0.09</td>
<td></td>
</tr>
<tr>
<td>%PPI30</td>
<td>0.59**</td>
<td>0.61**</td>
<td>0.24</td>
<td>-0.1</td>
<td>-0.09</td>
<td>0.16</td>
<td>-0.07</td>
<td>0.11</td>
<td>-0.05</td>
<td>-0.02</td>
<td>-0.09</td>
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</tr>
<tr>
<td>%PPI60</td>
<td>0.86</td>
<td>0.15</td>
<td>0.16</td>
<td>-0.07</td>
<td>0.02</td>
<td>0.16</td>
<td>-0.02</td>
<td>0.11</td>
<td>-0.05</td>
<td>-0.02</td>
<td>-0.02</td>
<td></td>
</tr>
<tr>
<td>%PPI120</td>
<td>0.33*</td>
<td>-0.01</td>
<td>0.10</td>
<td>-0.08</td>
<td>-0.13</td>
<td>0.20</td>
<td></td>
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<tr>
<td>Hab</td>
<td>-0.03</td>
<td>0.07</td>
<td>0.51**</td>
<td>-0.26</td>
<td>-0.08</td>
<td>0.16</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>CPTto</td>
<td>-0.02**</td>
<td>-0.01</td>
<td>-0.10</td>
<td>-0.04</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CPTcomA</td>
<td>0.27</td>
<td>0.13</td>
<td>-0.29</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CPTcomX</td>
<td></td>
<td>-0.23</td>
<td>-0.04</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>StopTRSS</td>
<td></td>
<td>0.12</td>
<td>-0.05</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRL6rec</td>
<td></td>
<td>0.40*</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>DRL6eff</td>
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</table>

PA (1–5) = Magnitude of the SR in the first block; PA (6–38) = Magnitude of the SR in the second block; PA (38–42) = Magnitude of the SR in the third block; %PPI30 = Percentage of PPI when prepulse is presented 30 ms before the pulse; %PPI60 = Percentage of PPI when prepulse is presented 60 ms before the pulse; %PPI120 = Percentage of PPI when prepulse is presented 120 ms before the pulse.

Hab, Habituation of the SR; CPTomi, CPT omissions; CPTcomA, CPT A Commissions; CPTcomX, CPT X Commissions; StopTRSS, Stop Reaction Time to the Stop signal; DRL6rec, DRL6 rewards; DRL6eff, DRL6 efficiency.

*P < 0.05.

DISCUSSION

To the best of our knowledge, this is the first study in which impulsivity and SRBT startle-response paradigms have been shown to be correlated in the alcoholic population. The most relevant findings were that in abstinent alcoholic men, the magnitude of the SR correlated

Correlations between impulsivity measures and clinical variables

We found a significant negative correlation between the age of alcohol use initiation and the X Commissions of the CPT (R = -0.42, P < 0.01). In addition, we have also found a significant positive correlation between alcohol consumptions (grams/day) before the period of abstinence and the Omissions of the CPT (R = 0.44, P < 0.01) and A Commissions of the CPT (R = 0.44, P < 0.01). No significant correlations were found with the SST and the DRLR. No significant correlations were found between number of previous detoxifications and measures of impulsivity.

first block: R = 0.17; Commissions X of the CPT and habituation of the SR: R = -0.03; SSRT of the SST and magnitude of the SR: R = 0.18; SSRT of the SST and habituation of the SR: R = 0.09; Rewards of the DRL and magnitude of the SR in the first, second and third block: R = -0.18, -0.15, -0.13 respectively).
significantly with measures of both dimensions of impulsivity: inhibitory control and delay of reward; whereas SH had a significant correlation with the inhibitory control dimension of impulsivity.

Alcohol-dependent patients showed a lower magnitude of the SR compared to healthy controls. This finding has been described in detail elsewhere (Marin et al., 2012). The fact that alcohol-dependent patients exhibit a reduced magnitude of the SR could be due to the effect of the repeated exposure of the brain to alcohol. Several studies have demonstrated that in healthy subjects (Grillon et al., 1994; Hutchison et al., 1997) and in heavy drinkers (Hutchison et al., 2003) alcohol reduces or suppresses the magnitude of the SR. In addition, it could also be due to a characteristic of alcohol-dependent patients or because of anhedonia and depressive symptoms that alcoholic patients often exhibit, as low baseline startle has been found in individuals with depressive symptoms and anhedonia (Mneime et al., 2008).

However, the magnitude of the SR correlated positively with commissions of the CPT in alcohol-dependent patients, but not in controls and with the SSRT. On one hand, Commissions of the CPT have been considered as an index of impulsivity, as they denote an individual’s inability to refrain from pressing the keyboard when the critical signal of the task has not yet appeared (Epstein et al., 2001). The fact that the magnitude of the SR correlated with the Commissions of the CPT, but not with the RTSS of the SST, which was the other task we used to assess behavioural inhibition, could be due to the fact that these two tasks evaluate different aspects of behavioural inhibition. Whereas in the CPT the subject has to suppress an action that has been already initiated, in the SST the subject has to demonstrate the ability to refrain the beginning of an action when a stop signal is presented (Verbruggen and Logan, 2008). The SSRT refers to the time needed to inhibit Go-responses in 50% of the cases and constitutes the main parameter of the SST. Long SSRT intervals suggest a poor inhibition (Logan, 1994). On the other hand, we also found that in alcohol-dependent patients the magnitude of the SR correlated negatively with the rewards of the DRLR task, which is a laboratory measure of the delay of reward dimension of impulsivity. The number of rewards indicates the ability of a subject to delay reward. The less rewards a subject obtains, the more impulsive he is (Ferster and Skinner, 1957).

This means that overall, among alcohol-dependent patients, those with a higher reactivity of the SR exhibit higher levels of impulsivity, defined as both poor inhibitory control and an inability to delay reward. This contrasts with previous research in which extroverts, characterized by sociability, impulsiveness, liveliness and excitability (Eysenck, 1967), showed a low reactivity of the SR (Blumenthal et al., 1995, 2001). There are several factors that should be taken into account when explaining the discrepancy between our results and previous findings. First, the Blumenthal studies were not performed using an alcoholic sample. Additionally, those studies used self-report measures of impulsivity, which assess impulsivity as a trait and we have used behavioural tasks, which assess impulsivity as a state. It has been found that self-reported measures of impulsivity do not correlate strongly with behavioural tasks assessing impulsive behaviour (Reynolds et al., 2006).

It is also important to point out that in alcoholism, the magnitude of the SR has shown the most inconclusive results among the paradigms of the startle reflex, in both human (Marin et al., 2012; Schellekens et al., 2012) and animal studies (Rassnick et al., 1992; Slawecki et al., 2006). Some studies have shown a reduction of the SR (Grillon et al., 1994; Hutchison et al., 1997; Marin et al., 2012), whereas others show an increase (Howard and Ford, 1992; Krystal et al., 1997; Schellekens et al., 2012).

A possible explanation for our findings is that this increase in the magnitude of the SR is a phasic state-related change, a fear potentiated startle, which reflects an anxiogenic response induced by the anticipation of aversive startling stimuli and/or by the experimental context itself (Grillon et al., 1997). Those alcohol-dependent patients who exhibit a more anxious state under the experimental condition, reflected by an increase in the magnitude of the SR, could perform worse in impulsivity tasks. There is a form of alcoholism etiologically linked to anxiety, which is explained through a ‘self-medication’ hypothesis. This hypothesis states that individuals consume alcohol to relieve anxiety symptoms (Merikangas et al., 1996; Morris et al., 2005). A greater magnitude of the SR has been described in patients with anxiety disorders (Morgan et al., 1993; Grillon et al., 1997) and alcohol has been found to produce a decrease in the SR (Grillon et al., 1994; Hutchison et al., 1997). It could be possible that a group of alcoholic patients initiated their alcohol consumption in order to relieve their anxiety symptoms, reflected by a higher reactivity of the SR, in an impulsive way, and after being exposed chronically to alcohol, their magnitude of the SR is reduced as a consequence of alcohol consumption shown by a decrease in the magnitude of the SR after drinking.

Additionally, in animal models, alcohol-prefering lines of rats have been shown to express a greater fear-potentiated startle (McKinzie et al., 2000; Barrenha and Chester, 2007), and alcohol has been shown to decrease the fear-potentiated startle to a greater degree in mice selectively bred for high alcohol preference (Barrenha et al., 2011). This could reflect that, on one hand, exposure to stress may interact with underlying anxiety states to produce a high reactive disposition that may lead to a propensity for heavy alcohol drinking behaviour (McKinzie et al., 2000) and on the other hand, that organisms with a genetic propensity for alcohol consumption are more sensitive to the anxiolytic effects of alcohol (Barrenha et al., 2011).

Another alternative to this first explanation would be that in alcoholic patients, previous detoxifications have neurotoxic effects which lead to the nervous system, reflected by an increase in the magnitude of the SR. As alcohol consumption produces a decrease in the magnitude of the SR (Grillon et al., 1994; Hutchison et al., 1997), it could be theorized that alcohol-dependent patients drink impulsively in order to dampen this hyperexcitability (Krystal et al., 1997). However, in our study we did not find a significant correlation between the number of previous detoxifications and the SRBT and impulsivity measures.

Recently, it has been described that detoxified early-onset alcohol-dependent patients exhibit a greater SR compared with late-onset alcohol-dependent patients (Schellekens et al., 2012). We have found that early initiation of alcohol intake is correlated with higher levels of impulsivity and poor inhibitory control. In this way, early onset of AUD could be mediating both startle reactivity and impulsivity, and early-onset of alcohol consumption is mediated by a delay of reward impulsivity (Rubio et al., 2008), whereas its maintenance is mediated by a poor inhibitory control (Rubio et al., 2008).

In our study, alcohol-dependent patients, but not controls, had a correlation between a higher reactivity of the SR and impulsivity. This means in turn, that when coping with stressful situations, such as the aversive startling stimuli and/or the experiment itself, alcohol-dependent patients develop an anxiety state and in this context, they behave in an impulsive way, which leads them to engage in compulsive drinking behaviour, probably trying to relieve anxiety symptoms. This, in the long term, would make these patients more sensitive to the reinforcement effects of alcohol and to the development of an AUD.

Our other important finding was that habituation (SH) correlated positively with commissions of the CPT and the SSRT of the SST. This
means that, in alcoholic patients, a faster SH is associated with impulsivity, in the form of disinhibitory behaviour. We have extended results from LaRowe’s study, where it was found that tendencies towards impulsivity and behavioural disinhibition were associated with faster habituation in healthy volunteers (LaRowe et al., 2006). However, LaRowe’s study only used questionnaires and scales to assess impulsivity, and our study used laboratory measures. Rapid SH has been hypothesized to serve as a biological indicator of externalizing psychopathology, impulsivity and a disinhibited personality type (LaRowe et al., 2006). This neurobehavioural disinhibition has been widely described to be an important component of the propensity to develop AUD (Dom et al., 2006a,b,c; Rubio et al., 2007, 2008).

According to our findings, AUD could be developed through two different pathways. On one hand, some alcoholics would have high arousal or higher levels of anxiety when coping with stressful situations, which in turn would lead them to increase their alcohol consumption in order to alleviate anxiety symptoms. On the other hand, alcoholics would also have impulsive and disinhibitory personality traits and start drinking alcohol for sensation and novelty, which are features that define this personality type. In our study, the modulation of the SR is related with both pathways.

The fact that we did not find any correlation between impulsivity and PPI could be due to the concept of PPI itself. PPI is used as a measure of sensorimotor gating (Swerdlow et al., 2006), which refers to the ability to filter out irrelevant stimuli and in this way, it is more associated with attentional mechanisms than with hyperarousal. Impulsivity and attention impairments are mediated by different neurological pathways, which are not necessarily correlated. However, we did not find significant correlations between PPI and omissions in the CPT, which is considered as an index of attention and vigilance. This is probably due to the fact that, whereas PPI is a measure of an unconscious preattention, omissions in the CPT are an index of sustained attention (Braff et al., 1992; Comners, 1995).

Several limitations of this study should be noted. First, the study only included a clinical population, so that the results may not be extended to a nonclinical population. In addition, we included only alcohol-dependent men and results cannot be generalized to females. The reason for not including females, as explained above, is the existence of gender differences in the performance of the startle test (Kofler et al., 2001; Aasen et al., 2005; Kumari et al., 2008) and in impulsivity levels (Winhusen and Lewis, 2012; Kong et al., 2013; Perry et al., 2013), which could constitute a confounding variable.

Second, this was an exploratory study involving a small sample. The exclusion criteria were also very broad, leading to considerable heterogeneity in parameters such as age, period of abstinence, time since onset of AD or history of grams of alcohol intake. Because of these broad exclusion criteria confounding variables such as nicotine dependence and a history of other SUDs might have interfered with the results reported.

We used a cross-sectional design and both parameters assessed: impulsivity and paradigms of the SR, have a bidirectional relationship with alcohol. On one hand, impulsivity has been shown to predict the development of AUD (Dom et al., 2006a,b,c) and vice versa, it is well known that heavy alcohol use can trigger impulsive behaviours (Jentsch and Taylor, 1999; Goldstein and Volkow, 2002). On the other hand, exposure to a dose of alcohol is associated with a global suppression of the SR (Grillon et al., 1994; Hutchinson et al., 1997) and vice versa, impairments in the SR have been described in offspring of alcohol-dependent patients even before having been exposed to alcohol (Grillon et al., 1997). Altogether, this means that we cannot explain whether the association found between impulsivity and SR could constitute a risk factor for the development of AUD, or whether it appears as a consequence of toxicity of alcohol in the Central Nervous System.

Finally, the present study only used laboratory measures of impulsivity, and we did not provide questionnaires and scales assessing self-report impulsivity. This is because the objective of the study was to assess the association between SR parameters (that are considered state tasks, and not trait tasks) and state impulsivity, but not trait impulsivity. Personality traits refer to stable characteristic individual differences in ways of perceiving the world and responding to it. In contrast, laboratory tasks typically refer to relatively specific cognitive processes. Thus, it is not clear that measures of the two types of processes should necessarily relate strongly and in fact, as pointed out above, it has been described that self-report measures of impulsivity do not correlate strongly with behavioural tasks assessing aspects of impulsive behaviour (Reynolds et al., 2006).

In summary, the aim of this study was to investigate the existence of an association between two widely known vulnerability markers for the development of AUD, such as impulsivity and SR paradigms and explore whether they could constitute a common endophenotype for the development of these disorders. We have found that impulsivity and paradigms of the SR are correlated in the alcoholic population, but not in non-alcoholic subjects. It can be theorized that this interaction could mediate a pathway towards the development of AUD. However, further studies are needed to assess whether both parameters could share a common genetic origin and constitute endophenotypes for the development of AUD.

**FUNDING**

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**CONFLICT OF INTEREST STATEMENT**

None declared.

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