ORIGINAL ARTICLE

Distinct Effects of Protracted Withdrawal on Affect, Craving, Selective Attention and Executive Functions among Alcohol-Dependent Patients

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INTRODUCTION

Protracted alcohol withdrawal constitutes an important initial step of the treatment and the rehabilitation of alcoholic patients. When performed in hospital, the appearance of withdrawal symptoms (i.e. shakes, sweats, rapid heartbeat and depressive symptoms) are minimized by the implementation of a withdrawal substitution treatment usually consisting in selective attention and executive functions (EFs) in alcohol-dependent patients. Methods: Selective attention (The D2 Cancellation Test), flexibility (Trail Making Test), inhibition (Stroop Task), decision making (Iowa Gambling Task), craving (Obsessive–Compulsive Drinking Scale) and state affectivity (Positive and Negative Affectivity Schedule) were assessed in alcohol-dependent patients (DSM-IV, n = 35) matched to non-alcohol-dependent participants (n = 22) at the onset (T1: day 1 or 2) and at the end (T2: days 14–18) of protracted withdrawal during rehab. Results: Alcohol-dependent patients' abilities to focus their attention on relevant information, to switch from one pattern to another, to inhibit irrelevant information and to make advantageous choices were lower than those of control participants during both times of a withdrawal cure. No effect of time emerged from analyses for selective attention and EF deficits. Conversely, significant differences between T1 and T2 were observed for craving and affect scores indicating a weakening of alcohol craving and negative affect as well as an improvement of positive affect among patients from onset to the end of cure. Conclusion: Control functions of the Supervisory Attentional System (Norman and Shallice, 1986) were impaired and did not improve during a 3-week withdrawal cure, whereas alcohol craving and negative state affectivity significantly improved in parallel during this period. Implications for understanding the clinical processes of withdrawal are discussed.

MATERIALS AND METHODS

Participants

A group of 35 alcoholic patients and a control group of 22 alcohol non-abusers, matched for age, gender and educational level (see Table 1) were tested. All the participants in the alcoholic patient group were recruited among alcohol-dependent patients during a detoxification and rehabilitation programme at the Department of Adult Psychiatry at the Cliniques Universitaires St Luc and Clinique La Ramée, Brussels. They received a diagnosis of alcohol dependence as first axis I diagnosis according to DSM-IV criteria (American Psychologis Association, APA, 1994) supports the view that the drive to drink and the disturbance of a number of EFs among recently abstinent alcoholic individuals (i.e. sober for 3 weeks) and reported deficits of inhibition of prepotent response (Noël et al., 2001) and cognitive flexibility decision making (Goudriaan et al., 2006), planning (Joyce and Robbins, 1991) and abstraction (Parker et al., 1991). To date, only one study tested the evolution of EFs during withdrawal, but it only focused on flexibility (Mann et al., 1999). It is therefore critical to better understand the influence of withdrawal on a wider selection of EFs. Importantly, the SAS is also involved in attentional control. The issue of attention has not been much explored in research on alcohol addiction (Becker et al., 1983; Tedstone and Coyle, 2004) and never in test–retest settings during withdrawal.

The goals of the present study were therefore to examine whether a 3-week detoxification programme exerts similar or distinct effects on drive for drinking, affectivity, selective attention and a number of EFs, in order to compare these changes to those observed in a control group in a test–retest design.
logical Association, APA, 1994), clinically evaluated by psychiatrists (P.d.T., M.D.). At onset of withdrawal, systematically patients received a withdrawal substitution treatment consisting of appropriate doses of benzodiazepines (diazepam: usually 30–40 mg per day) to minimize withdrawal symptoms. This medication was progressively tapered during detox. Vitamin B1 was also given to all patients. Only the patients that had drunk alcohol on the date of application or the day before were included in the study. Patients who relapsed during their stay, or who consumed addictive substances other than alcohol (and cigarettes) or presented symptoms of dementia were also excluded. The alcohol non-abusers were recruited by word of mouth and were paid for their participation. They did not report any history of alcoholism or other addiction. The current study was accepted by the ethical committee of the hospitals, and all patients signed an informed consent form.

Measures

Two questionnaires evaluated craving and state affectivity, whereas four tests evaluated selective attention and some EFs such as flexibility, inhibition and decision making, respectively.

A questionnaire on cognitive aspects of alcohol craving, the Obsessive–Compulsive Drinking Scale (OCDS)¹ (Anton et al., 1995, 1996), was administrated in a French version (Ansseau et al., 2000). The OCDS is a self-report questionnaire, which can be divided into two subscales, an ‘obsessive’ subscale and a ‘compulsive’ subscale. We used a modified version that excluded items related to drinking, as alcohol consumption was prohibited during the stay. Positive (PA) and negative (NA) mood states were assessed by a validated French version (Gaudreau, 2000) of the Positive and Negative Affectivity Schedule (PANAS) (Watson et al., 1988). The first cognitive task was the D2 Cancellation Test (Brickenkamp, 1981) which assesses selective attention, visual scanning ability and mental concentration. The test is composed of several lines with letters, in which participants have to mark as many targets per line as possible. The dependent variables are total number of items identified in the total lines (GZ) and the total number of errors (F). A second task, the Trail Making Test

¹ Regarding the OCDS, it was necessary to use a modified scale during the second period of assessment in which patients were totally abstinent. Thus, participants were given a version in which several items related to consumption (including some compulsion items) had been removed because the patients had not consumed alcohol for 3 weeks at that point.

Table 1. Sociodemographic data for the clinical and the control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alcoholic group</th>
<th>Control group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, ± SD</td>
<td>AT1/AT2 n = 35</td>
<td>C n = 22</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48.40 ± 8.2</td>
<td>44.36 ± 9.64</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>17 (48.5%)</td>
<td>14 (63.63%)</td>
<td>ns</td>
</tr>
<tr>
<td>Male</td>
<td>18 (51.5%)</td>
<td>8 (45.47%)</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>49.94 ± 8.09</td>
<td>46.25± 11.45</td>
<td>ns</td>
</tr>
<tr>
<td>Educational level</td>
<td>Secondary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>level, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>15 (42.85%)</td>
<td>7 (31.81%)</td>
<td>ns</td>
</tr>
<tr>
<td>Higher Education</td>
<td>20 (57.14%)</td>
<td>15 (68.18%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns, not significant; n = P > 0.05.
²-independent t-tests for independent samples.
Pearson chi-square test.

RESULTS

Statistical analyses

All variables were tested at the onset (T1 = day 1) and end (T2 = days 14–18) of withdrawal in the same subjects with the exception of the GT task which could not be repeated due to potential learning test–test effects (Tranel et al., 2000). Therefore, the GT was not conducted twice on the same cohort but on two different cohorts by splitting the alcohol group in two, which performed GT either at T1 or at T2. A 2 (Group) × 2 (Time) MANOVA was conducted with Time (T1 vs T2) as a within-subjects factor and with Group (alcoholics vs controls) as a between-subjects factor to test for differences in all scales and tests except for the IGT. The observed interactions were supplemented by calculating t-tests for dependent samples. The magnitude of observed effects was directly calculated: $\eta^2$ for F-test and Cohen’s d for t-test (Cohen, 1988). Student’s t-tests for independent samples were used to specifically compare the evolution of IGT scores between T1 and T2.

Scores exceeding three standard deviations (SD) from the mean (for the alcoholic and the control groups, respectively) were excluded from analysis. Consequently, the number of participants differs slightly for each variable as shown in Table 2.

Craving questionnaire

Analyses revealed a main effect of Time, $F_s (1,51) > 11.51$, $Ps < 0.001$, $\eta^2 > 0.18$, a main effect of Group, $F_s (1,51) >
Table 2. Cognitive measures in alcoholic patients (AT1 and AT2) vs control participants (CT1 and CT2)

<table>
<thead>
<tr>
<th>Tests and parameters</th>
<th>Alcoholic patients</th>
<th>Control participants</th>
<th>Main effects[^d]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
<td>Time 1</td>
</tr>
<tr>
<td></td>
<td>AT1 (n)</td>
<td>AT2 (n)</td>
<td>CT1 (n)</td>
</tr>
<tr>
<td>DII, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GZ</td>
<td>386.07 ± 107.14 (30)</td>
<td>448.03 ± 106.38 (30)</td>
<td>505.23 ± 80.05 (22)</td>
</tr>
<tr>
<td>F</td>
<td>16.93 ± 12.08 (30)</td>
<td>14.97 ± 9.37 (30)</td>
<td>15.09 ± 15.66 (22)</td>
</tr>
<tr>
<td>TMT, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>36.34 ± 11.35 (31)</td>
<td>31.22 ± 9.69 (31)</td>
<td>29.99 ± 10.16 (21)</td>
</tr>
<tr>
<td>TMT B</td>
<td>88.30 ± 31.39 (31)</td>
<td>73.29 ± 24.50 (31)</td>
<td>67.08 ± 16.21 (21)</td>
</tr>
<tr>
<td>TMT B–A</td>
<td>51.95 ± 25.90 (31)</td>
<td>42.02 ± 18.72 (31)</td>
<td>37.09 ± 15.04 (21)</td>
</tr>
<tr>
<td>Stroop Test, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congruent</td>
<td>1125.19 ± 462.49 (34)</td>
<td>882.06 ± 310.42 (34)</td>
<td>663.43 ± 167.28 (21)</td>
</tr>
<tr>
<td>Neutral</td>
<td>1049.85 ± 350.32 (34)</td>
<td>862.73 ± 288.11 (34)</td>
<td>645.59 ± 141.79 (21)</td>
</tr>
<tr>
<td>Incongruent</td>
<td>1307.18 ± 485.29 (34)</td>
<td>1097.47 ± 399.03 (34)</td>
<td>807.95 ± 244.74 (21)</td>
</tr>
<tr>
<td>Interference index[^c]</td>
<td>285.21 ± 210.54 (31)</td>
<td>253.35 ± 186.17 (31)</td>
<td>162.36 ± 143.49 (21)</td>
</tr>
</tbody>
</table>

[^a]All data (except F for DII Test) concern RTs in milliseconds.
[^b]Only cases excluding outliers and missing participants are included.
[^c]Interference index (1) is calculated as median RTs on incongruent items – median RTs on neutral items.
[^d]Main effects were calculated by a 2 (Group) × 2 (Time) MANOVA.

15.85, *P* < 0.001, η² = 0.23, and an interaction between Time and Group, *F* (1,51) = 13.13, *P* < 0.001, η² = 0.20, for the total score of craving and also for obsessive and compulsive components of craving. The interaction is explained by a significant decrease of craving from onset to end of withdrawal among alcohol-dependent patients by using t-tests, *t* (31) = 4.26, *P* < 0.001, Cohen’s *d* > 0.62, as compared to the control group, *t*(20) < 0.1, *ns*. However, the alcoholics ‘craving scores’ remained higher than controls at the end of the withdrawal cure, *t* (51) > 2.1, *P* < 0.04, Cohen’s *d* > 0.59 (see Fig. 1).

Affective state questionnaire

Concerning the score of PA, a main effect of Time, *F* (1,52) = 13.13, *P* = 0.001, η² = 0.20, and an interaction between Time and Group, *F* (1,52) = 5.39, *P* = 0.027, η² = 0.09, were shown while no Group effect was observed, *F* (1,52) = 0.21, *ns*. The interaction is explained by a significant increase of PA scores from onset (*M* = 26.9, SD = 7.37) to end (*M* = 33.47, SD = 6.86) of withdrawal among alcohol-dependent patients, *t*(29) = −5.02, *P* < 0.001, Cohen’s *d* = −0.92, as compared to the control group, *t*(20) = 1.92, *ns* (T1: *M* = 29.48, SD = 7.4) to end (*M* = 29.19, SD = 7.91). The PA scores were not different from those of controls at both times of withdrawal cure, *t*(49) < 2, *ns*.

Analyses revealed a main effect of Time, *F* (1,52) = 13.13, *P* = 0.001, η² = 0.20, a main effect of Group, *F* (1,52) = 16.25, *P* < 0.001, η² = 0.24, and an interaction between Time and Group, *F* (1,52) = 5.52, *P* = 0.02, η² = 0.1, for the NA score. The interaction is explained by a significant decrease of NA scores from onset (*M* = 22.5, SD = 7.42) to end (*M* = 18.3, SD = 8.4) of withdrawal among alcohol-dependent patients, *t*(29) = 3.62, *P* < 0.001, Cohen’s *d* = 0.53, as compared to the control group, *t*(20) = 1.92, *ns* (T1: *M* = 12.9, SD = 2.68) to end (*M* = 12.33, SD = 2.94). However, NA scores remained higher than controls at the end of the withdrawal cure, *t*(49) = 3.12, *P* = 0.003, Cohen’s *d* = −0.88.
0.02, \( \eta^2 = 0.10 \), indicating that participants in general committed more errors at T1 than at T2. To determine whether a speed accuracy trade-off (i.e. a relation between quantity (total number of items identified) and quality (total number of errors)) was present or not, a Pearson correlation was computed between speed (GZ) and errors (F). The non-significant correlations GZ and F \((r < 0.24, \text{ns})\) allowed us to eliminate the possibility of a speed accuracy trade-off at both times for each group.

**Cognitive flexibility.** Given that the error rate in the TMT was low (<4%) for both parts A and B of the test and that no differences between groups were observed, analysis was focused only on RTs. Concerning the psychomotor speed component (TMT A), a main effect of group \((F(1,50) = 6.96, P = 0.01, \eta^2 = 0.12)\) and a main effect of time \((F(1,50) = 22.011, P < 0.001, \eta^2 = 0.31)\) were evidenced, while no Time \(\times\) Group interaction, \((F(1,50) = < 1, \text{ns})\) was observed, indicating that participants spent in general more time compared to controls and that all participants spent more time at T1 than at T2 (see Table 2). Regarding TMT B, a cognitive flexibility index, patients were also impaired compared to controls as shown by a main effect of group, \((F(1,50) = 6.62, P = 0.013, \eta^2 = 0.12)\) (see Table 2). A main effect of time was also observed, \((F(1,50) = 8.19, P = 0.006, \eta^2 = 0.14)\), showing that all participants at T1 had lower performance than participants at T2. However, no Group \(\times\) Time interaction was present, \((F(1,50) = < 3, \text{ns})\). Finally, for TMT B–A, a more accurate index of cognitive flexibility without any speed component, the MANOVA revealed only a main effect of group, \((F(1,50) = 3.77, P = 0.05, \eta^2 = 0.10)\), indicating that the switching performance of patients was lower than that of controls in general during withdrawal.

**Prepotent response inhibition.** Given a floor effect of error rates (<6%) for all categories of stimuli, the analyses only focused on the median RTs for congruent, neutral and incongruent stimuli rather than on the number of errors. A main effect of group, \(F_s(1,53) > 14.80, P_s < 0.001, \eta^2_s > 0.23\), revealed that alcoholic patients were slower than controls in general and for all stimuli. A main effect of time was also observed for all stimuli, \(F_s(1,53) > 8.10, P_s < 0.01, \eta^2_s > 0.13\), indicating that all participants had lower performance at T1 than at T2. Moreover, the Group \(\times\) Time interaction for all stimuli was also significant, \(F_s(1,53) > 8.98, P_s < 0.01, \eta^2_s > 0.14\). As shown by paired \(t\)-tests, for all types of stimuli an improvement was found only for alcoholic patients, \(t(33) > 3.94, P_s < 0.001, \text{Cohen’s } d_s > 0.47\). However, this improvement was partial as the performance of patients was lower than that of controls at the end of the withdrawal as shown by \(t\)-tests for independent samples comparing groups, \(t(53) > 2.82, P < 0.01, \text{Cohen’s } d_s > 0.78\).

The interference index, the most reliable index to assess inhibition or interference of the prepotent response, was computed as follows: median RTs incongruent items – median RTs neutral items. On this measure, there was only a significant main effect of group, \(F(1,50) = 3.90, P = 0.05, \eta^2 = 0.07\), showing more interference for patients than controls during withdrawal. Overall, this result supported the hypothesis that alcohol-dependent patients have similar difficulty inhibiting interference responses at both times of a 3-week withdrawal cure.

**Decision making.** The alcoholic group was randomly split into two independent groups. Indeed, the IGT was only administered once because of the potential for test–retest effects. Results showed that alcohol-dependent patients at both times took more cards from disadvantageous decks \((A’ + B’)\) (i.e. two high reward decks but which also give higher levels of punishment compared to advantageous decks \((C’ + D’)\) with low levels of reward but low levels of punishment) \((T1: (M = 47.04, SD = 8.99), T2: (M = 48.80, SD = 6.99))\) than controls did \((M = 41, SD = 8.01)\) as shown by \(t\)-tests for independent samples, \(T1: t(41) = 2.33, P = 0.025, \text{Cohen’s } d = 0.71,\) and \(T2: t(30) = 2.65, P = 0.013, \text{Cohen’s } d = 1.01\). In addition, patients had lower net scores \((A’ + B’) - (C’ + D’))\) (i.e. the difference between advantageous and disadvantageous decks was smaller) \((T1: (M = 6, SD = 17.72), T2: (M = 4.11, SD = 10.22))\) than controls \((M = 17.54, SD = 15.50), T1: t(41) = −2.855, P = 0.025, \text{Cohen’s } d = 0.69,\) and \(T2: t(29) = −2.391, P = 0.024, \text{Cohen’s } d = 0.96\). In the alcohol-dependent groups, no significant differences were observed for both indexes between the group tested at T1 and the one at T2. Fig. 2 shows a sample line graph displaying the net scores \((C’ + D’) - (A’ + B’))\) of cards selected (20 by 20) for each group. The learning of the task appears graphically quicker for controls than alcoholics at T1 and T2. Nevertheless, the difference was statistically significant only for the 4th block (61–80 selected cards) \((ts (40) > 1.99, P_s < 0.05, \text{Cohen’s } d_s > 0.66)\).

**DISCUSSION**

In the current study, we addressed the question of whether a withdrawal cure among alcohol-dependent patients has an effect on craving, affectivity and control abilities such as selective attention and EFs. We observed a partial decrease in the obsessive, compulsive and total self-reported craving scores as well as in negative affect scores during withdrawal. At the end of withdrawal, however, values remained higher than those of the controls. Moreover, the effect sizes concerning the improvement in craving and negative affect were similar according to Cohen’s indexes \((Cohen, 1988)\). In fact, the scores of both variables decreased with a large magnitude between both times. In addition, concerning positive affective state, we also observed a significant increase during withdrawal although at both times scores were not different from those of controls.

Concerning control abilities, we first measured selective attention. A deficit in procession speed was observed at the D2 task among alcoholic patients during withdrawal. These findings regarding selective attention are not in parallel with those of a previous study \((Tedstone and Coyle, 2004)\), which found no differences between sober alcoholics and controls in the Eriksen task. However, this difference may be explained by the fact that in the latter work, patients were tested after 6 weeks of residential rehabilitation, which in comparison with our shorter 2–3-week period of abstinence may permit a recovery of attention. Regarding cognitive flexibility, measured by the TMT B–A, alcoholic patients exhibited impaired performance during the 3-week withdrawal and no improvement between the two time periods. This is consistent with previous studies performed with early abstinent alcoholics using the TMT \((Noël et al., 2001)\) in addition to other tasks \((Hildebrandt et al., 2004)\). However, another study \((Mann et al., 1999)\) found some recovery of TMT performance after 6 weeks of cure.
Importantly, results concerning selective attention scores and other scores involving basic processes such as perceptual and motor (i.e. GZ, TMT A, TMT B, congruent, neutral and incongruent stimuli) show differences between T1 and T2 for both alcoholics and controls, indicating a test–retest effect between T1 and T2. However, because these indexes (i.e. TMT B–A and interference index of the Stroop (Stroop, 1935)) remained stable at both times for both alcoholics and controls, the learning effect did not affect performance of pure EFs that are not affected by these basic processes (Lezak, 1995).

From a clinical standpoint, we frequently observe that alcoholic individuals at the end of withdrawal are excessively optimistic about their ability to remain abstinent, a factor that we intuitively do not consider as a good predictor of future sobriety. The remaining deficits in selective attention and in EFs may contribute to their inability to anticipate the difficulties they might meet after going back home, and thus increase the possibility of relapse. Indeed, the EF deficits and the persistence of significant levels of negative affect and craving suggest that alcohol-dependent patients have only weak abilities to resist drinking after a classical 3-week withdrawal period. Therefore, it would be of interest to examine empirically if these executive deficit factors may serve as predictors of relapse (Noël et al., 2002; Moriyama et al., 2002). Future research should also be dedicated to investigating the evolution of these cognitive functions over a longer time period after withdrawal to better understand if spontaneous improvement may be expected during long-term abstinence (Pitel et al., 2009) or if EFs and selective attention deficits remain altered as in short-term abstinence (Zinn et al., 2004). This knowledge could be used to form the basis of specific rehabilitation programmes to prevent relapse.

This study is not without limitations. First of all, some uncertainty remains as to the exact conditions that were obtained by our specific design (T1 vs T2) to understand observed effects. At T1, the subjects had stopped drinking for <24 h and were starting or about to start a medication of benzodiazepines. At T2, most subjects had stopped benzodiazepines. We therefore compared a status induced by a period of alcohol drinking or perhaps of early withdrawal (T1) with early sobriety (T2). We do not believe, however, that the observed negative affect at T1 might be attributed solely to effect of withdrawal. Indeed, in an earlier publication of our group (de Timary et al., 2008), there were no significant changes in negative affect as assessed by depression and anxiety measures between onset of withdrawal (equivalent to T1 in the present study) and 3 days after the onset, which is commonly considered as the time for peak withdrawal effects (Kosten and O’Connor, 2003). Therefore, we believe that negative affect observed at T1 is mainly due to the effects of a prolonged period of alcohol drinking that induces negative mood (Schuckit, 1994). The recovery at T2 is due to early sobriety. Secondly, a larger sample size could have increased the significance of the effects, considering the number of variables. In addition, the lack of information about any other secondary axis I diagnosis (such as mood or anxiety disorders) does not preclude the fact that some of the observed scores on the PANAS or on the neuropsychological tests might not be due to alcohol dependence. However, it is difficult if not impossible to give a diagnosis of anxious disorder or major depression when patients are in a state of alcoholization (de Timary et al., 2008; Schuckit, 1994).
CONCLUSION

In conclusion, these results suggest that a 3-week alcohol detoxification period affects only the drive for drinking alcohol and state affectivity does not affect selective attention or EFs, which remained impaired at both time periods of the cure. These observations may be relevant for clinicians to better understand the abilities and deficits of their patients during and after a 3-week detoxification period and to implement new neurocognitive treatments to decrease the risk of relapse.

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