CONTRIBUTION OF FRONTAL CEREBRAL BLOOD FLOW MEASURED BY ⁹⁹mTc-BICISATE SPECT AND EXECUTIVE FUNCTION DEFICITS TO PREDICTING TREATMENT OUTCOME IN ALCOHOL-DEPENDENT PATIENTS

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Abstract — Aim: To determine whether inhibition and working memory deficits, and reduced regional cerebral blood flow (rCBF) (previously shown to be related), measured at the end of a detoxification programme, predict alcoholic relapse 2 months later.

Methods: Twenty uncomplicated alcoholic inpatients were investigated at the end of detoxification, at least 7 days since the last dose of diazepam, and a mean of 18.8 days since the last drink. Their performance was assessed on the inhibition (Hayling) test, working memory (Alpha-span task), episodic memory (California Verbal Learning Test) and abstract reasoning (Progressive Matrices). Frontal CBF was assessed at the same time with a semiquantitative ⁹⁹mTc-Bicisate SPECT procedure. Patients were contacted 2 months later. Patients who abstained (n = 9) did not differ from those who relapsed (n = 11) on age, gender, smoking, duration of alcohol misuse, number of previous detoxifications, amount of ethanol consumed the month prior to admission to the detoxification programme, state anxiety, trait anxiety, or depression. Results: Relapsed subjects had shown a lower uptake of ⁹⁹mTc-Bicisate in the bilateral medial frontal gyrus than intersubject variation (n = 11: 0.85 ± 0.19), and poorer performance on the Alpha-span task and the Hayling test. The other tests were not different. Conclusions: Inhibition and working memory deficits, associated with low levels of CBF in the medial frontal gyrus, are related to the difficulty of maintaining short-term abstinence from alcohol.

INTRODUCTION

Alcohol misuse is a major public health problem with almost one in four Americans reporting having had this problem at some point in their lives (Kessler et al., 1994). Despite several decades of research in treatment and much progress, even those individuals who receive apparently effective treatments still have a poor prognosis (Hunt et al., 1971; O’Malley et al., 1992). The question of which factors predict relapse is, therefore, an important one, since by understanding what such factors are, strategies for minimizing their effects can be developed.

Listed among the many predictors of whether or not alcoholism relapse will occur are life events, mood states, self-efficacy, coping behaviours, social support resources, readiness for change, commitment to abstinence, intention to avoid high-risk situations, and use of multiple drugs (for a review, see Comings et al., 1980; Jones and McMahon, 1994; Brown et al., 1995; Miller et al., 1996). Personality factors such as antisocial personality (Poldrugo and Forti, 1988), introversion, or external locus of control have also generally been associated with a poor prognosis (Tarnai and Young, 1983). Additionally, although somewhat equivocal, there exists some evidence suggesting that those alcoholics with the highest degree of cognitive impairment have the poorest prognosis for abstinence (Abbott and Gregson, 1981; Fabian and Parsons, 1983; Parsons et al., 1990; Allsop et al., 2000). However, the magnitude of the observed relationship between neuropsychological performance and treatment outcomes is usually surprisingly modest and sometimes null (Bergman, 1987; Walker et al., 1983; Hua et al., 1998).

In the absence of well-defined neurological complications, chronic alcoholism has been associated with global changes in brain morphology such as cortico-subcortical atrophy (Brewer and Perrett, 1971; Jennigan et al., 1991) or decreased brain weight (Harper and Blumberg, 1982) and mild to severe neuropsychological impairments especially in tasks requiring memory, perceptual–motor skills, abstraction and problem solving (for a review, see Knight and Longmore, 1994; Parsons, 1998).

More recently, data have suggested that frontal lobe structures may be specifically altered in uncomplicated alcoholics. Firstly, moderate neuronal loss has been reported in the frontal cortex and in the cingulate gyrus (Kril and Harper, 1989; Kril et al., 1997). Also, functional neuroimaging studies using positron or single photon emission computed tomography (PET or SPECT) in recently detoxified alcoholics have revealed global cerebral metabolic or perfusion deficits in frontal regions (Erbas et al., 1992; Nicolas et al., 1993; Adams et al., 1993; Volkow et al., 1994, 1997; Dao-Castellana et al., 1998) that persist during several years of sobriety (Gansler et al., 2000). Moreover, frontal lobe dysfunction, observed with SPECT perfusion imaging, exceeded that observed in structural scans (Erbas et al., 1992; Nicolas et al., 1993).

Finally, neuropsychological studies highlighted frontal (executive) function impairments including planning (Pishkin et al., 1985; Joyce et al., 1995), abstraction (Parker et al., 1991), attention (Goldman, 1990; Smith and Oscar-Berman, 1992), shifting of attention (Sullivan et al., 1993), mental flexibility (Glenn et al., 1993) and concept generation (Beatty et al., 1993).

In a recent study (Noël et al., 2001), we confirmed that alcoholics with no other complications, who were discharged from a detoxification programme and who were sober for a period of 3–4 weeks, were impaired on several executive functions including, among others, inhibition as well as the...
capacity to coordinate storage and manipulation of information (i.e. working memory). Coincidently, Collette et al. (1999, 2001) examined brain substrate involved in several executive functions. Inhibition processes were related to an increase of metabolism bilaterally in the middle and inferior frontal gyrus (Collette et al., 2001). Manipulation of information in working memory induced activation mainly bilaterally in the middle frontal gyrus and in the left parietal area (Collette et al., 1999). More recently, we conducted a SPECT study in another group of recently detoxified alcoholic subjects (Noël et al., 2001) in order to explore the relationship between inhibition and working memory deficits and cerebral blood flow (CBF) of regions of interest selected on the basis of the PET studies of Collette et al. (1999, 2001). In our study, we explored 20 uncomplicated alcoholic inpatients toward the end of a detoxification programme and 20 control subjects. The results confirmed the existence of deficits affecting inhibition and working memory. In addition, we showed that deficits affecting inhibition processes are specifically correlated with regional CBF (rCBF) in both the bilateral inferior (left and right BA 47) and the median frontal gyrus (BA 47; BA10) but not with a region of reference (occipital/cerebellum). Furthermore, working memory deficits were correlated with the bilateral median frontal (left and right BA10/46) but not with the bilateral parietal area (left BA 7).

The aim of the present follow-up study was to examine whether inhibition and working memory deficits (on the Hayling test and the Alpha-span task), assessed when chronic alcoholics had completed a detoxification treatment, along with CBF for their respective regions of interest (measured at the same period with a 99mTc-Bicisate SPECT procedure), can predict a 3-month period of abstinence.

SUBJECTS AND METHODS

Subjects

Alcoholic inpatients were recruited from the Alcohol Detoxification Program of the Brugmann hospital (Noël et al., 2001) and underwent medical, neurological, and psychiatric examinations at the time of selection. They were interviewed with the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994). Reasons for exclusion were the presence of diagnosis on Axis 1 of DSM-IV other than alcohol dependence, a history of significant medical illness, head injury resulting in loss of consciousness for more than 30 min that would have affected the central nervous system, medication that could influence cognition, and overt cognitive dysfunction as assessed by the Mini-Mental State Examination (Folstein et al., 1975). All reported consuming ≥560 g of alcohol weekly for 2 of the 3 years preceding entry into the study. To increase the reliability of anamnestic information, the patient and the family were interviewed separately.

The detoxification regime was composed of B vitamins and a standardized fixed reducing course of diazepam.

Twenty patients, who had entered the outpatient care programme with the goal of maintaining abstinence, were recruited. After a minimum of 7 days after the last dose of detoxification medication, neuropsychological and SPECT evaluations were conducted. Subjects were abstinent from alcohol for a minimum of 14 days and a maximum of 22 days.

The Montgomery and Asberg (1979) depression rating scale and the State–Trait Anxiety Questionnaire (Spielberger, 1993) were used to evaluate severity of depression and anxiety. Clinical and demographical data are presented in Table 1.

**Neuropsychological assessment**

Subjects performed the Alpha-span task (Belleville et al., 1998) and the Hayling test (Burgess, 1997). We added abstract reasoning (Progressive Matrices of Raven; Raven, 1960), and an episodic verbal measure [California Verbal Learning Test (CVLT): Delis et al., 1987, 1988]. All tests were performed between 1 and 2 h before the imagery procedure.

The Alpha-span task (Belleville et al., 1998) investigates the ability to manipulate information stored in working memory by comparing the recall of information in serial order (involving mainly a storage component) and in alphabetical order (involving storage and manipulation of information). First, a classical word-span task was given to assess the span level of each subject. After the span measurement, the subject was asked to repeat word sequences in two different conditions: direct recall and alphabetical recall. In both conditions, the number of words to be recalled corresponded to the subject’s span minus one item. For example, if subjects performed a span size of five words, they were asked to recall groups of four words in serial and alphabetical order. In the direct condition, the subject performed an immediate serial recall of ten sequences of words. In the alphabetical condition, the subject was asked to recall ten sequences of words in their alphabetical order. Performance was assessed by comparing the performance in alphabetical recall with that in serial recall. In addition, a score was derived for each subject as follows:

\[
\text{score in alphabetical condition} = \frac{\text{score in direct condition} - \text{score in alphabetical condition}}{\text{direct condition}} \times 100.
\]

This represents the reduction in performance in the alphabetical relative to the direct recall condition shown by each subject.

The Hayling task (Burgess, 1997, French adapted version, Meulemans et al., 2001) assesses the capacity to suppress (inhibit) an habitual response. The test consisted of two sections (A and B) of 15 sentences each, in which the last word was missing. Sentences were read aloud by the experimenter.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45.5 ± 7.5</td>
</tr>
<tr>
<td>Education (total years)</td>
<td>11.7 ± 3.3</td>
</tr>
<tr>
<td>Years of heavy consumption of alcohol</td>
<td>14.4 ± 8.1</td>
</tr>
<tr>
<td>Daily alcohol consumption (g ethanol/kg body weight)</td>
<td>3.9 ± 1.9</td>
</tr>
<tr>
<td>No. of prior detoxification treatments</td>
<td>2.2 ± 2.3</td>
</tr>
<tr>
<td>No. of abstinence days prior to testing</td>
<td>18.8 ± 2.8</td>
</tr>
<tr>
<td>Initial diazepam dose administered (in mg)</td>
<td>44.6 ± 5.65</td>
</tr>
<tr>
<td>Montgomery and Asberg (1979) depression score</td>
<td>16.7 ± 11.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Trait</td>
<td>49.7 ± 13.11</td>
</tr>
<tr>
<td>State</td>
<td>44.8 ± 18.8</td>
</tr>
</tbody>
</table>

n = 22.
In section A (initiation/automatic) subjects were asked to give the word that made sense. In section B (inhibition), participants were asked to give a word that made no sense at all in the context of the sentence. These responses were scored 3 if the word made sense of the sentence, 1 if, although not making sense, it was semantically connected to the sentence and 0 if it made no sense at all. In both sections, subjects were asked to reply as quickly as possible and performance was measured by the time taken to respond (latency).

The Raven’s Progressive Matrix (Raven, 1960) is a multi-choice test of reasoning ability that is intended to make few demands on the subject’s verbal skills. Each of the 60 items contains an incomplete figure. The subject’s task is to select the response that best completes the stimulus figure from the six to eight alternatives presented beneath.

The CVLT (Delis et al., 1987, 1988 consists of five learning trials of a 16-word target list. The mean number of words correctly recalled in the five trials was calculated.

**Brain SPECT procedure**

Cerebral imaging was done with $^{99m}$Tc-Bicisate (Neurolite; Dupont Pharma) using a gamma camera (Sopha DSX rectangular) equipped with a high-resolution parallel collimator. The energy window was set to 140 KeV $\pm$ 10%. A syringe containing the 740 Mbq dose in a small volume (± 1 ml) was placed on the bed, and counted for 1 min just before injection to get the injected dose, and then under the patient’s head to measure the cranial attenuation. The bolus was injected via an antecubital vein catheter and a 150 $\times$ 1 s dynamic acquisition was performed using $128 \times 128$ matrix size. After this equilibrium period, CBF distribution was measured by SPECT: the camera performed a 64-step 360° rotation. Each projection ($128 \times 128$ matrix) had a 15 s preset time. Reconstruction was performed by filtered back projection using a Hann filter (cut-off 1 Ny) without attenuation correction. Sagittal slices were rotated to horizontalize the y-axis (see Talairach and Tournoux, 1988) and summed by 3 to obtain six 14 mm slices centred on each stereotactic coordinate. For dynamic processing, a cerebral region was drawn and a 150 $\times$ 1 s curve derived. After a short uptake period, a plateau was reached. The mean value between 60 s and 90 s after the maximum was compared to the injected dose and corrected for cranial attenuation. For slice processing, all regions took the form of a cube: 3 x 3 pixels area and 3 pixels depth of slice. The size of one pixel is 4.6 mm; therefore, each side of the regions of interest was ~14 mm. The regions of interest were selected from data showing that the inhibition process of the Hayling test involves bilateral BA 10 and BA 47 (Collette et al., 2001), and that the manipulation of information in working memory involves bilateral BA 10/46 and left BA 7 (Collette et al., 1999, see Fig. 1). Since no relationship has been found between occipital lobe metabolism, inhibition and working memory (Collette et al., 1999, 2001),
bilateral CBF (mean CBF of left and right occipital regions of interest) measured in BA 19 was our region of reference. Moreover, in the SPECT study conducted with the detoxified alcoholics selected in the present work, the rCBF in the bilateral inferior (BA47) and the median (BA 10) frontal gyrus had been correlated with inhibition performance measured by the Hayling test (Noël et al., 2001). Therefore, these and the BA 10/46 were selected in this study.

SPECT imaging data were evaluated by semiquantitative analysis and calculated as the ratio of mean cortical regions of interest activity to mean cerebellar activity. We chose cerebral activity to normalize the data, because it was reported that CBF did not change in alcoholics unless cerebral degeneration occurred (Gilman et al., 1990; Melgaard et al., 1990).

Statistics

Pearson’s product-moment correlation, two-tailed Student’s t test or analysis of variance (ANOVA) and post hoc analyses (Newman–Keuls test) with an α level of 0.05 and χ²-test were applied. Correction for multiple comparisons was realized using the Bonferroni correction. All analyses were performed using SPSS 8.0. (SPSS, Inc., Chicago, IL, USA).

RESULTS

Nine of the alcohol-dependent patients had not relapsed during the 3-month period; 11 relapsed. These two groups did not differ in age; the mean age (± SD) of the non-relapsed patients was 42.1 ± 7.5 years, whereas that of the relapsed patients was 48.6 ± 6.6 (t = 2.53, df = 18, P = 0.053). They also did not differ in gender (χ² = 1.8, df = 1, P = 0.2), nicotine use (t = 0.04, df = 18, P = 0.97), duration of alcohol misuse (t = –0.09, df = 18, P = 0.93), amount of previous detoxifications (t = 0.04, df = 18, P = 0.97), trait anxiety (t = 0.7, df = 18, P = 0.49), state anxiety (t = –0.69, df = 18, P = 0.5), or depression (t = –0.24, df = 18, P = 0.82).

Neuropsychological measures

On the Alpha-span task, the t-test was used to compare the verbal span size of relapers (mean ± SD = 4.1 ± 0.6) and abstainers (4.3 ± 0.67). The analysis revealed that the two groups had comparable span size [t(1,18) = –0.87, P = 0.39]. Furthermore, performances on the serial and alphabetical conditions were analysed by means of a two-way ANOVA 2 groups (relapers, abstainers) × 2 conditions (serial, alphabetical recall). The analysis revealed a main effect of condition [F(1,18) = 111.7, P < 0.001] and of group [F(1,18) = 5.7, P < 0.05]. A significant interaction between group and type of recall was also found [F(1,18) = 8.4, P = 0.01]. Post-hoc analysis revealed that abstainers had a higher score than relapers on the alphabetical but not on the serial condition (Fig. 2). Finally, the manipulation score differed significantly between both groups [t(1,18) = 2.4, P < 0.05] indicating that relapers showed a larger performance decrease between serial and alphabetical recall than abstainers.

On the Hayling test, the average response latencies (sum of latencies across 15 trials in seconds) in section A were 12.3 ± 0.7 and 12.5 ± 0.8 for abstainers and relapers respectively. The same measure in section B was 59.1 ± 35.8 and 92.8 ± 40. The 2 (group) × 2 (section) ANOVA revealed a significant effect of section [F(1,18) = 111.7, P < 0.001] and a tendency towards a group effect [F(1,18) = 3.8, P = 0.07]. The interaction between these two factors also failed to reach significance [F(1,18) = 3.9, P = 0.07]

Concerning part A, both the abstainers and the relapers always gave the correct response. On section B (see Table 2), relapers gave more expected words (error score 3) [t(1,18) = –3.1, P < 0.01] and gave fewer unrelated words (error score 0) [t(1,18) = 2.24, P < 0.05] than abstainers. Nevertheless, they did not give more words semantically linked to the expected word (error score 1) [t(1,18) = –0.9, P = 0.37].

The overall error scores (sum of score 0, 1 and 3) were 6.4 ± 2.8 and 9.5 ± 3.3 for abstainers and relapers, respectively. A t-test revealed that relapers showed a higher overall error score than abstainers [t(1,18) = –2.24, P < 0.05].

On the CVLT, abstainers and relapers recalled 10.1 ± 3.3 and 9.4 ± 2.1 correct words respectively. The performance of the two groups did not differ significantly [t(1,18) = 0.61, P = 0.55].

The scores on the PM 38 were 38.3 ± 10.1 for alcoholics who relapsed and 37.9 ± 6.1 for those who did not. Here again, there was no significant difference between the two groups [t(1,18) = 0.11, P = 0.9].

Global CBF uptake

The mean ± SEM brain uptake, strongly related to global CBF, was 7.65 ± 1.59%. It should be noted that the total brain uptake of ⁹⁹mTc-Bicisate in our sample is quite similar to the mean brain uptake data for normal subjects reported by Dupont Pharma, the manufacturer, and other studies (Friberg, 1994; Pupi, 1994). Thus, differences between our sample of
alcoholic participants and normal subjects appear to characterize rCBF distribution, but not global brain perfusion.

**Regional CBF measures**

These are shown in Table 3. In order to compare the CBF measured in BA 47, BA 10 and BA 10/46 in relapsers and abstainers, t-tests were computed, revealing that relapsers had lower CBF in BA 47 than abstainers. The two groups did not differ with regard to the CBF measured in BA 10 and 10/46.

**DISCUSSION**

The objective of this follow-up study was to assess in alcoholic subjects whether the capacity to inhibit and to manipulate information stored in working memory and related brain activity, measured during a period of a detoxification programme, could predict short-term alcohol relapse. It appeared that, 2 months after hospital discharge, >50% of the alcoholics (11 out of 20) had resumed consuming significant doses of alcohol. This percentage is in general agreement with abstinence rates documented in other studies (Hunt et al., 1971; O’Malley et al., 1992; Volpicelli et al., 1992).

Those who relapsed showed, in the period of the detoxification, a significantly poorer performance, on the Alpha-span task and on the Hayling test, than those who did not. In contrast, the two alcohol-dependent subgroups did not significantly differ on episodic memory and abstract reasoning tasks. Relapsers also showed lower $^{99m}$Tc-Bicisate SPECT uptake in the bilateral middle frontal gyrus area (BA 47).

These results are in accordance with those of previous studies showing that relapers performed worse than abstainers on neuropsychological testing (Abbott and Gregson, 1981; Fabian and Parsons, 1983; Parsons et al., 1990). However, our data suggest that the inhibition and working memory deficits constitute a better predictor of short-term alcohol relapse than multi-determined tasks (involving executive and non-executive functions, e.g. PM 38 and free recall of CVLT). This observation, of lower executive (inhibition and working memory) abilities in alcoholic subjects who relapse 2 months after discharge from a detoxification programme than in those who did not, has led us to formulate some clinical proposals. First, these results are consistent with Tiffany’s (1990) view that executive or non-automatic functions are crucial to control ‘largely automatic’ drug-use behaviours and consequently to prevent alcoholic relapse. The question could also be formulated in terms of the control to action model developed by Norman and Shallice (1980). This model distinguishes two control to action mechanisms. The first, called contention scheduling, is involved in routine situations in which actions are triggered automatically. The second, called the Supervisory Attentional System (SAS), is a separate mechanism at the highest level of control of action, coping with novelty. This mechanism is required in situations where the routine selection of an action is unsatisfactory, and is involved in the genesis of plans and willed actions. In alcoholism, the repeated consumption of alcohol leads to the development of reflexive actions and thoughts. These reflexes may be triggered by external (e.g. smell of alcohol) or internal cues (e.g. stress, withdrawal signs), and lead to the consumption of alcohol. The inhibition of these automatic responses appears to depend on the SAS. In this context, deficits affecting the SAS represent a main risk factor of relapse in alcoholics. However, the precise relationship between SAS (executive) deficits and alcohol relapse is far from clear and represents an exciting challenge for further investigations. An interesting speculation could be that individuals with SAS deficits may lack the mental resources required to appraise accurately high-risk situations, and they may fail to generate and implement coping strategies that could play an important role in, at least,
excluding in individual support therapy but did not benefit from a step programme and had entered residential or intensive day treatment at a private hospital-based chemical dependency treatment programme. In contrast, most of our patients were included in an individual support therapy but did not benefit from any residential or day treatment. It might be argued that the real impact of executive function deficits on adaptation abilities might, at least partially, be attenuated by a structured environment. Indeed, residential or intensive day treatment or Alcoholics Anonymous sessions could be helpful for planning new activities and for resisting acquired reflexive patterns of thought and action.

In our imagery data, relapsers also showed lower $^{99m}$Tc-Bicisate SPECT uptake in the bilateral middle frontal gyrus area (BA 47) than those who did not relapse. According to a recent review, the existence of a link between executive functioning and the frontal lobes is now well established (Collette and Van der Linden, 2002). Indeed, some prefrontal areas are activated when normal subjects perform various tasks that explore the central executive of working memory. More specifically, BA 47 has been shown to be involved in inhibition processes as assessed by the interference condition of the Stroop test (i.e. naming the font colour of letters that spell a colour word different from the colour-to-be-named) (George et al., 1994; Taylor et al., 1997; Bush et al., 1998). Also, the Hayling task has been used to study inhibition processes (Nathanial-James et al., 1997; Collette et al., 2001). Unlike the Nathanial-James et al.'s (1997) study, which found no supplementary activation when the inhibition condition was compared with the initiation condition, Collette et al. (2001) found the activity of the middle and inferior frontal areas did increase during the inhibition condition. However, in this study, the inferior frontal area (BA 45/47) was already activated when subjects had to initiate a response highly constrained by the context. According to Tompson-Schills et al. (1997), this area is involved in generic semantic retrieval operations, such as the selection and evaluation of a semantic response. Both the initiation and inhibition condition require the evaluation of the appropriateness of the other proffered responses, compared to the expected response. This matching process is more demanding in the inhibition condition than in the initiation condition, since, in the latter, a single correct response exists whereas, in the former, subjects have to choose among a set of appropriate responses the one that is the least related to the sentence.

To summarize, our results suggest that a low capacity of inhibition (assessed by means of the Hayling test) as well as a low capacity to coordinate storage and manipulation of information (assessed by means of the Alpha-span task), and decreased CBF in the inferior frontal gyrus, are related to early relapse in detoxified alcohol-dependent patients. Of course, the present findings are quite tentative and further investigation is needed to explore the precise relationship between executive/SAS functions, their neural basis and the processes of alcoholic relapse.

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REFERENCES


