EVENT-RELATED CORRELATES OF RESPONSE SUPPRESSION AS INDICATORS OF NOVELTY SEEKING IN ALCOHOLICS


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Abstract — Novelty Seeking including impulsive behaviour is a personality dimension which has been shown to be related to early-onset alcoholism and to high relapse rates. The cued Continuous Performance Test (CPT) is an experimental paradigm for active response control requiring a choice reaction between execution (Go) and inhibition (NoGo) of a prepared motor response. Metabolic functional methods have shown right frontal brain activation throughout the period of a CPT, and the spatial analysis of the associated event-related brain electrical (ERP) field potentials revealed that this right frontal activation was due to the NoGo subset of the task. The ERP fields allow distinction between the Go and NoGo conditions with one spatial parameter (NoGo-anteriorization) in single cases, and the magnitude of this parameter is thought to be related to inhibitory frontal lobe control. Twenty patients with severe alcohol dependence and 20 age- and sex-matched healthy controls were included in the study and investigated with a 21-channel electroencephalogram while performing a cued CPT. Consistent with previous studies, NoGo-anteriorization was present in every case in both groups. The ERP field differed between alcoholics and controls in the Go condition \( (P < 0.05) \) and NoGo-anteriorization in alcoholics was correlated inversely with Novelty Seeking in Cloninger’s Temperament and Character Inventory \( (r = 0.67, P < 0.01) \). This indicates a reduced frontal lobe contribution during response control in alcoholics with impulsive behaviour and identifies a possible biological marker for the clinical evaluation of the risk of relapse in alcoholism.

INTRODUCTION

In alcoholic patients, Novelty Seeking in the Temperament and Character Inventory (TCI; Cloninger et al., 1993) has been found to be associated with early-onset alcoholism (Cloninger et al., 1988) and high relapse rates (Meszaros et al., 1997). Novelty Seeking is considered to be a personality trait which has been integrated into a psychobiologically based four-dimensional model of temperament and character with the dimensions Novelty Seeking, Harm Avoidance, Reward Dependence, and Persistence. Novelty Seeking includes the subfactors Exploratory Excitability, Impulsiveness, Extravagance, and Disorderliness (Cloninger et al., 1993). As well as being clinical rating tools to quantify character traits, the neuropsychological and psychobiological brain functional correlates of these traits and their relation to clinical features are of enormous theoretical and practical interest for understanding the role of impulse control in alcoholism.

The Continuous Performance Test (CPT) is a well-established neuropsychological task to investigate sustained attention (Rosvold et al., 1956; Earle-Boyer et al., 1991). In its cued version, it contains an execution/inhibition conflict, and is therefore assumed to activate brain mechanisms relevant for impulsive vs controlled behaviour. In fact, impulsiveness was associated with shorter reaction times in a comparable Go–NoGo paradigm (Newman and Kosson, 1986; Newman et al., 1990). The cued CPT requires the anticipation of a motor reaction and a consecutive choice reaction to execute (Go) or to suppress (NoGo) the response. Beyond the behavioural parameters (reaction times and error rates; Cornblatt and Keilp, 1994), the test is also a suitable tool for the investigation of the functional brain correlates of response control, since the subsets of the task are ideal mutual control conditions.

There have been several attempts to characterize the brain substrates of CPT performance.
Studies with positron emission tomography (PET; Buchsbaum et al., 1990) and near-infrared spectroscopy (NIRS; Fallgatter and Strik, 1997) demonstrated activation of right frontal brain regions in healthy subjects. While methods like PET and NIRS allow assessment of the changes which occur during the entire period of the CPT, the distinct investigation of split-second activations as the basis of the choice reactions required by the test is not possible, due to acquisition times and to the inertia of the measured metabolic effects.

Electrophysiological methods, on the other hand, are capable of measuring both directly and in real time the changes of the brain electrical mass activity generated by very fast brain events. The time-locked brain electrical activity (event-related potential, ERP) elicited by the Go and NoGo signals of the cued CPT contains a pronounced P300 component in healthy controls (Schupp et al., 1994; Fallgatter et al., 1997). This widespread scalp potential with central-parietal positivity is related to cognitive processing and appears 300–400 ms after stimulus onset. In this and in other Go/NoGo tasks, the P300 component had higher amplitudes at the fronto-central electrode sites after the NoGo signal when compared to the Go condition (Pfefferbaum et al., 1985; Gevins et al., 1989; Jodo and Inoue, 1990; Schupp et al., 1994). A comprehensive spatial analysis of the P300 fields (Lehmann, 1987) demonstrated a more anterior location of the positive P300 field area during the NoGo subtask compared to the Go subtask in a cued CPT in healthy subjects (NoGo-anteriorization; Fallgatter et al., 1997). Though consistent with the waveform analyses, due to methodological interactions discussed elsewhere (Strik et al., 1994; Fallgatter et al., 1997), only this spatial analysis distinguished the Go from the NoGo ERPs at a single-case level. Additionally, a three-dimensional source analysis of NoGo-anteriorization showed a right frontal activation during the NoGo condition compared to the Go condition. This finding completed the PET and NIRS studies with the important chronological information that the frontal metabolic activation observed throughout the test is due to a phasic frontal activation time locked to the NoGo condition (Strik et al., 1998). The evidence indicates that NoGo anteriorization is a neurophysiological expression of inhibitory frontal lobe control on choice reactions. The parameter may, therefore, be hypothesized as a biological correlate of impulsivity at a behavioural level with its magnitude reflecting the subject’s functional frontal brain capacities for response suppression.

The aim of the present study was to investigate NoGo-anteriorization during the cued CPT in alcohol-dependent patients and its relationship with the Novelty Seeking score in the TCI.

MATERIALS AND METHODS

Subjects

Thirty patients fulfilling the DSM-IV criteria for severe alcohol dependence (303.90, American Psychiatric Association, 1992) were investigated. In each subject, the investigation took place on the 10th day of an in-patient detoxification programme. All of the patients were drug-free, completely detoxified, and without any co-morbidity. Twenty of the patients [four women and 16 men, mean age (±SD) 44.1 ± 9.1 (range 25–59) years] had 19 or more artefact-free ERP single sweeps after the Go and NoGo stimuli. For 17 of these 20 patients, the Novelty Seeking score of the German version of the TCI (Richter and Eisemann, 1995) was available.

Four female and 16 male age-matched healthy subjects with a mean age of 40.8 ± 11.1 years (range 25–60) were investigated as controls. None of the healthy subjects had a life-time or family history of alcohol dependence or other psychiatric disorders. All healthy and alcohol-dependent subjects were self-reported to be right-handed and none received psychotropic drugs.

Continuous performance test

The experiment took place in an electrically shielded and sound-proofed, dimly lit room. Subjects were seated in a relaxed position on a comfortable chair 120 cm in front of a computer screen with the chin resting on a padded support to minimize head movements. Subjects were instructed to focus on two thin vertical lines in the centre of the monitor to reduce eye movements.

A modified cued version of the CPT was applied (Fallgatter et al., 1997; van Leeuwen et al., 1998). Twelve different letters were presented
sequentially on the computer screen between the two vertical lines. There was no sequence of identical letters. Presentation time of each letter was 200 ms, the inter-stimulus interval was 1650 ms. The letters on the screen were 12 mm high and 11 mm wide, resulting in a visual angle of 1.15° horizontally and 1.05° vertically.

Subjects were instructed to pay attention whenever the letter O (primer) appeared on the screen and to push a response button with the index finger of their right hand as fast as possible whenever the letter O was followed by the letter X (Go condition). The remaining ten letters A, B, C, D, E, F, G, H, J, and L were either signals to suppress the prepared motor response when directly following an O (NoGo condition), or meaningless distractors when presented after another letter. Every subject performed a short training session to ensure correct understanding of the instructions. Speed and accuracy were emphasized equally during the explanation of the test. Each testing session took about 13 min and included the presentation of 400 stimuli of which 80 were primers (O, 20%); on 40 occasions the O was followed by an X (Go condition, 10%), and on 40 occasions by another letter (NoGo condition, 10%); 240 stimuli were distractors.

Electroencephalogram (EEG) recordings

A 21-channel EEG was recorded with electrode sites following the international 10/20-system, three additional electrodes were placed at the outer canthi of both eyes and below the right eye to record eye movements. The presentation of each stimulus was marked in a separate trigger channel. Recordings were made on a 32-channel DC-amplifier (Brain-star system) with data acquisition software (Neuroscan), calibrated with an external 100 μV/10 Hz signal. The hardware filter was set to a bandpass from 0.1-70 Hz, A/D rate was 256 Hz. Recording references were linked mastoids with compensating resistors of 10 kΩ each. All electrode impedances were below 5 kΩ.

Data analysis

EEG epochs with amplitude values exceeding 98 μV in any of the electrode channels or in one of the bipolar eye channels within the first 500 ms post stimulus were excluded from analysis. The artifact-free EEG epochs of each subject were averaged offline separately for the Go and NoGo conditions to obtain the respective ERPs. Thereafter, the spatial DC-offset was removed (average reference). The P300 latency was determined by the individual Global Field Power (GFP) peaks within the P300 microstate (278-434 ms) identified in a previous study (Fallgatter et al., 1997); the P300 parameters characterizing the field strength and the topography were calculated for this time point. In particular, the amplitude range was applied as a global estimator for the P300 field strength (Lehmann, 1987; Strik et al., 1994) and the centroids as topographical descriptors (Lehmann, 1987; Fallgatter et al., 1997). The centroids are amplitude-weighted locations of the positive and negative areas of the brain electrical field. These locations were quantified by a coordinate system resulting from the planar projection of the electrode array onto a rectangular grid where the electrode locations were coded by whole numbers from 1 to 5 in the left–right and anterior–posterior direction (Fig. 3). In this system, the Fz electrode position, for example, is quantified with 3 in the left–right and 2 in the anterior–posterior direction. The individual magnitude of the NoGo-anteriorization was expressed as the difference between the positive centroid locations in the anterior–posterior axis between Go and NoGo.

Statistical analysis

Latencies, amplitudes, and locations of the positive and negative centroids in the P300 segment were analysed with paired t-tests to compare the Go and NoGo conditions in alcoholics. For comparisons between alcoholics and healthy subjects, unpaired t-tests were applied. All reported P-levels were two-tailed. Spearman’s rank correlations were computed to examine the relationship between the Novelty Seeking scores of the TCI and NoGo-anteriorization in the alcoholic group.

RESULTS

In both groups, the error rate in the CPT was very low. On 40 decisions, patients averaged 0.7 (0–3) errors of omission (misses) and 1.2 (0–9) errors of commission (false alarms). The respective error rates in healthy subjects were 0.7 (0–6; t = 0.13, n.s.) errors of omission and 0.6 (0–2; t = 1.27, n.s.) errors of commission. Reaction
Table 1. Comparisons of the Go and NoGo conditions in the P300 segments of alcoholics and healthy controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alcoholics (d.f. = 19)</th>
<th>Controls (d.f. = 19)</th>
<th>t-value (d.f. = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go</td>
<td>357.0 ± 47.4</td>
<td>357.0 ± 40.0</td>
<td>0.00</td>
</tr>
<tr>
<td>NoGo</td>
<td>380 ± 29.0</td>
<td>384.0 ± 25.6</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>-2.04**</td>
<td>-3.15***</td>
<td></td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go</td>
<td>16.76 ± 4.49</td>
<td>19.08 ± 4.51</td>
<td>1.63</td>
</tr>
<tr>
<td>NoGo</td>
<td>20.33 ± 4.06</td>
<td>21.38 ± 5.59</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>-4.06***</td>
<td>-1.54</td>
<td></td>
</tr>
<tr>
<td>CX+</td>
<td>3.16 ± 0.26</td>
<td>3.16 ± 0.34</td>
<td>-0.06</td>
</tr>
<tr>
<td>CX-</td>
<td>3.19 ± 0.44</td>
<td>3.27 ± 0.31</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>-0.22</td>
<td>-1.43</td>
<td></td>
</tr>
<tr>
<td>CY+</td>
<td>2.93 ± 0.21</td>
<td>3.00 ± 0.34</td>
<td>0.86</td>
</tr>
<tr>
<td>CY-</td>
<td>2.98 ± 0.14</td>
<td>2.93 ± 0.19</td>
<td>-1.05</td>
</tr>
<tr>
<td></td>
<td>-1.01</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-6.69††</td>
<td>-5.69††</td>
<td></td>
</tr>
<tr>
<td>Go</td>
<td>4.04 ± 0.33</td>
<td>3.74 ± 0.52</td>
<td>-2.18*</td>
</tr>
<tr>
<td>NoGo</td>
<td>2.99 ± 0.34</td>
<td>3.03 ± 0.37</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>12.38§</td>
<td>7.56††</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. Paired two-tailed t-tests were made for Go and NoGo comparisons, whereas unpaired t-tests were used for comparisons between groups.

§ P < 0.0000000001; † P < 0.00001; †† P < 0.0001; ††† P < 0.001; ** P < 0.01; * P < 0.05; ° P < 0.10.

In patients, 1325 of 1600 single ERP sweeps (82.81%) were artefact-free. An average of 34.5 (range 19–40) of the Go and 31.8 (19–40) of the NoGo stimuli were included.

In accordance with a previous study (Fallgatter et al., 1997), the positive P300 centroids were located significantly more anterior in the NoGo, compared to the Go, condition in both healthy controls and alcohol-dependent patients (Table 1, Fig. 1). This parameter (i.e. NoGo-anteriorization) again distinguished the Go from the NoGo ERP in every subject (Fig. 2). In a between-groups comparison, the magnitude of NoGo-anteriorization, expressed as the difference between the Go and the NoGo locations in the anterior–posterior axis, was higher in alcoholics (1.06 ± 0.38) than in controls (0.72 ± 0.42, t = −2.67, P = 0.01). This was due to a more posterior location of the positive centroid in the Go condition in alcohol-dependent patients (Table 1, Fig. 3).

Alcohol-dependent patients achieved an average score of 19.5 ± 5.3 (12–29) on the Novelty Seeking dimension of the TCI, and NoGo-anteriorization correlated significantly and inversely with this personality parameter (r = −0.67, P < 0.01). To identify the pattern of the correlations with the sub-items of the dimension, an exploratory analysis was performed on the four Novelty Seeking sub-scales resulting in significant inverse correlations for Impulsiveness (r = −0.51, P < 0.05), Extravagance (r = −0.68, P < 0.01), and Disorderliness (r = 0.63, P < 0.01). No correlations were found for Exploratory Excitability (r = 0.15, n.s.).

**DISCUSSION**

The evoked brain electrical activity associated with the execution and the inhibition of a prepared motor response within a cued CPT was investigated in 20 alcohol-dependent patients and 20 healthy controls. The positive area of the P300 fields was located more anterior when associated with the inhibition, compared to the execution of a prepared motor response (NoGo-anteriorization). This result was present in every case in both patients and controls. It therefore represents an independent replication of a preceding study in 10 healthy subjects and further supports the proposal to introduce NoGo-anteriorization as a neurophysiological standard index for inhibitory brain activity (Fallgatter et al., 1997). Furthermore, the stability of the feature which distinguishes NoGo from Go ERPs at individual levels is an impressive validation of the descriptive reference-independent spatial analysis as a method of extracting physiologically meaningful parameters from multichannel recordings (Lehmann and Skrandies, 1980, 1984; Lehmann, 1987).

The cued CPT applied in this study had long presentation times and interstimulus intervals and was easy to perform for all subjects. As a result, both alcoholics and controls had very low error rates. This may be hypothesized as one reason for...
the very clear-cut neurophysiological results, since more difficult tasks which affect error rates and reaction times are supposed to overcharge the system capacities and, consequently, may lead to irregularities in neurophysiological responses.

In alcoholics, NoGo-anteriorization was less pronounced in subjects with higher scores in the Novelty Seeking dimension of the TCI (Cloninger et al., 1993). This was true also for the subscores Impulsiveness, Extravagance, and Disorderliness, which were significantly and inversely correlated with NoGo-anteriorization. These subscores are related to an uncontrolled urge for action. The factor Exploratory Excitability, however, does not imply uncontrolled activity and was not correlated with NoGo-anteriorization. In a previous three-dimensional source analysis of the multichannel recordings of a cued CPT, both Go and NoGo P300 components were explained by two main sources, one occipito-temporal and one frontal, both slightly lateralized to the right. The descriptive finding of NoGo-anteriorization was explained by a significantly higher right frontal lobe activity during the NoGo compared to the Go condition (Strik et al., 1998). This indicates that the location of the positive P300 area in the anterior-posterior direction is determined by the relative contribution of inhibitory frontal lobe activity. An intriguing interpretation of the findings is that frontal lobe control of execution/inhibition choice reactions is reduced in alcoholic subjects inclined to exhibit impulsive behaviour. This indicates NoGo-anteriorization as a potential neurobiological marker for the evaluation of the subject’s capacities of behavioural control which has been shown to be related to early-onset...
alcoholism (Cloninger et al., 1988) and to the risk of relapse (Meszaros et al., 1997).

The group comparison showed that NoGo-anteriorization was more pronounced in alcoholics than in controls. No conclusions can be drawn, however, about the differences between patients and controls with regard to inhibitory brain capacities. This effect was due to a significantly more posterior-positive centroid in the Go condition in patients than in controls (Table 1, Fig. 3).

Figure 2. Location of the positive P300 centroid in the Go and NoGo conditions on the anterior–posterior axis in individual alcoholic subjects.

Figure 3. Electrode grid for the location of the positive (posterior) and negative (anterior) P300 Go centroids. The shade of the rectangles describes the group (alcohol-dependent patients: black; healthy subjects: grey), whereas the size characterizes the respective standard error.

Based on a study indicating the location of the positive P300 area to be due to the inhibitory right frontal lobe contribution (Strik et al., 1998), it might cautiously be speculated that frontal lobe control was reduced in patients compared to controls in the Go condition.

In conclusion, NoGo-anteriorization was confirmed to represent a very robust and physiologically meaningful index of the brain's inhibitory capacity in response control. Its inverse correlations with the Novelty Seeking scale of the TCI in alcohol-dependent patients supports its utility as a neurobiological correlate of behavioural dimensions. Future studies will further clarify the relations between NoGo-anteriorization and impulsive behaviour and its validity in the clinical evaluation of alcoholic patients.

REFERENCES


