Research Article

Using Cognitive Event-Related Potentials in the Management of Alcohol Use Disorder: Towards an Individual Approach

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Abstract

Objective: Alcohol use disorder (AUD) is associated with important cognitive impairments. These deficits play a significant role in the maintenance of consumption, despite the negative effect that it has on the daily life of alcohol addicts. The main objective of this case report is to illustrate how cognitive event-related potentials (ERPs) can be an adjuvant tool to propose an individualized and effective management of this disorder.

Method: Three patients worried about their alcohol consumption were evaluated in a Go-NoGo task during an electroencephalographic recording. The peak amplitude of the NoGo N200, NoGo P300 and ERN evoked response were confronted to behavioral scores as well as to a clinical assessment.

Results: ERPs allowed to distinguish between two types of cognitive deficits associated with alcohol consumption and treatment seeking. This was not possible when investigating only the behavioral and clinical scores which merely allowed to differentiate patients with AUD from the ones without AUD.

Conclusion: Cognitive ERPs are biomarkers of great relevance in the management of AUD by identifying altered cognitive processes that are not observable at the single behavioral level.

Significance: Further longitudinal studies should be designed in order to investigate the effect of an individualized cognitive retraining program, based on the observed cognitive alterations as well as on the relapse' rate of these individual patients.

Introduction

This case report aims at investigating how cognitive Event-Related Potentials (ERPs) can be used in clinical practice in order to refine the diagnosis, prognostic and care proposed to patients suffering from Alcohol Use Disorder (AUD). To date, despite a significant amount of ERP research which has tried to provide a better understanding of alcohol abuse, ERPs still need to be implemented in the clinical management of AUD [1]. Indeed, besides technical difficulties [2], the main reason why ERPs are still absent in clinical practice is that most of these ERPs studies mainly focused on the evaluation of "grand-average data" rather than on the evaluation of

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"individual parameters". Yet, this step is necessary for a meaningful utilization of these data in clinical practice [3]. Through this paper, we would like to highlight how individual ERPs data could instruct us more about cognitive efficiency and therefore provide a better management of AUD patients from a clinical perspective. AUD remains a major public health concern, with 283 billion people suffering from excessive consumption problem worldwide [4], a relapse rate which remains high (around 80% of relapse within one year of treatment [5]), and a delay of approximately one to four years after the onset of AUD for people to receive treatment (i.e., the treatment gap), because of the strong resistance and the frequent denial of their conditions [6]. Altogether, we state that it is crucial to reinforce prevention (an earlier and more sensible detection) and care for AUD. To reduce the treatment gap, the Brugmann's hospital (Brussel, Belgium) has developed an innovative project in which a thorough evaluation is proposed to people worried about their alcohol consumption. The main objective of this program is to strengthen the insights into their disorder and to help patients to have a better understanding of their medical conditions. During two days, the participants notably undergo a clinical and an electrophysiological evaluation. The clinical evaluation comprised some important medical parameters (blood test, Fibroscan®, liver echography, dietetic evaluation) as well as a clinical psychological interview and classical questionnaires (described below).

The electrophysiological screening comprised an EEG recording during a Go-Nogo task (described below). In this paper, we will focus on the electrophysiological evaluation which is aimed at assessing the integrity of the main cognitive functions known to be altered by AUD: the inhibition and the monitoring of actions. As a matter of fact, it is now well agreed that substance use disorders are associated with dysfunction of cognitive processes [7]. According to the Dual Process Model theory, addicted patients present a default in the balance between a strengthened automatic system of impulsive habits (rewarding system) and a weakened executive processes system (goal-directed behavior) [8]. On the one hand, we observe an abnormal bottom-up system generating a "craving" response (attentional biases towards alcohol cues). On the other hand, we find a weakened top-down process (cognitive control processes allowing goal-directed behavior) [9] that is currently observed among AUD studies (medium effect size) [10]. This leads to a vicious circle [11]: cognitive control processes, such as inhibitory control or error processing, are impacted in AUD by alcohol-related urges known as craving, and conversely, weakened top-down processes do not allow a sufficient control of impulsive behaviors related to craving. These altered processes are therefore described as good indicator and predictors of substance use disorders (SUD) treatment outcomes [10].

Among the methods used to evaluate these cognitive processes, ERPs stand out compared to classical clinical approaches, as ERPs are known as valuable endophenotypic markers of greater sensitivity and sensibility. Indeed, their ability to reflect post synaptic released neurotransmitters (like GABA [12], Glutamate [13]) and neuromodulators (Acetylcholine [14], Dopamine [15]) plays a significant role in cortical functions altered by addictive substances [16]. Moreover, as successful inhibition processes and error monitoring produce little or no observable behavior, ERPs are of great interest to understand the internal processes [17]. During a cognitive task, the time-locked electro-encephalographic signals to specific events, giving us access to these ERPs which are consequently considered as brain's response to the stimuli. Those ERPs inform us about the different stages of information processing, allowing us to achieve specific performances [18]. This way, they allow us to identify the "onset" of a dysfunction, and then to infer the impaired cognitive stages. Thus, the analyses of different ERPs can provide information regarding the functional impairments associated with excessive alcohol consumption, even for minor neurocognitive dysfunctions (e.g. when behavioral impairments are still not detected [19]). This way, they are good indicators of dysfunctional cognitive processes which are not accessible to the classical clinical approach [3] and can be considered, therefore, as interesting first line tools for the differential diagnosis, the monitoring of treatment and the therapeutic course' evaluation of psychiatric disorders [20]. A limit to the use of ERPs is the lack of specificity that represents the evaluation of one single component. Indeed, a similar electrophysiological pattern of alteration can be found in various forms of mental disorders. It is consequently recommended to use ERPs in a different way. By taking into consideration several ERPs, we can reveal specific and individualized electrophysiological profiles reflecting the disturbed cognitive functions. This will also, ultimately, increase the specificity of the assessment and allow the prediction of a clinical trajectory of individual patients [3,21].

The Go-NoGo task is commonly used to measure inhibitory control. This task has the advantage of eliciting three major components: the N2d and P3d (observed on NoGo minus Go Wave) which reflect the inhibitory control processes [22,23] and the Error-Related Negativity (ERN) reflecting the error processing [24]. The N2d is a negative going wave emerging 200-300 ms after the onset of a stimulus. This component is mainly generated by the anterior cingulate cortex (ACC) and refers to the conflict monitoring processes and the cognitive parts of inhibition [25]. The following P3d, is a positive wave that peaks 300-600 ms after the presentation of a stimulus. This component is subtended by the inferior frontal gyrus (IFG) and the supplementary motor area and reflects the motor aspect of inhibition [26]. Although, the inhibitory N2-P3 complex has been predominantly studied in clinical trials [27-30], a third component deserves our attention in the

field of AUD: the ERN. This component presents a negative deflection following an erroneous response after 50-150 ms an erroneous and is subtended by the ACC. It reflects early error detection processing [31], and it has been reported to be impacted by excessive alcohol consumption [32]. Excessive alcohol intake can affect these electrophysiological components in two different ways. Firstly, altered inhibitory skills can be associated with a poor performance associated with a decrease in neural activation indexed by decreased amplitude. This effect is supported by evidence of a dysfunction in inhibition-related receptor like GABA that, by affecting the level of neural excitability, enhances the risk of developing alcohol dependence [33]. Secondly, it is also possible to find a preserved performance associated with an enhanced amplitude in heavy drinkers reflecting a compensatory neurofunctional mechanism allowing drinkers to inhibit responses similarly to control subjects, despite latent cognitive impairments [22,34,35]. These subjects seem to still be able to activate the inhibitory system, but this is more demanding in terms of cognitive resources allocated to do so. The identification of these two types of alteration is important because it informs us about the objective that must be reached by cognitive retraining programs (CRP): allowing the patient to allocate more resources to realize this cognitive function or decreasing the amount of cognitive resources needed to perform the task adequately [36,37]. This could also be a potential explanation as to why some treatments work for some patients but don't for others, in a perspective of stratified psychiatry [38]. For example, in a recent follow-up study involving AUD inpatients, researchers found that a preserved ERN at the onset of a detoxification program seems to be a protective factor against relapse one month after the cure. In other words, it seems that AUD patients with distorted metacognitive processes are more likely to quickly relapse (and even if they recover an intact ERN at the end of the detoxification program). This is suggesting that, as a consequence of their inability to benefit from "insight metacognitive properties", they show a high risk of relapse. Therefore, other cognitive processes, such as cue reactivity or inhibitory [39,40] skills, should be rehabilitated through neurocognitive programs to reduce this risk of relapse [23].

The aim of the present study is to explore the way ERPs can be used in such a clinical perspective. Supporting the idea that an added value can be found in the use of ERPs in psychiatric care, how could such ERPs data be relevant at a clinical and individual level? Our main hypothesis is that relevant ERPs data can help to identify cognitive vulnerabilities and the appropriate neurocognitive program, predict the risk of relapse of specific patients, evaluate the treatment outcomes and follow up psychiatric disabilities. Obviously, such ERPs data should be complementary add-on tools to individual psychological, social and pharmacological care.

Materials and Methods

Participants

In this case report, we compare three patients presenting different type of alcohol consumption. These patients were matched for gender (female), age (55 years ±9 years), educational level (master's degree) and history of detoxification cure (none). Each of these three patients has been seen in the context of the "Alcool et vous" ("You and Alcohol") outpatient module, which is designed for subjects displaying hazardous drinking behavior and wishing to reduce their alcohol consumption. During this program, a physical evaluation including blood testing, fibroscan®, and liver echography is carried out, and no significant differences were observed between our 3 patients. In the present paper, we focus on the psychological evaluation including an electroencephalogram (EEG) and a clinical assessment (psychological interview and some questionnaires). *The Alcohol Use Disorder Identification Test (AUDIT [41])* is a self-reported 10 items assessment of alcohol related behavior that maps out the problems of harmful alcohol consumption (items 1 to 3), drinking behavior (items 4 to 6), adverse reactions to alcohol (items 7 to 8), and alcohol-related problems (items 9 to 10). The score on items 1 to 8 can range from 0 to 4, and that on items 9 to 10 can be 0, 2 or 4). Subjects with a score between 8 to 12 are considered as having a hazardous to harmful alcohol consumption, while a score of 13 to 40 indicates a likely alcohol dependence [42]. *The Beck Depression Inventory (BDI-II [43])* is a self-reported 21 items assessment of depression symptoms and severity. The items are rated from 0 (not at all) to 3 (extreme form) for each symptom. A score above 13 is indicative of depression (14 to 19 = mild depression; 20 to 28 = moderate depression; 29 to 63 = severe depression) [44]. *The Spielberger State and Trait Anxiety Inventory (STAI [45])* is a self-reported 20 items assessment of the general propensity to be anxious. The items are rated from 1 (almost never) to 4 (almost always). A score above 40 is considered high [46]. *The UPPS-c impulsive behavior scale [47]* is a short version of the UPPS scale that includes 20 items. Normative data are, to our knowledge, not available but a higher score is indicative of a higher level of impulsivity. *The Obsessive Compulsive Drinking Scale (OCDS [48])* is self-reported 14 items scale that measures various aspects of craving for alcohol. A score of 7 and higher discriminates alcohol-dependent patients from social drinkers. Furthermore, a score from 7 to 15 is representative of non-treatment seeking alcoholics, a score from 15 to 20 is representative of treatment seeking patients and a score from 20 to 25 is representative of inpatient alcoholics [48]. The patients signed an informed consent allowing us to follow up their clinical situation. The local ethics committee of Brugmann Hospital ("Comité d'Ethique Hospitalière CE2014/73) provided its approval for this study.

ERPs Task and Procedure

During the ERPs Go/Nogo, the patients were seated in a darkened room on a comfortable chair. The person who instructed the patients and managed the recording was alongside the patient during the complete registration procedure. Patients were seated at one meter from a screen, on which was centrally displayed the letter M ("Go" trials; button click with the right forefinger, as quickly and accurate as possible) and the letter W ("No-go" trial; no button click required). A block, repeated twice, comprised 133 letters displayed in a semi-random order to avoid the consecutive presentation of 2 "No-go" trials and was divided into 93 "Go" (70%) and 40 "No-go" (30%) letters. Each block started with the presentation of a background screen (for 500 ms), and the letters M or W (Arial yellow capital letters; 500x400 mm in size) were the displayed on this background for 200 ms, followed by a return to the initial background display (for 1300 ms). Thus, the participant had a maximum of 1500 ms to press the button before the next letter was displayed. Characteristics of stimuli presentation are presented in figure 1. This task was consistently used in our laboratory: more details can be found in these papers [49,29,36].

EEG Recording and Analysis

Electroencephalograms (EEG) were recorded by 21 electrodes fixed in an electrode Quick-cap with a linked mastoid physical reference (M1, M2). The electrode positions included the standards 10 to 20 system location (Fpz, Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T7, T8, P3, Pz, P4, P7, P8, O1, Oz, O2). The amplification of the EEG was realized by a battery-operated A.N.T. ® amplifier with a gain of 30,000 and a band-pass of 0.01-100 Hz. The ground electrode (AFz) was positioned between FPz and Fz along the midline. The impedance of the electrodes was maintained below 10kΩ during the experiments. The recording of the EEG was continuously at a sampling rate of 256 Hz with A.N.T. ® Cognitrace software. A cutoff of 30 mV was used to define trials that were contaminated either by eye movement or muscular artifacts, which were cut out offline in order to only analyze the artifact-free trials. Once acquired, a band-pass filter 0.3 to 30 Hz was applied. To generate the "Go" and "No-go" ERPs components, a stimulus-locked epochs of 1000 ms (200 ms before and 800 ms after the stimulus onset) were created with a baseline of -200 to 0 ms. Incorrect response (i.e., missed hit for "Go", or a hit for "Nogo") were excluded from further analysis. Specific "inhibitory No-go effect" tagging inhibitory control skills were obtained by computing the difference "No-go minus Go" wave form giving rise to the No-go N2d and the No-go P3d (d for difference) waves [36,37,50,51]. As ERPs latencies provide information about the processing speed, the individual latency has been quantified, according to the peak latency method [52]. The time after the stimulus onset at which the peak reaches the maximum negative amplitude for the N2d (within the 150- to 300- ms) and then the maximum positive amplitude for the P3d component (within the 300- to 500- ms), were identified in a cluster of classical frontal and
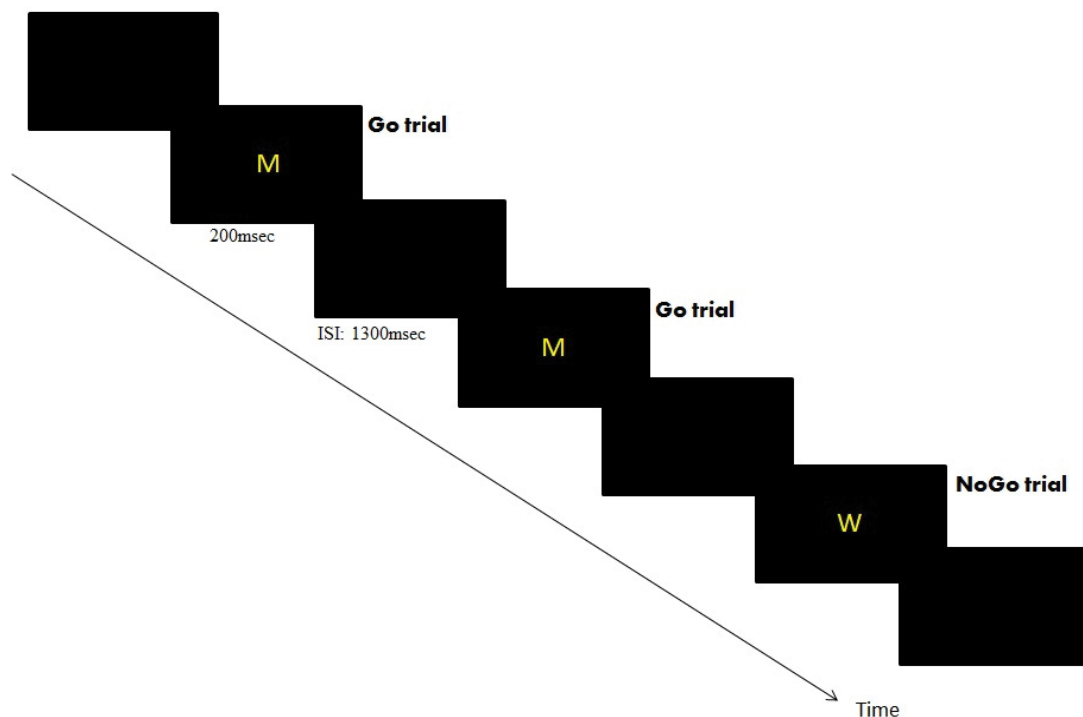

Figure 1: Illustration of the Go-NoGo task.

central electrode (Fz, F3, F4 and Cz). As ERPs amplitudes provide information concerning the intensity of processing, the individual amplitude has been recorded at the first maximal amplitude value observable on the classical frontal and central electrode (Fz, F3, F4 and Cz) [36, 37]. To generate the "ERN" and "CRN" waveform, response-locked epochs of 700 ms (200 ms before and 500 ms after the response onset) were created. Only trials related to correct hits for targets and hits for non-targets (commission errors) were included in these averages. The types of response (key press for targets, key press for non-targets) were coded differently in order to compute different averages of ERP: (1) the ERN produced in association to key press on non-targets (= errors); and (2) the correct-related negativity (CRN) produced in association to correct key press on targets. The averages were computed for each patient individually. The process of error detection, tagging the difference in conflict between correct and error trials, was obtained by computing the difference "ERN-CRN" waveform giving rise to the $\Delta ERN_{substract}$ waveform [24,53]. As the ERP's latency and amplitude provides information about the processing speed and the intensity of processing respectively, the individual latency and amplitude have been quantified according to the peak latency method (within the range of 0 to 100 ms) for the ERN, CRN and $\Delta ERN_{substract}$. This time window has been chosen regarding the recommendations established in previous research [53,54].

Results

Clinical Data

Here we report the clinical data of the three patients concerning (1) the history of alcohol consumption and, (2) the scores on the clinical questionnaires.

Patient K.C: K.C is 53-year-old woman. She has been drinking alcohol since she is twelve years old. She came to the program because she reported experienced what she called "a loss of control" since one year ago. Indeed, since that time, she reports "not being able to experience any period of abstinence". She has never been in treatment for her alcohol consumption before. Concerning her scores on the different scales, we observe a result of 13 on the AUDIT, indicating a heavy consumption [41,42]; a score of 13 on the BDI-II which is indicative of a mild depression [43,44]; a score of 65 on the STAI-state which revealed a high level of anxiety [45,46]; a total score of 45 on the UPPS-c; a score of 10 on the OCDS scale, indicating a moderate concern about alcohol (infrequent thought but frequent craving) [48]. She consumes five units of alcohol per day. On this basis, patient K.C. is the participant with the least risky alcohol consumption in the present paper.

Patient S.V: S.V. is a 47-year-old woman. She has been drinking alcohol since the age of 16. She reports a loss of control that occurred a few years ago and she drinks

approximately 14 units of alcohol per day. She has not been able to experience any period of abstinence for 2 years. At the time of the assessment, she had never received a treatment for her alcohol consumption, but we know that she entered in a three-week detoxication cure 9 months later. Concerning her scores on the different scales, we observe a result of 34 on the AUDIT, which is indicative of a high risk of alcohol dependence [41,42]; a score of 13 on the BDI-II which is indicative of a mild depression [43,44]; a score of 71 on the STAI-state scale, indicating a high level of anxiety [45,46]; a total score of 42 on the UPPS-c and a score of 25 on the OCDS scale, indicating persistent thoughts about alcohol and frequent craving [48].

Patient R.M: R.M. is a 65-year-old woman who drinks alcohol since the age of 4. She reports a loss of control that occurred at the age of 18. Since that time, she has been able to experience only three months of complete abstinence. She is treated by a psychiatrist as outpatient and has an anti-craving medication composed of Campral® (333 mg) three times a day and Solian® two times a day. But she has never been in detoxification cure for her alcohol consumption. She currently drinks 8 units of alcohol per day. Concerning her scores on the different scales, the patient scored 26 on the AUDIT scale which is indicative of a high risk of alcohol dependence [41,42]; a score of 8 on the BDI-II, indicating mild depression [43,44]; a score of 48 on the STAI-state scale, indicating a moderate anxiety [45,46]; a total score of 46 on the UPPS-c and a score of 15 on the OCDS scale indicating moderate concern towards alcohol but frequent craving [48]. At this stage, from a clinical point of view, these 3 patients present very similar clinical characteristics (same level of depression, anxiety, education (master's degree), no previous detoxification cure). They only differ as regards their alcohol consumption and pharmacological treatment. Patient K.C. has a less problematic intake than the two others, who both present a different hazardous consumption pattern. Indeed, Patient S.V. has a more recent but intense loss of control than Patient R.M. who has a long history of drinking problems. Please refer to table 1 for a more global overview of the clinical data.

Behavioral Data

Here we report behavioral data of the three patients, concerning (1) performance: omissions (missing response for Go trials), commissions errors (false alarms for NoGo trials); and (2) reactions times (click on Go trials).

Patient K.C: She omitted no answers (0 omission errors for Go trials) and committed only 2 errors (2 commission errors). She had a reaction time of 424 ms.

Patient S.V. vs KC: Like patient K.C., Patient S.V. omitted no answers, but she committed much more errors (17 commission errors) showing difficulties in inhibition. She

was also faster to respond (357 ms) attesting of a pre-potency for the dominant response.

Patient R.M. vs KC: Compared to patient K.C., patient R.M. omitted more responses (2 omission errors) and committed also more errors (12 commission errors), showing difficulties in inhibition of the dominant response. She was also the slowest (661 ms).

Patient S.V. vs R.M: Compared to patient S.V., patient R.M omitted more responses but committed less errors. This can be explained by the slower reaction times observed for patient R.M. which is suggesting some behavioral compensatory mechanism aiming at facilitating the task. Overall, from a behavioral point of view, we observe that the two patients with the most problematic alcohol consumption are also those who present more inhibition errors. Patient R.M., presenting a consumption period of 47 years, presents a lengthening compared to the 2 other patients. Interestingly, the lengthening of the reaction time does not permit her to inhibit more efficiently the automated response, suggesting an altered inhibitory process. Such data are important, because it allows us to distinguish between the two patients with inhibition difficulties (S.V. and R.M.) and the patient without (K.C.). Please, refer to table 2 for a larger overview of the behavioral data. The next section will help us to check whether using ERPs may add clinically relevant aspects to the care of these patients.

ERPs Data

In this section, we will verify whether the evaluation of the N2d, P3d and ERN components can add complementary information to the clinical and behavioral data analysis allowing us a conclusion which can have an impact on the further treatment procedure for the patient(s).

Patient K.C: Concerning the N2d component, patient K.C. shows a peak of -2,2 µV amplitude which appears at a latency of 329 ms. Then, concerning the P3d component, she shows a peak of 3,2 V amplitude which appears at a latency of 500 ms. Finally, the $\Delta ERN_{substract}$ could not be achieved due to the low rate of errors committed by the patient. We thus dispose of any information concerning her metacognitive processes.

Patient S.V. vs KC: The N2d amplitude of Patient S.V. appears slightly reduced compared to the one of Patient K.C. suggesting that she allocates less cognitive resources for the cognitive part of inhibition. Conversely, the P3d component appears higher (5,3 µV) suggesting that a larger amount of cognitive resources is needed to perform the task. We thus observed a compensation at the level of the

Table 1: Clinical Data. Abbreviations: AUDIT- Alcohol Use Disorders Identification Test; BDI-II- Beck depression Inventory; STAI- State and Trait Anxiety Inventory; UPPS- Urgence Premeditation Perseverance Sensation seeking impulsivity scale; OCDS- Obsessive Compulsive Drinking Scale.

	Patient K.C.	**Patient S.V.**	**Patient R.M.**
Age	53 year-old	47 year- old	65 year-old
Educational level	Master degree	Master degree	Master degree
1st consumption	12 years old	16 years old	4 years old
Onset of the problem	1 year ago	Few years	From 18 years old
Unit of Alcohol / day	5	14	8
Detoxification Cure	0	1	0
AUDIT	13	34	26
BDI-II	13	13	8
STAI-state	65	71	48
UPPS-c tot	45	42	46
OCDS	10	25	15

Table 2: Behavioral data concerning the reaction time, the rate of correct response for Go Trials and the rate of commission errors (response for NoGo trials).

	Patient K.C.	**Patient S.V.**	**Patient R.M.**
Reaction Time	424 ms	357 ms	661 ms
Correct Response	186/186	186/186	184/186
Commission Error	Feb-80	17/80	Dec-80

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motor (part of) inhibition which is not sufficient regarding the patient's behavioral performances. The latencies of these components are very close to those observed with Patient K.C. The $\Delta ERN_{substract}$ could be achieved for patient S.V. Since the $\Delta ERN_{substract}$ could not be recorded in patient K.C., a comparison is not possible. We will therefore compare it, in the next section, with the one observed for the patient R.M.

Patient R.M. vs K.C: In the same way as for Patient S.V., we observed, for patient R.M., a reduction in the amplitude for the N2d component compared to the one observed for patient K.C. But in contrast, the amplitude of the P3d components appeared to be reduced compared to the one detected for patient K.C., suggesting that patient R.M. does not allocate more cognitive resources to the motor part of the inhibition to compensate a weakened cognitive part of inhibition processes. We also observed a delayed N2d

and P3d latency which seems to mirror the behavioral data and provides a certain facilitation in the task achievement. However, this compensatory mechanism is again not sufficient to compensate the initial cognitive impairments. Concerning the $\Delta ERN_{substract}$, we observe a smaller amplitude for this patient comparing to patient S.V., suggesting reduced metacognitive abilities.

Patient S.V. vs R.M: Patient S.V shows faster a reaction time compared to patient R.M. and much a more reduced amplitude for the N2d and P3d components. This is suggesting that Patient R.M. is not able to allocate enough cognitive resources to the cognitive and motor part of inhibition even when using a compensatory mechanism such as slowing down the reaction times (please refer to Figure 2 for more details).

	Patient K.C.	Patient S.V.	Patient R.M.
N2d Latency	329 ms	330 ms	385 ms
N2d Amplitude	-2,2µV	-1,62µV	-1,24µV
P3d Latency	500 ms	495 ms	540 ms
P3d Amplitude	3,2 µV	5,3 µV	2,5 µV

	Patient K.C.	Patient S.V.	Patient R.M.
$\Delta ERN_{substract}$ Latency		74 ms	55 ms
$\Delta ERN_{substract}$ Amplitude		-8,5 µV	-2,4 µV

Figure 2: Grand averaged event-related potential waveforms obtained on Fz (as the best signal quality illustration) for the three patients during the Go/NoGo task for (A) the Go, NoGo and NoGo minus Go and (2) the $\Delta ERN_{substract}$.

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Discussion

The first aim of this study was to explore the way ERPs can inform us about the cognitive state of a patient presenting a risky alcohol consumption. Therefore, we have evaluated three patients presenting a problematic alcohol consumption and who underwent two days in the "Alcool et vous" program of the CHU Brugmann. They were matched for their age, gender and educational level and were selected based on their different patterns of alcohol consumption. The first main result is that the behavioral scores allow us only to distinguish the patients with inhibition difficulties from the one who had no inhibition difficulties. Indeed, compared to patient K.C., patient S.V. and patient R.M. show a higher rate of commission errors. But only the ERPs allow to distinguish different subgroups among the patients and which kind of support would be the most beneficial for them. This constatation is in line with previous research attesting that ERPs are a useful tool to detect neural vulnerabilities reflecting latent inhibitory restrictions, even in the absence of significant behavioral modifications. These modifications can influence the clinical trajectory and guide the care [29]. To highlight these modifications, we focused on two components that have been predominantly studied and which are indicative of alterations of the inhibitory processes, the N2d and P3d [31-34], as well as the ERN which is showing some promises as vulnerability factor for risky behavior (substance abuse) [40] and to influence clinical trajectory [24]. Specific behavioral and electrophysiological alterations can be observed in the two patients with excessive alcohol consumption attesting to their inhibition difficulties. Indeed, the more important rate of commission errors observed in S.V. and R.M., is accompanied by different kind of electrophysiological modification. First, S.V. and R.M. are presenting a decreased N2d amplitude compared to K.C., which indicates an absence of the "NoGo N2 effect". Indeed, while the Patient K.C. showed a larger N2d amplitude compared to Go N2, patients S.V. and R.M. didn't show this effect or a reduced version of this effect [32]. Since the N2d is derived from the subtraction of the "NoGo Curve minus Go curve", it directly reflects the "NoGo N2 effect". This indicates a lower activation when it comes to detecting response conflict and recognizing the need for inhibition. As a result, they need to engage more cognitive resources to complete the inhibition task, as recorded by a higher P3d amplitude [35,51]. It is at this level that we were able to observe a difference between the Patient S.V. and R.M. Patient S.V. presents, as expected, an enhanced amplitude of the P3d, reflecting a compensatory effect of the impaired detection of inhibitory need and inhibition preparation. She needs to engage more cognitive resources to inhibit a prepotent response. Despite this compensation, she presents a higher rate of commission errors compared to the Patient K.C. Furthermore, her relatively fast reaction time is also indicative of a prepotency to the dominant response. The inhibition difficulties are therefore also caused by a priming of the motor system compared to the executive one, which makes any withholding attempts even more difficult [55].

In contrast, we do not observe this compensatory effect for the Patient R.M., recorded by the lowest P3d amplitude. Accordingly, we understand that this patient also presents an impaired conflict detection and inhibition preparation, but in contrast to Patient S.V., she is no more able to allocate more cognitive resource in the motor aspect of inhibition. Hence, this patient extends her reaction time in order to reduce the difficulty of the task, and despite this, she maintains a higher number of commission errors and also omits to respond, sometimes, when necessary. This could be explained by the neurotoxic effects of her long-term alcohol consumption on the central nervous system, such as brain atrophy and/ or dysfunction that are correlated with the lifetime dose of ethanol consumed [56,57] or by her current anti-craving medication. However, the impact of these anti-craving drugs on the ERP components had not yet been demonstrated to our knowledge. Further studies should investigate the effect of these treatments on the electrophysiological components in order to promote the use of ERPs as biomarkers of treatment efficiency or to guide practitioners towards the more efficient pharmacological treatment. Now focusing on the ERN, we observe that our results are consistent with those found by Claus and colleagues [55]. Patient R.M. who has been consuming alcohol for a longer period of time, and thus exhibits a more severe alcohol consumption, seems to invest less resources in the detection of committed errors compared to the patient S.V., who has been consuming alcohol for a shorter period of time. This could be explained by the neurotoxic effect of a long-term alcohol consumption on the anterior cingulate cortex [45] and could be interpreted as a lower error-monitoring skills. This ultimately leads to the inability to adjust behavior after an error has been committed. In a more clinical and ecological perspective, we can thus imagine that patients with a reduced ability to adjust behavior, will be less likely to seek treatment to diminish their alcohol consumption.

To our knowledge, no study has yet investigated the way in which diminished error-monitoring skills can influence the treatment seeking in AUD. This is however of greater interest as we already know that alcohol-dependent patients who, at the beginning of their detoxification program, did not show a preserved ERN component are also at high risk of relapse [24]. A lack of error monitoring skills could be an additional factor for explaining the delay to start with a detoxification program in addition to the high rate of relapse as it is an indicator of risky behavior (substance abuse) [54]. It also reinforces the belief that an earlier detoxification program is a perquisite for reducing the relapse rate, since a better metacognitive property will help patients to take more benefit from the proposed clinical care. Accordingly, a neurocognitive

program tagging these altered cognitive processes could also be proposed to patients presenting cognitive alterations due to their long-term alcohol consumption [25,58-61].

Conclusion

In conclusion, the presented cases support the aim of a rational use of event-related potentials in a clinical perspective, not as a diagnostic tool, but as a relevant indicator of cognitive vulnerabilities. The principle behind this is that within a single nosological entity, there exists different subgroups of patients presenting different patterns of cognitive difficulties that may influence the maintenance of AUD. The identification of these difficulties and of cognitive alterations as biomarkers is crucial in a perspective of stratified psychiatry [33]. This case report seems to indicate that ERPs can deliver an important support regarding their ability to (1) inform us about individual cognitive deficits even when no behavioral difficulties are visible; (2) investigate the complete stream of information processing (e.g. N2d, P3d, ERN) in order to determine the stages that need to be trained in a specific cognitive function (here, inhibition); (3) follow the individual characteristics of a patient in order to evaluate the benefits of the proposed care or the evolution of a specific disease; (4) predict the relapse risk of one patient in order to orient him/her towards social supports or neurocognitive programs well-known to trigger relapse [38,47,48].

In addition, (in this case report) we were able to distinguish, thanks to ERPs, two different patterns of cognitive alterations in patients presenting similar clinical characteristics. These patterns of deficits were mostly linked with a history of consumption and metacognitive abilities. Indeed, longer alcohol consumption causes greater cognitive impairments, which manifest themselves sat the electrophysiological level by an inability to recruit more cognitive resources. Moreover, better metacognitive abilities appear as a protective factor leading the subject who is facing difficulties to take steps to receive the support that s/he needs. Taking all this into consideration and given the cognitive alterations that can be observed by the discussed ERPs, different kinds of rehabilitation programs seem to be necessary in order to reduce the risk of relapse. A longitudinal study concept following patients from a first electrophysiological evaluation towards an individualized cognitive retraining program, followed by second evaluation at the end of the detoxification program and finally a follow up procedure attesting of the relapse state, should be of great relevance for future research and open further perspectives. In addition, such a study should allow us to replicate the first results presented in this case report. These single subject data should also be completed and validated by a group study of patients presenting similar and different cognitive impairments within the same AUD condition.

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