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ORIGINAL ARTICLE / ARTICLE ORIGINAL

Chronic alcoholism: Insights from neurophysiology

Alcoolisme chronique et apports de la neurophysiologie

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Summary
Introduction. — Increasing knowledge of the anatomical structures and cellular processes underlying psychiatric disorders may help bridge the gap between clinical signs and basic physiological processes. Accordingly, considerable insight has been gained in recent years into a common psychiatric condition, i.e., chronic alcoholism.
Material and methods. — We reviewed various physiological parameters that are altered in chronic alcoholic patients compared to healthy individuals — continuous electroencephalogram, oculomotor measures, cognitive event-related potentials and event-related oscillations — to identify links between these physiological parameters, altered cognitive processes and specific clinical symptoms.
Results. — Alcoholic patients display: (1) high beta and theta power in the resting electroencephalogram, suggesting hyperarousal of their central nervous system; (2) abnormalities in smooth pursuit eye movements, in saccadic inhibition during antisaccade tasks, and in prepulse inhibition, suggesting disturbed attention modulation and abnormal patterns of prefrontal activation that may stem from the same prefrontal ''inhibitory'' cortical dysfunction; (3) decreased amplitude for cognitive event-related potentials situated along the continuum of information-processing, suggesting that alcoholism is associated with neurophysiological deficits at the level of the sensory cortex and not only disturbances involving associative cortices and limbic structures; and (4) decreased theta, gamma and delta oscillations, suggesting cognitive disinhibition at a functional level.
Discussion. — The heterogeneity of alcoholic disorders in terms of symptomatology, course and outcome is the result of various pathophysiological processes that physiological parameters

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may help to define. These alterations may be related to precise cognitive processes that could be easily monitored neurophysiologically in order to create more homogeneous subgroups of alcoholic individuals.

MOTS CLÉS
Neuropsychiatrie cognitive ;
EEG ;
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EROs ;
Alcoolisme

Résumé
Introduction. — L'étude des bases anatomiques et cellulaires des maladies psychiatriques a pour objectif principal une meilleure connaissance des liens unissant les symptômes cliniques présents dans une affection psychiatrique et leur traduction au niveau cérébral. Des avancées considérables ont été réalisées dans ce domaine pour l'alcoolisme.
Matériel and méthodes. — Quatre paramètres neurophysiologiques déficitaires dans l'alcoolisme seront revus et reliés à des mécanismes cognitifs précis afin d'en arriver à une meilleure compréhension des symptômes cliniques présentés par ces patients.
Résultats. — Les alcooliques présentent : (1) une hyperactivité bêta et thêta dans leur tracé électroencéphalographique de base, suggérant une hyperexcitabilité de leur système nerveux central ; (2) des troubles des mouvements de poursuite et de saccades oculaires, pouvant être expliqués par un dysfonctionnement inhibiteur préfrontal, ainsi qu'une réaction d'alerte altérée suggérant un déficit attentionnel également lié à un déficit préfrontal ; (3) des réponses évoquées altérées en amplitude et en latence tout au long du traitement de l'information, mettant en évidence des déficits présents dès les étapes sensorielles du continuum cognitif ; et (4) des réponses oscillatoires bêta, delta et gamma déficitaires, suggérant au niveau fonctionnel des mécanismes inhibiteurs altérés.
Discussion. — Nous disposons d'outils neurophysiologiques simples nous permettant d'évaluer diverses fonctions cognitives précises. La mise en relation de ces processus cognitifs altérés et des symptômes cliniques auxquels ils donnent lieu peut nous amener à la création de sous-groupes de patients alcooliques, dont l'homogénéité au niveau des troubles cognitifs et neurophysiologiques présentés pourrait amener à une optimisation de la prise en charge thérapeutique.

Introduction

There is broad consensus that alcohol dependence (also known as alcoholism) is a serious public health issue. Alcohol dependence is a condition characterized by the harmful consequences of repeated alcohol use, a pattern of compulsive alcohol use, and physiological dependence on alcohol. Physiological dependence is characterized by:

- tolerance symptoms, which refer to a need for markedly increased amounts of the substance to achieve intoxication or the desired effect;
- symptoms of withdrawal (e.g., delirium, grand mal seizures), or use of the same (or a closely related) substance to relieve or avoid these symptoms [4].

Only 5% of individuals with alcohol dependence ever experience severe complications of withdrawal. However, repeated intake of high doses of alcohol can affect nearly every organ system, especially the gastrointestinal tract (e.g., liver cirrhosis, pancreatitis), the cardiovascular system (e.g., low-grade hypertension, elevated risk of heart disease), and the peripheral nervous system (e.g., muscle weakness, paraesthesias and decreased peripheral sensation). Moreover, it is well established that, because of alcohol neurotoxicity, chronic alcoholism leads to deleterious effects on the central nervous system (CNS), such as brain atrophy and/or dysfunction [44,156], these brain impairments being correlated with the lifetime dose of ethanol consumed [112]. Improvements in neuroimaging technology have contributed significantly to our understanding of these effects, revealing alcoholic-specific changes in the CNS associated with neuropsychological abnormalities.

Indeed, the discipline of neuropsychiatry tries to bridge the gap between neurology on the one hand and psychiatry on the other, in order to achieve greater insight into the biological basis of psychiatric disorders [115]. New tools have been developed in the last few decades to investigate these brain deficits. Among these, brain-imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have offered the possibility to investigate which brain regions are involved in specific human cognitive functions. In addition to brain shrinkage in alcoholics, which can largely be accounted for by loss of white matter, alcohol-related neuronal loss has been documented in specific regions of the cerebral cortex, such as the superior frontal association cortex, the hippocampus and the amygdala, which are known to be involved in many ''high-order'' psychological functions, including executive functioning. It is now largely accepted that each cognitive function is specifically related to the activation of a distributed neural network [18]. However, all these brain structures do not activate at the same time; indeed, a cognitive function can be defined as the occurrence of different stages of information-processing that can be distinguished from each other and each of which relates to a specific neural process. Therefore, although PET and fMRI, because of their excellent spatial resolution, are interesting tools for defining the brain regions involved in a

particular cognitive function, they cannot describe the temporal dimension in which these brain regions are activated. Moreover, increasing knowledge about the anatomical structures and cellular processes underlying psychiatric disorders may help to bridge the gap between clinical manifestations and basic physiological processes [17]. The specialty of neurophysiology offers tools that can monitor brain electrical activity with a high temporal resolution (up to 1 millisecond) and is therefore of interest in determining the relationships between behavioural performance and cerebral activity [146].

Alcoholism is a multi-factorial psychiatric disorder, with psychosocial and biochemical/genetic factors associated with its manifestation in any individual [43]. Tension reduction models suggest that type I alcoholics use alcohol to reduce negative affect [23]. In other words, while type II alcoholics are characterized by earlier onset and are related more to a familial history of alcohol consumption, type I alcoholics use alcohol because of a perceived inability to cope with stressors that lead to high-arousal, negative emotional states [14]. Interestingly, reduced skin conductance (SC) reactivity to threats of punishment has been demonstrated in men at high risk of alcoholism [49] and in alcohol dependent persons [161]. Accordingly, it has been shown that SC hyporeactivity in conjunction with poor perceived coping is associated with an increased risk of substance use disorder [14]. Indeed, SC hyporeactivity suggests a weakness in the ''behavioural inhibition system'', which responds, for example, to cues for punishment [50]. SC hyporeactivity also suggests a deficit in ''attention allocation processes'' that interact with motivational system, as these attentional processes are supposed to detect and monitor environmental and interoceptive stimuli relevant to the motivational state of the organism [105,118]. From this perspective, alcohol dependence may be seen as an impaired ability to respond to interoceptive cues in ''stressful'' conditions, which affects the person's subjective feeling of being able to cope with these stressors. This deficient emotional reaction leads individuals to engage in excessive use of alcohol, because of the impaired ability to inhibit behaviour in the presence of punishment cues, in order to decrease negative affect. What is important here is that Bobadilla and Taylor [14] suggest an interaction between motivational, attentional and executive systems explaining the lower rate of substance use disorder symptoms among persons displaying a concordant pattern of physiological (SC) reactivity and perceived coping. Indeed, their study suggests that:

- people with low SC reactivity and low perceived coping displayed substance abuse;
- people with low SC reactivity and high perceived coping may process stressors more deeply in order to feel able to cope with them;
- people with high SC reactivity and low perceived coping may be better attuned to their high arousal state, but these people are associated with an intermediate level of alcohol use, suggesting that alcohol may help them to cope with anxiety but not to the extent of people with low SC reactivity, because they are able to avoid engagement in behaviours that could result in punishment.

The authors stress that these interpretations are still speculative and need to be confirmed. However, the findings highlight the importance of examining cognitive and physiological factors when trying to understand substance use disorders.

We fully agree with Bobadilla and Taylor's perspective. Indeed, psychiatry has the great potential to define the array of clinical symptoms that constitute a disorder and that can specifically affect an individual patient. Today, cognitive neuropsychology offers the possibility to relate precise clinical symptoms to definite psychological constructs, and clinical neurophysiology has developed different tools to monitor the integrity of this information-processing system in humans. Our aim in this review is, therefore, to discuss how the clinical applicability of these electrophysiological parameters is hampered by the fact that most are diagnostically non-specific and not reliable enough to be useful for the individual patient. However, if we link these physiological parameters to precise psychological constructs, that can themselves be related to the definition of a precise neural network, we will be able to define for an individual psychiatric patient the disturbed cognitive processes that lead to specific clinical manifestations, and link these disturbances to precise anatomical dysfunction. This may help optimize our choice of medication (by adapting drugs to the specific pathophysiology in that patient) and psychotherapy (by focusing psychotherapeutic interventions to the specific disturbed cognitive processes, e.g., perception, attention, mnesic, executive functions). Moreover, this highlights the need to integrate data from several disciplines (neurology, psychiatry, psychology) into a common framework; neurophysiology has the potential to act as the interface between these separate branches [17].

The present paper will focus on clinical data from:

- electroencephalogram (EEG);
- oculomotor measures;
- cognitive event-related potentials (ERPs);
- event-related oscillations (EROs).

The purpose is to compare data from alcoholic patients and healthy control subjects in order to link specific physiological dysfunctions to specific cognitive disturbances inducing particular clinical symptoms in chronic alcoholism. We suggest that subgroups of alcoholics that display specific clinical symptoms and cognitive disturbances with consistent biological markers could be identified and that this may help a future generation of clinicians to develop preventive programs aimed at helping predisposed individuals to avoid the development of alcohol problems.

Clinical neurophysiology and alcoholism

The brain activity of alcoholics and non-alcoholics differs in several characteristic ways, and various electrophysiological methods have been used to investigate these differences.

The resting electroencephalogram

The resting EEG registers the ongoing rhythmical electrical activity of the brain while the person being examined is

relaxing [131]. The EEG can be described by various parameters, including amplitude (magnitude of oscillation voltage measured in microvolts -μV) and rhythm (oscillation frequency measured in Hertz - Hz). EEGs can be divided into frequency bands, each one reflecting a different degree of brain activity. The bands that are typically distinguished are: delta (1—3 Hz), theta (3.5—7.5 Hz), alpha (8.0—11.5 Hz), beta (12—28 Hz), and gamma (28.5—50.0 Hz). In the awake-resting EEG of a healthy adult, medium (8—13 Hz) and fast (14—30 Hz) frequencies predominate, with only a sparse occurrence of low (0.3—7.0 Hz) and high (greater than 30 Hz) frequencies. The resting EEG is stable throughout healthy adult life and is highly heritable [164].

Theta rhythm

The normal adult awake EEG record contains very low theta power. It has been demonstrated that tonic theta is decreased under conditions that are associated with increased processing capacity (e.g., during high alertness). On the contrary, tonic theta is increased under conditions that are associated with reduced cognitive processing capacity [82], as in altered cholinergic functioning states, such as Alzheimer's disease [69], with age [110], and in altered neurophysiological states of the brain, such as the transition from wakefulness to sleep [160], in slow wave sleep or in fatigue [85].

Numerous studies have shown higher tonic theta power in alcoholics; compared to respective matched controls, theta power seems to be higher in male alcoholics, particularly in the central and parietal regions, and in the parietal region in female alcoholics [136]. Increased resting theta does not seem to be present in the offspring of alcoholics, suggesting that this measure may indicate a state-dependent condition [132].

At the functional level, elevated tonic theta power in the EEG may reflect a deficiency in the information-processing capacity of the CNS [85]. Indeed, it has been suggested that theta rhythms are associated with different cognitive processes, such as conscious awareness, episodic retrieval, recognition memory, and frontal inhibitory control [86,84,85,74]. Steriade et al. [156] reported a link between slow EEG activity (theta and delta) and cholinergic activity and central cholinergic pathways. In vitro studies [99] have revealed that acetylcholine may have an inhibitory or an excitatory effect on cortical pyramidal neurons. Inhibition results from the excitation of the intrinsic inhibitory neurons in the cortex [136]. Therefore, it has been suggested that the increase in theta power observed in alcoholics may be an electrophysiological indicator of the imbalance in excitatory and inhibitory neurons in the cortex [132].

Alpha band

The alpha rhythm is the predominant EEG rhythm in most normal individuals during states of alert relaxation. It is obtained whether the eyes are open or closed, and when the person's eyes are closed it is strongest over the occipital regions [131].

Early studies, dating back to the 1940s, found evidence of unstable or poor alpha rhythm in alcoholics [10], indicating a poor capacity for relaxation. Finn & Justus [48] reported reduced alpha power in the children of alcoholics. Others have shown that men with alcoholic fathers as well as women at high risk for developing alcoholism have higher voltage alpha power than controls [37]. Further, Enoch et al. [40] reported the presence of a distinctive EEG phenotype in 5 to 10% of individuals, referring to an ''alpha variant'', i.e., low-voltage alpha (LVA). This EEG trait is characterized by the virtual absence of alpha rhythmicity, and, if present, the alpha waveform is scanty and of low amplitude [40]. The same authors reported that this variant is associated with a subtype of alcoholism that co-occurs with anxiety disorder. More recently, while studying young African-American adults, Ehlers et al. [38] found evidence of considerable ethnic variation in the prevalence of LVA EEG variants.

Beta band

Beta rhythm is a fast, low-voltage rhythm that is distributed over the scalp and occurs while the subject is alert. Beta rhythm implies a balance in networks of excitatory pyramidal cells and inhibitory interneurons engaging gamma-aminobutyric acid type A (GABA A) action as a pacemaker [173]. Porjesz et al. [128] found a genetic link between a GABA A receptor gene and beta rhythm. Several studies also reported a very strong association of the same GABRA2 receptor gene (GABA A receptor, alpha 2) with both alcohol dependence and the beta frequency [36,25,175]. These discoveries, combined with biological evidence for a role of GABRA2 in both phenotypes, suggest that variations in this gene affect the level of neural excitability, which in turn affects the predisposition to develop alcohol dependence [36]. Neuroimaging studies have reported specific deficits in GABA benzodiazepine receptors in the brains of alcoholics [1] and of individuals at risk [167], supporting the involvement of the GABAergic system in alcoholism. Taken together, these data suggest that the lack of CNS inhibition (due to hyperexcitability) in the brains of alcoholics and individuals at risk may be explained by GABA deficits, which may play a role in the predisposition to develop alcoholism [132].

Studies of scalp-recorded EEGs in alcoholics and individuals at risk tend to confirm this hypothesis. Indeed, most of these studies have reported that alcoholics differ from controls by having increased beta power [8,173,135]. The children of male alcoholics also show this difference [136]. Moreover, relapsing alcoholics show faster beta power than abstainers [173,8], suggesting that desynchronized beta activity may be a valuable indicator of relapse in abstinent alcoholics. This aberrant beta activity has been localized especially over frontal areas, suggesting a functional disturbance of the prefrontal cortex [173]. Given that the increase in beta power in abstinent alcoholics is not related to length of abstinence [135] and is also present in children of alcoholics at risk of alcohol dependence [137], excess beta power is believed to be a vulnerability marker rather than a trait or a state variable (i.e., may be antecedent to the development of alcoholism). The strong association of a GABA A receptor gene with the beta frequency band of the EEG, coupled with GABAergic deficits observed in the brains of alcoholics and the elevated beta power in the EEG of alcoholics and subjects at risk is consistent with Begleiter and Porjesz's idea that instability in neural excitation—inhibition homeostasis is at the origin of the development of alcohol dependence [12] as well as the susceptibility to relapse [8].

EEG data and alcoholism: a summary
Studies indicate that the resting EEG in alcohol-dependent patients and individuals at risk of developing the disease differs significantly from that of normal controls. Indeed, even though the alpha band differences are not poorly defined, high beta and theta power is a characteristic feature in alcoholics and high-risk subjects. Using the resting EEG for diagnostic and preventive purposes, therefore, makes sense. Moreover, EEGs may also be of prognostic value, as EEG patterns in patients who relapse differ from those in patients who continue to abstain [147]. In summary, as slow theta activity is believed to be inhibitory, alpha activity to reflect normal brain functioning, and fast beta activity to be excitatory, the low-voltage fast desynchronized patterns described in alcoholics may reflect hyperarousal of the CNS.

Oculomotor measures

Smooth pursuit paradigm
Smooth pursuit eye movements (SPEM) have proven to be a valuable measure in the assessment of the neurophysiological effects of a wide range of clinical and subclinical conditions [24]. In healthy individuals, the oculomotor system can track a visual target moving continuously across the visual field at velocities of up to 30°/s, thereby maintaining a stable foveal image [7]. In impaired individuals, this pursuit movement is not smooth, and may be disrupted or replaced by more rapid saccadic movements. Impairments in SPEM have been detected among patients with cerebellar disease [106], Parkinsonism [138], and Huntington's disease [9]. Acute and chronic alcohol use have also been related to SPEM abnormalities. More specifically, Moser et al. [107] recorded horizontal and vertical eye movements in response to unpredictable target jumps and during scanning of a classical kitchen scene and a traffic scene in healthy volunteers under various blood alcohol concentrations. The results indicated that alcohol consumption impaired the velocity and initiation of saccadic and smooth-pursuit eye movements, but that subjects could nevertheless still recognize exciting and relevant areas of visual scenes. The significant increase in fixation time did not, however, allow the entire visual scene to be scanned for an adequate period of time. SPEMs are complex because oculomotor activities depend on the presence of motion signals from a stimulus, on intact pathways in the brain for processing the motion signals, and on an intact motor apparatus for executing the eye movements. For this reason, pursuit has traditionally been viewed as a relatively automatic behaviour, driven by visual motion signals and mediated by pathways that connect visual areas in the cerebral cortex to motor regions in the cerebellum. However, recent findings indicate that pursuit involves an extended network of cortical areas (including structures previously associated with the control of saccades, such as the basal ganglia, the superior colliculus, and nuclei in the brainstem reticular formation), and, of these, the pursuit-related region in the frontal eye fields appears to exert the most direct influence. This viewpoint considers that eye tracking movements result from descending control signals interacting with circuits in the brainstem and cerebellum responsible for gating and executing voluntary eye movements [91,92]. In other words, pursuit eye movements are not automatic responses to retinal inputs but are regulated by a process of target selection that involves a basic form of decision making, including many higher order functions (such as attention, perception, memory and expectation), which can influence behaviour and the singular and coordinated motor actions that follow [91]. Therefore, the reduced visual exploration caused by alcohol, which is independent of a subjective feeling of sedation after ethanol consumption [68], reflects impaired sensori-motor processing of active visual perception.

Antisaccade paradigm
The antisaccade task requires a subject to make a saccade to an unmarked location in the opposite direction to a flashed stimulus. This task was originally designed to study saccades made to a goal specified by instructions. Interest in this paradigm surged after the discovery that frontal lobe lesions specifically and severely affect human performance of antisaccades, while prosaccades (i.e., saccades directed to the visual stimulus) are facilitated [3]. Vorstius et al. [168] showed that the saccade latency data strongly suggest that alcohol intoxication impairs temporal aspects of saccade generation, irrespective of the level of processing triggering the saccade. Furthermore, the specific impairment of saccade amplitude in the anti-saccade task under alcohol suggests that higher level processes involved in the spatial remapping of target location in the absence of a visually specified saccade goal are specifically affected by alcohol intoxication. Moreover, children at high risk of alcohol use disorder also display impaired oculomotor response inhibition in this kind of antisaccade task [59].

The startle response
In the startle eye blink modification paradigm, the startle eye blink is reliably modified in humans by presenting a non-startling stimulus (prepulse tone) shortly before a startling stimulus [55]. When the interval between the prepulse tone and the startle stimulus is short (around 250 ms), the magnitude of the startle eye blink response is reduced compared with that evoked in response to the startle stimulus alone. This ''prepulse inhibition'' reflects the action of an automatic sensori-motor gating system that is protective of early pre-attentive processing of the prepulse (i.e., a pre-attentional habituation phenomenon). However, if the interval is longer (e.g., 2000 ms), the startle eye blink reflex is enhanced: This ''prepulse facilitation'' reflects a combination of arousal and sustained attention elicited by the prepulse (see [47] for a review). A PET study in healthy individuals showed that greater prepulse inhibition during prepulse tones was correlated with higher glucose metabolism in the medial and lateral prefrontal cortex [65].

A common finding is that alcohol significantly diminishes the magnitude of the startle response [71,58]. Moreover, a significant association between startle magnitude after alcohol consumption and the frequency of drinking alcohol has been shown [70]. The acoustic startle reflex also seems to be reduced in sons of alcoholics, independently of comorbid anxious disorders [179]. A recent study [94] showed that although drinking behaviour and craving decreased significantly over time, the pattern of the affective modulation

of the startle reflex did not change. However, startle modulation and relapse were related, and within the group of relapsers, startle modulation was a significant predictor of drinking behaviour. These results suggest that the startle reflex may reflect more enduring and permanent processes of emotional response to alcohol-related cues than autonomic arousal and self-reported craving, and that startle modulation by alcohol-associated cues may be a better predictor of drinking behaviour for relapsers than other measures.

Oculomotor measures: summary

Oculomotor tasks have been designed as highly sensitive tools to evaluate components of executive function. Findings indicate that alcohol consumption impairs the velocity and initiation of saccadic and smooth-pursuit eye movements as well as the response inhibition to a prepotent response and the sensori-motor gating of the startle response. These results reflect deficits in executive function and sensori-motor control, and are consistent with dysfunction of a large and distributed neural network, including the frontal lobes, possibly due to disrupted inhibitory mechanisms [57,174].

Cognitive event-related potentials (ERPs)

ERPs allow us to monitor brain activity during the entire information-processing stream, ranging from sensory to higher cognitive processes. Therefore, during a cognitive task, ERPs allow one to identify the electrophysiological component representing the onset of a dysfunction, and then to infer the impaired cognitive stages [146].

The P300 component (P3a, P3b)

Numerous studies have identified a number of neuroelectric features that seem to be anomalous in abstinent alcoholics [120,119,22,157]. In all of these studies, the primary findings were P300 abnormalities.

P300 (or P3) is a long-lasting positive component that occurs between 300 and 700 ms after the stimulation onset [30,31,159]. It appears when a subject detects an informative task-related stimulus [64]. The P3 is thought to reflect premotor decisional processes, such as memory updating [126] or cognitive closure [165], and to involve activation of inhibitory processes over widespread cortical areas [150,165,162]. The amplitude of P3 is associated with stimulus probability, stimulus significance, task difficulty, motivation and vigilance [152]. P300 latency is believed to reflect classification speed, which is proportional to the time required to detect and assess a target stimulus [96].

The ERP task most usually used to elicit the P300 is the ''oddball task'', in which two different types of stimuli are delivered: Rare oddball stimuli and frequent stimuli. In this task, the subject is asked to monitor and identify infrequent ''target'' stimuli implanted within a series of rapidly presented frequent ''standard'' stimuli. This response may take the form of verbal reporting (silent-counting task) or of an overt signal, typically button-pressing. In normal individuals, the P300 occurs following the presentation of the target stimulus. It is a large positive response that is of maximum amplitude over the parietal area with a peak latency of about 300—350 ms for auditory and 350—450 ms for visual stimuli.

The P300 response is not a single phenomenon but can be divided into two main subcomponents: P3a and P3b [153]. The P3b is the component recorded in response to task—relevant targets. It has a more centro-parietal distribution and a longer latency, usually comprised between 280 to 600 ms [64]. The P3a component occurs after novel events independently of task relevance, i.e., when the subject is ignoring (is not asked to attend to rare stimuli). It has a more frontal distribution and its latency usually ranges from 220 to 280 ms [64]. At a functional level, P3a is thought to reflect initial signal evaluation (and is particularly modulated by stimulus novelty) whereas P3b is associated with subsequent attention resource and memory processes that store stimulus information [87].

The P300 is thus produced by brain processes related to attention and memory operations. In keeping with global neurophysiological patterns and various physiological explanations for the P3 component [30,53], several investigators [151,67] have proposed that the P3 component might be elicited by a widely distributed inhibitory event that operates under various processing functions. Hence the P300 and its underlying subprocesses could reflect rapid neural inhibition of ongoing activity to ease transfer of stimulus/task information from frontal (P3a) to temporal-parietal (P3b) locations [124]. P300 signals could arise from the initial need to increase focal attention during stimulus detection relative to the contents of working memory [88]. Consequently, minimization of inappropriate stimulus processing would facilitate the transmission of incoming stimulus information from frontal to temporal—parietal areas to heighten memory operations.

An alternative to the oddball task to obtain the P300 is the ''Go—NoGo'' task, requiring participants to respond to one type of stimulus (Go), but to not to another (NoGo). In the No-Go task, the ''No-Go P3'' has been identified as one of the markers for response inhibition [151]. Response inhibition involves activation of the executive system of the frontal lobes [73]. Conversely, the neural basis for this executive system is believed to be a distributed circuitry that involves the prefrontal areas and anterior cingulate gyrus [133], the orbitofrontal cortex [52], the ventral frontal regions [15], the dorsal and ventral prefrontal regions [80,172], the anterior cingulate cortex [34], the premotor and supplementary motor areas [163], and the parietal regions [172,34]. In summary, P3a and P3b involve a circuit pathway between the frontal and temporal/parietal brain areas [87,123].

In alcoholics, a reduced amplitude and a delayed latency of P3 to task-relevant target stimuli (P3b) has been widely observed, particularly over the parietal regions [11,158]. This deficit appears in both auditory and visual tasks, but is more pronounced in visual tasks [130,132]. Although not as significant as in males, recent studies have indicated that smaller P3 amplitudes are also present in female alcoholics [158]. Other studies [119,75] documented not only low amplitude P3b components to target (Go) stimuli, but also reduced frontally distributed P3 amplitudes to No-Go stimuli. These deficits observed in both Go and No-Go conditions suggest that both response activation and response inhibition are dysfunctional in alcoholic individuals [75].

Furthermore, while normal controls manifest their largest P3b amplitudes in response to targets over parietal regions of the scalp and their largest P3a amplitudes in response to rare non-targets over frontal regions, alcoholics manifest poor differentiation (i.e., similar low amplitude P3 s) between task conditions [75]. Hada et al. [60,61] showed different current source density (CSD) between alcoholics and controls in an oddball paradigm in terms of topographic differences. Assessing the amplitude and topographic features of ERPs and CSD in a Go/No-Go task, Kamarajan et al. [75] also found less anteriorization of CSD polarity in alcoholics during No-Go processing. This finding indicates an impaired/decreased frontal lobe participation. These authors also showed that the topographic patterns of CSD in alcoholics are significantly different from controls, which suggests that alcoholics maybe activate extraneous brain networks during cognitive processing. The reduced No-Go P3b along with the less anteriorized CSD topography during No-Go conditions suggests poor inhibitory control in alcoholics [75], perhaps reflecting underlying CNS hyperexcitability [12].

In summary, compared to control subjects, abstinent chronic alcoholics show decreased amplitudes and delayed latencies in both P3a and P3b components. They also exhibit a difference in the distribution of CSD maps to the non-target stimulus suggesting that their P3a generation is disrupted. Although the frontal region is not the only source of P3a [176], it is the most important area associated with P3a generation. Taken together, the lower amplitude and weaker sources to rare stimuli associated with the lack of topographic specificity in the CSD maps suggests that alcoholics respond in a disorganized way, perhaps reflecting an inefficiency in brain functioning. This global pattern of electrophysiological response suggests a lack of differential inhibition in alcoholics, perhaps reflecting underlying CNS hyperexcitability. Moreover, differences in P300 amplitude and latency were found between alcoholics and non-alcoholics, between unaffected relatives of alcoholics and relatives of controls, and between unaffected children of alcoholic fathers and of controls. These data provide significant support for P300 as an endophenotype for alcohol dependence.

Most studies have focused on measuring P3 components while investigating electrophysiological deficits in alcoholics. Indeed, impairment of the P3 component in this population is well established. The P300 is functionally linked to decisional processes and closure of cognitive processing before activating the motor response, which therefore would be deficient in alcoholics. However, stimulus processing is not a ''one-step process'' but is composed of different stages, each having electrophysiological correlates; for example, perception level with P100 and N170, attention level with N200 [63], and decision level with P300 [18]. Therefore, the impairment observed in alcoholics does not necessarily reflect problems at the decision level, which only represents the end of the cognitive information-processing stream. A deficit in the earlier stages of processing cannot be excluded. Surprisingly, until recently, very few studies had explored other electrophysiological components. Thus, little was known about the initial level of impairment during the processing of stimuli. More recent studies have, therefore, taken earlier ERP components into account in order to define whether earlier deficits of the information-processing stream can be demonstrated in alcoholism.

Error-related negativity (ERN)

One of these earlier components involves error-related negativity (ERN). An ERN is a negative deflection in the EEG detectable over the fronto-central regions of the scalp and elicited around 50—150 ms after an error response during tasks that require speed and correct response choices [42]. ERN appears in tasks where subjects know the accurate answer but fail to execute the correct response, and is followed by a later positivity peak at 200—250 ms [28].

Although error positivity has remained elusive to date, ERN has generated a high level of interest and investigation by cognitive neuroscientists because of the importance of online action monitoring for theories of cognitive regulation. A distinction can be made between two types of ERN. In tasks that demand prior knowledge of correct stimulus—response mappings (e.g., a Stroop or flanker task), the subject knows that he/she has made a mistake without needing any feedback. In this case, an ERN occurs about 50—150 ms after the mistake, and is called a response-locked ERN (R-ERN) [41]. A R-ERN reflects low-level error recognition, as it does not require conscious awareness of the error [113]. Some other tasks have unpredictable outcomes (e.g., pseudo-random gambling games), and they require subjects to use positive and negative feedback to evaluate their response as correct or incorrect. In this case, another type of ERN occurs: Feedback ERN (F-ERN), which arises about 200—300 ms after negative feedback [62]. A few studies [102,141,35] have demonstrated that consumption of moderate amounts of alcohol leads to a reduction in the ERN amplitude. ERN has been shown to be generated by a high-level evaluative system in the brain that involves the anterior cingulate cortex [23]. Authors have, therefore, suggested that alcohol consumption impairs the monitoring of ongoing performance. Of particular note is that this system partly overlaps with brain regions involved in response inhibition [103]. Ruchsow et al. [145] found that impulsivity, which is strongly related to alcoholism, was associated with weakened R-ERNs in a flanker task.

Mismatch negativity (MMN)

Mismatch negativity (MMN) (also called N2a) is an ERP component that is usually evoked by a physically deviant auditory stimulus that occurs in a series of frequent standard stimuli [108,109]. MMN generation involves a neural, sensory-memory representation of the standard stimulus [90]. This sensory-specific mechanism is related to preconscious detection of stimulus deviation that activates frontal mechanisms associated with conscious discrimination of stimulus deviation and with the orienting response [90]. MMN probably reflects cortical information-processing at the earliest level of the sensory cortex, although recent findings suggest that the transient auditory sensory memory representation underlying the MMN is facilitated by a long-term memory representation of the corresponding stimulus. MMN overlaps the N100 and the P200 components, with a peak latency around 150 ms after stimulus onset and reaches maximal amplitude at frontal scalp loca-

tions [148]. The amplitude of the MMN has been found to be lower in alcoholics than in non-alcoholic controls [140]. The component has been proposed as an index of the brain inhibitory deficit associated with alcoholism [78,178]. Thus, as indexed by MMN and P300, alcoholics seem to exhibit impairments in early and in late cortical information-processing. Therefore, in terms of automatic-controlled processing theory, the deficit in MMN observed in alcoholics could be interpreted as automatic dysfunction processing in contrast with the deficits in P300 that would reflect attentive (or effortful) information-processing impairment. However, not all studies found differences in ERP between alcoholic and control subjects [56,45,56]. Thus, while there is a strong link between alcohol abuse and symptoms of disinhibition, the MMN response does not offer any direct physiological evidence of this fact. These results question the use of MMN as an index of disinhibition in alcoholism [45].

P50 sensory gating

The auditory P50 component is the earliest (around 50 ms) and the smallest in amplitude of the auditory ERPs [134]. When normal controls are confronted by repetitive auditory stimuli, an inhibitory mechanism is activated to block out irrelevant, meaningless or redundant stimuli. The inhibition of responsiveness to the repeated stimuli is neurophysiologically indexed by a reduced P50 [122]. The P50 sensory gating effect refers to this amplitude diminution of the P50 ERP to the second stimulus of a pair of identical stimuli presented with a short inter-stimulus interval [2]. P50 gating is one of the early brain sensory processing stages linked to screening-out and filtering mechanisms of redundant incoming information that can be measured, and it reflects a neuronal inhibitory process [51]. It has been reported that abstinent chronic alcoholics show reduced P50 sensory gating [97], which would indicate an inhibitory deficit in early pre-attentive auditory sensory processing.

Contingent negative variation (CNV)

CNV [169] is a slow negative shift in the human EEG that occurs between two successive stimuli that are associated with or contingent on each other. The first stimulus (S1) usually serves as a preparatory or warning signal for the second imperative stimulus (S2), which necessitates a motor response. It is believed that the CNV reflects neuronal activity that is needed for sensorimotor integration and is linked to the planning or execution of externally paced, voluntary movements [20]. In addition to the reticular formation and the limbic system, the frontal cortex has long been considered a prime candidate for generation of the scalp-recorded CNV [95], in part because the CNV has a fronto-central scalp distribution and in part because the CNV occurs in situations that involve behaviours typically ascribed to the frontal lobes (e.g., anticipation, preparation, initiation, and behaviour dependent upon delayed consequences) [27,114,54]. There is considerable evidence that the frontal lobes are especially vulnerable to the chronic effects of alcoholism [171,121,45]. Moreover, heavy alcohol use has been shown to impair executive or frontal lobe functions [117,139]. Thus, one would expect alcoholics to exhibit abnormal CNV and frontal lobe functions. However, Olbrich et al. [116] and Wagner et al. [170] reported no significant differences in late CNV between abstinent alcoholics and controls. This is in contrast to previous studies that have found the amplitude of the CNV to be reduced by acute [144] and chronic [149] alcohol use. Recently, several investigators have attributed enhanced ERP components in abstinent alcoholics to post-withdrawal CNS hyperexcitability [127]. Because it is possible that a similar mechanism may have masked CNV differences between alcoholics and controls in the studies by Olbrich et al. [116] and Wagner et al. [170], Chao et al. [20] examined CNV in active heavy drinkers who were not under treatment for alcoholism. They found inverse relationships between frontal lobe grey matter volume, performance on the Trail Making Test B, and late CNV amplitude in heavy drinkers. They suggested that the ERP abnormalities observed may be indices of alcohol-related damage to the frontal lobe. They did not find any significant relationship between CNV amplitude and reaction time in heavy drinkers, which they suggest is a manifestation of a disrupt response preparation.

Other earlier components: visual P100 and N170

P100 is a positive potential which appears around 100 ms after stimulus onset and is maximal at occipito-temporal sites. The P100 is classically associated with the basic visual perceptual processing of the stimulus [66]. Chronic alcoholism leads to delayed latency [16], reduced amplitude [19] and abnormal topography [103] of this component. These aberrant findings seem to be associated with the lifetime dose of ethanol consumed [112] and to disappear after a period of abstinence [19]. A recent study by Maurage et al. [13] confirmed and expanded these results to complex stimuli (namely faces). These authors also found delayed latency and reduced amplitude in the N170 component, a negative ERP maximally recorded around 170 ms at occipito-temporal sites and particularly sensitive to face processing [13].

ERP findings: summary

In summary, impairment of the P3 component in alcoholics is well established. Moreover, many researchers agree that the decreased P3 could be an indicator of a global or regional lack of cortical inhibition. Current findings on ERN support this interpretation. However, more recent studies indicate that the deficit in alcoholism is not exclusively due to an ''executive'' impairment, and provide evidence that deficient early processes underlie the failure of later ''higher-level'' processing. Indeed, even though some studies have failed to detect any difference between alcoholic individuals and controls for some early components, for example mismatch negativity [45] or N100 [77], it has been shown that alcoholics also exhibit deficits in ERP components preceding P300, which reflect earlier levels of information-processing. Indeed, perceptive (P100, N100, N170) and attentional components (P50, MMN, N200) have been shown to be altered. So, reconsidering the P3 deficit in alcoholism by investigating its potential association with earlier impairments may help determine at which stage of cognitive processing the deficit observed in an individual alcoholic patient originates.

Event-related oscillations (EROs)

The neural oscillations that underlie ERPs are called EROs. EROs are measured in the same frequency bands as spontaneous resting EEGs namely, delta (1—3 Hz), theta (3.5—7.5 Hz), alpha (8.0—11.5 Hz), beta (12—28 Hz), and gamma (28.5—50.0 Hz). However, at a functional level, EROs are different from spontaneous resting EEG rhythms [76]. EROs are temporally associated with the sensory and cognitive processing of stimuli [5]. Faster frequencies correspond to synchronization of groups of neurons in more local areas, whereas slower frequencies are involved in synchronization over larger distances in the brain [89]. Sensory reception involves communication between groups of neurons that are close together and that fire together at fast rates in the gamma range. During cognitive processing (e.g., attention to an auditory rather than a visual stimulus), however, brain regions that are far from each other need to communicate and this involves synchronization between the brain regions in the alpha and beta frequency ranges. Higher cognitive processing (e.g., working memory, determining if a stimulus has been seen before) involves interactions between widely separated brain regions (e.g., frontal and parietal lobes) and, therefore, represents slow synchronization in the theta or delta frequency range [93].

Theta and delta oscillations underlie visual P3

There is evidence that P3 responses are primarily the result of oscillatory changes in delta and theta rhythms during stimulus processing [154,29], with a higher proportion of delta oscillations from the posterior regions of the brain, and theta occurring more in the frontal and central regions [5,76]. During attention tasks, the hippocampus and frontal and parietal regions of the brain synchronize in the theta range. The diminished P3 amplitudes reported in alcoholics may be induced by deficits in the theta and delta oscillations that underlie P3. Indeed, evoked delta and theta power were found to be significantly decreased among alcoholics compared with control subjects when processing the target stimuli in a visual oddball paradigm. Alcoholics also showed impaired delta and theta oscillatory responses in a Go/No—Go task, particularly during No—Go processing [74]. Further, lower NoGo-P3 amplitude has also been demonstrated in alcoholics [75]. An amplification in theta power is related to an intensification in theta power in the hippocampus, known to be an inhibitory rhythm associated with GABAergic activity [83]. An increase in theta power is associated with inhibition of non-relevant information while attending to relevant information (e.g., a target stimulus). As most information is irrelevant and must be concealed, this yields the high amplitude of P3 to relevant stimuli. Thus, the deficit in inhibitory theta oscillations underlying P3 in alcoholics suggests deficient inhibitory control during information-processing (e.g., attention and memory mechanisms). This finding provides further support for the hypothesis of Begleiter and Porjesz [12] that alcoholism is associated with CNS disinhibition.

Frontal midline theta

Suresh et al. [158] investigated event-related EEG changes during mental arithmetic in alcoholics and control subjects. EEGs were recorded during the performance of a simple addition problem (active theta) and during a resting interval (resting theta). The processing capacity is reflected by the difference between resting and active theta power; the lower the resting theta power and the higher the active theta power, the more efficient the brain processing [84]. Alcoholics manifested reduced resting theta and reduced active theta, indicating decreased and inadequate processing capacity. These deficits in performance, indexed by low evoked (active) theta power during mental effort, reflect frontal lobe dysfunction in alcoholics [158]. These deficits are manifested as deficits in working memory and sustained attention and involve inhibitory processes [76].

Gamma

Gamma oscillations are believed to be involved in visual perception, cognitive integrative function such as ''binding,'' and frontal input during sensory processing (top—down processing) [6,76]. Early phase—locked gamma is involved in selective attention and its response is larger to attended stimuli than to unattended stimuli, particularly over frontal regions [5,177]. Basar et al. [5] reported that in an oddball task, gamma oscillations and P3 components obtained in response to target stimuli were associated. One recent study found that alcoholics manifested lower gamma power than control subjects during target processing between 0 and 150 ms in a visual oddball paradigm. This effect was strongest frontally and lateralized to the left side. In contrast, no difference in gamma power was found between the groups for non-target and novel stimuli. Control subjects manifested significantly higher gamma power in the processing of the target relative to the processing of the non-target stimulus, whereas alcoholics did not manifest higher gamma power during target processing. Increased evoked gamma is thought to reflect a matching process between the template in working memory and the current stimulus. These findings of gamma deficits in response to target stimuli, particularly in the frontal regions, provide further evidence for deficits in cognitive processes (e.g., attention allocation, working memory) in alcoholics [131].

ERO findings: summary

In summary, ERO studies indicate that gamma, theta and delta power are decreased in alcoholics. These decreased responses are coherent with the hypothesis of cognitive and neural disinhibition in alcoholism.

Discussion

Merging electrophysiological findings with disturbed cognitive processes and clinical symptoms of chronic alcoholism

Pathological and imaging studies have demonstrated that heavy alcohol use structurally damages the human brain. Neuropsychological tests and electrophysiological studies have also shown that heavy alcohol use impairs cognitive function. Electrophysiological techniques have been extensively used to study the correlates and consequences of alcohol use.

From one aspect, looking at the electrophysiological measures described above, we can observe that alcoholic patients display:

- a resting EEG that differs significantly from that of normal controls, with increased theta (inhibitory) and beta (excitatory) activities indicating hyperarousal of the CNS;
- abnormalities in SPEM, saccadic inhibition during antisaccade tasks, and decreased prepulse inhibition that may stem from the same prefrontal ''inhibitory'' cortical dysfunction;
- decreased amplitude for cognitive ERPs situated along the continuum of information-processing, i.e., from P50 to P100, N170, ERN and P300, suggesting that chronic alcoholism is associated with neurophysiological deficits from the level of the sensory and attentional cortex and not only disturbances involving associative cortices and limbic structures;
- decreased theta and delta oscillations, that may indicate impaired inhibitory control.

From another aspect, chronic alcoholism is defined by a variety of clinical symptoms, such as a compulsive preoccupation with obtaining alcohol despite devastating consequences affecting social and occupational functioning, and a high vulnerability to relapse after cessation of drinking [4]. Many studies have been devoted to the identification of cognitive candidates that could trigger these habits. The most important are probably:

- the ability to inhibit or suppress mental representation loaded in working memory and behaviour, which is a fundamental aspect of behavioural control and leads to general states of ''disinhibition'' or ''dyscontrol'' characterized by impulsive and exaggerated behaviour [46];
- the capacity to shift from one idea to another, as it has been shown that alcohol-related stimuli have acquired conditioned incentive properties, so that these stimuli become perceived as highly attractive, thereby 'grasping' attention [143].

In other words, alcoholics suffer from deficits in their cognitive control mechanisms of 'inhibiting' and of 'shifting' and these deficits are exacerbated by cognitive biases for alcohol-related stimuli.

As described above, neurophysiology provides us with a large array of tools to examine these executive ''inhibitory'' and attentional ''shifting'' processes. One must also not forget that alcoholism is a complex and heterogeneous disorder with genetic and environmental determinants. We suggest that, in order to be able to identify subgroups of alcoholic patients displaying specific clinical symptoms and cognitive disturbances linked to consistent biological markers (identified thanks to neurophysiological tools), we need to integrate data provided by independent disciplines (neurology, psychiatry, psychology, genetic) into a common framework. This may help clinicians to improve their treatment of alcoholic patients by:

- focusing therapy on individual cognitive disturbances;
- adapting pharmaceutical approaches to the impaired pathophysiology.

Indeed, current medications, such as acamprosate and naltrexone, are effective as adjuvant therapies for alcohol dependence in adults. Acamprosate appears to be especially useful in a therapeutic approach targeted at achieving abstinence, whereas naltrexone seems more indicated in programmes geared to controlled consumption. We believe that this integrative approach may serve to target symptoms and to target the deficient (cognitive and neural) mechanisms on which medication should act in an individual patient. For example, patients showing inhibitory problems associated with great impulsivity or marked anxiety should probably be treated differently. Moreover, such an approach may also have a preventive role: by providing a better understanding of how the different parameters combine to lead to alcohol abuse, it could help to:

- decrease the number of relapses;
- help predisposed individuals to avoid alcohol problems.

Towards an integrative framework

Alcoholism and relapse: a fundamental problem

If we look, for example, at the reduction in the P3 amplitude, we can see that it is not only observed in alcoholism, but in a series of disinhibitory disorders, such as conduct disorder (CD), attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and antisocial personality disorder (ASPD) [81]. Clinically, one of the most common manifestations of disinhibitory disorders is ''altered impulsiveness''. Impulsivity can be defined as ''action without planning'' or ''behaviour that is prematurely executed and has maladaptive consequences'' [104]. This construct seems to be due to a decline in behavioural filtering processes outside of consciousness and leads to a compromised ability to make appropriate judgments about incoming stimuli [104]. Recent studies indicate that alcoholic subjects have higher levels of impulsivity, particularly those with cluster B personality disorders (antisocial and borderline symptoms) [33] or early-onset type alcoholism [32]. Chen et al. [21] also suggested that impulsivity may be an important factor underlying the pathogenesis of alcohol dependence. Indeed, these authors showed that subjects with alcohol dependence exhibited increased impulsivity which was linked to cognitive deficits and reduced P3 amplitudes. Moreover, dipole source localization of P3 revealed less activation in the frontal lobes, these brain regions being involved in response inhibition. The prevalence of enhanced impulsivity among substance abusers has been extensively discussed. Obviously, other ''psychological constructs'', such as depression or coping abilities, are also important in alcohol abuse. Comorbidity is another important feature that is often not taken into consideration in studies on alcoholism [98]. Yet, comorbidity is more the rule than the exception in the alcoholic population. Alcohol dependence and affective disorders (anxiety and particularly depression) co-occur at significantly higher rates than would be expected by chance within the general population [79]. In keeping with

this observation, a recent study by McKellar et al. [100] showed that self-efficacy was a robust predictor of short- and long-term remission after treatment. These authors suggest that clinicians should focus on keeping patients engaged in Alcoholics Anonymous, addressing depressive symptoms, improving patient coping, and enhancing social support during the first year, and reduce the risk of relapse by monitoring individuals whose alcohol problems and impulsivity improve unusually quickly. This view supposes that an individual framework should be created for each alcoholic patient, which would include assessment of:

- cognitive disturbances, notably concerning inhibition and attentional shifting;
- comorbid symptoms, evaluating degree of impulsiveness, ability to cope with stressors and the existence of psychiatric symptoms associated with alcoholism, such as depression or antisocial personality disorder;
- social environment, notably to evaluate potential social support from friends and/or family.

The first two factors can be achieved using neurophysiological tools, which may identify the pathophysiological mechanisms linking the clinical symptoms and deficient cognitive processes. Placing the patient into an integrative framework including psychological and social dimensions should help clinicians to:

- optimize the pharmaceutical approach;
- optimize the support given to the patient after detoxification, by identifying patients with a ''high-risk'' of relapse and offering them strong therapeutic support.

Indeed, as far as alcoholic pathology intervention is concerned, an important point is to offer a post-rehabilitation program. It is well known that a high percentage of treated alcohol-dependent patients resume drinking after treatment has stopped [125]. Therefore, identification of variables involved in this relapse is a major issue in current research on alcoholism. Investigation of the neurobiological basis of relapse may represent a promising approach. Indeed, a longitudinal follow-up study [26] showed that the electrophysiological profile of relapsers differed from that of abstainers; the auditory oddball P300 amplitude was significantly higher at Cz and Pz among patients who relapsed during the 3-month follow-up. The same effect appeared on a CNV protocol, where the amplitude of P300 was higher in patients who subsequently relapsed than for those who remained abstinent. Authors like Saletu-Zyhlarz et al. [147] also showed a significantly more pronounced hyperarousal of the CNS in relapsers compared to abstainers. Cognitive ERPs may, therefore, be clinically useful to improve the prediction of risk of relapse among alcoholic patients. Further, awareness that impulsivity, depression, low coping abilities and absence of social support are prominent risk factors for relapsing behaviour, should encourage assessment and treatment of these variables, which could help in the clinical management of alcohol dependence.

The future: identify predisposed alcoholics

Identifying factors that precede the development of alcoholism is crucial to fully understand the pathology of alcoholism. Initially, the smaller P300 found in alcoholics was thought to be a consequence of alcoholism and/or to be due to nutritional deficiencies [129]. However, it has been shown that after a sufficient period of abstinence, while many of the aberrant clinical characteristics of alcohol dependence — as well as the electrophysiological measures of hearing deficits returned to normal, the abnormality in P3 amplitude persisted [129]. This long-lasting deficit in chronic abstinent alcoholics suggests that P300 deficits may be genetically mediated and could antedate the development of alcoholism. Hence, P300 impairments might be a trait marker rather than a state marker of alcoholism. Indeed, several ''high-risk'' studies have revealed a reduction in P300 amplitude in children determined to be at high risk of developing alcoholism compared to those who are at low risk, based on their familial loading for alcoholism [11,155,72]. Furthermore, non-alcoholic high-risk individuals also have a different sensitivity to acute alcohol intake than low-risk individuals [111]. Recent findings indicate that, in addition to P3, many of the aberrations in resting and event—related oscillations reported in alcoholics are already apparent in high-risk children of alcoholics before alcohol exposure [137,158]. As the electrophysiological differences are not linked to length of abstinence and are manifest in individuals at risk although they have not yet been exposed to alcohol, these neural oscillations could be considered as markers of risk [131]. The electrophysiological imbalances in excitation-inhibition observed in the children of alcoholics may be involved in the predisposition to develop alcoholism [12]. Inherited factors also include biologically rooted individual differences in behavioural tendencies and self-regulation. A number of authors have provided compelling evidence for the presence of externalizing traits (disinhibitory behaviour such as impulsivity, conduct disorder, and failure to conform to social norms) not only in alcoholics but also in children at high risk of developing alcohol dependence [180,49,101].

Alcoholism is a complex disorder and its development and evolution are influenced by underlying biological factors and by intricate interactions among genes and between genes and the environment. Taking all of these factors into account is necessary to bridge the gap from the laboratory to the clinic and to create clinical research protocols to optimize therapy. Therapy must include preventive and rehabilitation measures. Preventive measures must be targeted at families at high risk of alcoholism as well as at individuals with binge drinking habits.

Firstly, since there is evidence that some factors underlying the disease, such as impulsivity and neural disinhibition are genetically influenced, evaluating those vulnerability characteristics in subjects at high risk may be a promising strategy to prevent alcohol dependence. This approach would involve assessments of electric components known to underlie these characteristics using EGG, ERP and ERO measures as well as the presence of externalizing traits using behavioural measures. The aim would be to elaborate clinical therapy protocols in order to work on these potentially dangerous traits and to prevent subjects from developing alcoholism. However, one should remember that, in addition

to the popular P3 component, earlier components may be at the origin of the pathology and its associated impairments. Hence, a useful evaluation must consist of the identification of the origin of the deficit at the different stages of cognitive processing in every single patient.

Secondly, in adolescence, consuming a large number of drinks over a short interval of time (e.g., binging) is quite a common phenomenon. However, adolescence is an important neurodevelopmental period. Health researchers are, therefore, concerned about the effects of binge drinking on the adolescent brain. Ehlers et al. [39] showed in a recent study that adolescent alcohol exposure is linked to delayed latency of an early P3 component (P350). In the same study, decreases in P450 amplitude, a later component, were also found in young adults exposed to alcohol. However, that finding appears to be an integrated result of predisposing factors, such as a family history of alcoholism and the presence of other externalizing diagnoses. Taken together, these preliminary results suggest that adolescent binge drinking may lead to decreased P3 latencies and amplitudes, perhaps reflecting a loss or delay in the development of inhibitory brain systems [39]. These inhibitory deficiencies could in time lead to alcohol dependence. Binge drinking and alcohol dependence have indeed been shown to be strongly associated. Most binge drinkers are diagnosed as alcohol dependent [166]. Binge drinking in adolescence is associated with an increased risk of alcohol dependence and harmful drinking in adulthood [142,166]. Assessments of binge drinking patterns as well as appropriate treatment should therefore be included in prevention strategies.

Conclusions

The main purpose of the present paper was to show how clinical neurophysiology may help to improve our understanding of psychiatric disorders. Clinical neurophysiology has developed different tools to evaluate the integrity of the neural system in humans. If we take these tools separately (ERPs, EEGs, EOG, EROs, SC reactivity), their clinical applicability is hampered by the fact that most of these parameters are diagnostically non-specific (relative to bipolar disorder, schizophrenia or personality disorders) and not reliable enough to be useful for the individual patient. However, if we consider a large array of these electrophysiological parameters (from the emergence of the disease to remission periods and family studies) in conjunction, and use them to develop precise psychological constructs that can themselves be related to the definition of a precise neural network, we will be able to define, for an individual psychiatric patient, the disturbed cognitive processes that lead to specific clinical manifestations, and link these disturbances to precise anatomical dysfunctions. This may help us to optimize our pharmaceutical (by adapting drugs to the patient's specific pathophysiology), neuropsychological (by focusing interventions at the specific disturbed cognitive processes, i.e., perception, attention, mnesic, executive functions), and psychotherapeutic (mainly for psychological support if needed) approaches. Obviously, in addition to the evaluation of genetic and neuronal factors, it is also essential to detect environmental factors that may play a role and to elucidate their relative and interactive contributions in the onset and evolution of the disease.

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