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Chemosensory event-related potentials in alcoholism: A specific impairment for olfactory function

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ABSTRACT

Olfactory abilities are crucial in the development and maintenance of alcoholism, but while they have been widely explored in other psychiatric states, little is known concerning this sensorial modality among alcoholics. The present study explored the brain correlates of the olfaction deficit in alcoholism. Ten alcoholics and ten matched controls took part in psychophysical and electrophysiological olfactory testing. At behavioural level, we showed odor identification deficits in alcoholism, for orthonasal and retronasal testing. Electrophysiological data showed abnormalities (in latency and amplitude) for N1 and P2 olfactory components among alcoholics, which constitutes the first description of the cerebral correlates of olfactory impairments in alcoholism. This deficit appears associated with alterations in the brain structures responsible for the secondary, "cognitive" processing of odors. These results underline the need to take into account olfactory deficits in clinical practice and in studies exploring brain correlates of craving by means of alcohol odors.

1. Introduction

Alcohol dependence is the most spread psychiatric disorder in Western countries, and its consequences at cerebral (Baker et al., 1999; Fadda and Rossetti, 1998; Harper, 2009), cognitive (Chanraud et al., 2010; Lawrence et al., 2009; Noël et al., 2006; Schneider et al., 1998) and emotional (Jung et al., 2009; Kornreich et al., 2002; Philippot et al., 1999; Uekermann et al., 2005) levels are now very well established. An almost exhaustive clinical picture of the deleterious effects of alcoholism is thus available. Nevertheless, some abilities have surprisingly received little attention, and this is particularly true for olfaction as the huge majority of studies investigating alcohol effects focused on visual and auditory stimulations. Indeed, very few studies have investigated olfactory abilities in alcohol dependence. This constitutes an important shortcoming for the understanding of alcoholism because olfaction is in the heart of this affection for several reasons.

First, the olfactory system is crucial in the expansion and maintenance of alcohol dependence. Alcohol odor constitutes a powerful appetitive cue, as alcohol consumption involves a strong and double (i.e. orthonasal and retronasal) olfactory stimulation (Bragulat et al., 2008). Animal studies clearly showed that this olfactory stimulation is widely involved in the arisen of conditioned alcohol-seeking response (Katner and Weiss, 1999; Pautassi et al., 2009). In humans, several studies demonstrated that alcohol odors lead to a stronger craving response and desire to drink than visual or auditory alcohol-related cues (de Wit, 2000; Grüsser et al., 2000; Rohsenow et al., 1997; Schneider et al., 2001; Weinstein et al., 1998), particularly during withdrawal periods (Kareken et al., 2004; Little et al., 2005). While underexplored up to now, olfactory stimulations thus appear to play an important role in the appearance of alcohol dependence and in the relapse risk after detoxification.

Second, the olfactory impairment might significantly disrupt alcoholics' everyday life. While globally underevaluated and undertreated in the general population (Reiter and Costanzo, 2003), olfactory impairment is particularly disabling, notably by increasing the risk of injury and lowering social relationships' global satisfaction (Murphy, 1993; Schiffman, 1997). Moreover, as odors are implied in food perception and enjoyment (Smeets et al., 2009), impaired olfaction could partly explain the nutritional alterations

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frequently observed in alcoholism, which worsen its health consequences (Carey, 1989; Leevy et al., 1970). Nevertheless, no clinical assessment or rehabilitation program has yet been developed for olfactory deficits in alcohol dependence.

Third, olfactory abilities have recently been investigated in many other psychopathological states (Clepce et al., 2010; Krüger et al., 2006; Lombion et al., 2010; Luzzi et al., 2007; Pause et al., 2001; Roessner et al., 2005; Scinska et al., 2008; Striebel et al., 1999; Wiggins et al., 2009), which indubitably enriched the theoretical and clinical knowledge concerning these diseases. They suggested that each disorder could be characterized by a specific olfactory impairment pattern (Atanasova et al., 2008). Particularly, olfaction studies in schizophrenia exponentially grew recently, and olfaction is now considered as a central topic to understand the etiology and psychopathology of schizophrenia (Moberg et al., 1999; Rupp, 2010). Olfaction evaluation could thus become a very useful tool in psychiatry, and it appears prejudicial that this exploration of olfaction has not yet been applied to alcoholism.

Finally, the proposition that olfaction is crucial in alcoholism is further reinforced by animal genetic studies (Saba et al., 2006; Tabakoff et al., 2008, 2009): using quantitative trait locus analysis, they identified eight genes explaining a significant amount of the variance concerning alcohol preference in mice, and showed that these genes were all expressed in regions implied in olfactory processing (particularly limbic areas and orbitofrontal cortex). As underlined in these studies, the strong genetic links between olfaction and alcohol preferences reinforce the proposition that olfaction is highly implied in the development of alcohol dependence.

Hence, very few studies have explored the general olfactory abilities among alcohol dependent individuals. Moreover, they led to contradictory results as some showed impaired olfactory abilities (DiTraglia et al., 1991; Potter and Butters, 1979; Rupp et al., 2003, 2004, 2006; Shear et al., 1992) while others did not observe any deficit (Jones et al., 1975, 1978; Kesslak et al., 1991; Mair et al., 1986). Centrally, these studies presented two main shortcomings: (a) A lack of control for potentially biasing variables like medication or comorbid psychopathological states. As these frequent alcoholism comorbidities (Fein et al., 2008; Loas et al., 2000) are known to influence olfactory abilities (Clepce et al., 2010; Lombion et al., 2010), the olfaction impairment observed earlier could be due to these comorbidities rather than to alcohol consumption itself. (b) A focus on behavioural exploration. All previous studies solely relied on behavioural evaluation, so that nothing is known about the cerebral correlates of olfaction impairments in alcoholism.

The present study aims at overcoming these limits by exploring the cerebral alterations associated with olfactory impairment in alcohol dependence, with a strict control of potentially interfering variables and by means of chemosensory event-related potentials (ERP). ERP allow monitoring the electrical activity of the brain with high temporal resolution (Rugg and Coles, 1995). Visual and auditory ERP have been widely used to explore brain impairments in alcoholism, showing marked latency and amplitude alterations (see Campanella et al., 2009; Ceballos et al., 2009 for recent reviews). But chemosensory ERP, while now constituting a reliable tool to explore the cerebral correlates of olfaction (Hummel and Welge-Lüessen, 2006; Rombaux et al., 2006a), are still unexplored in alcoholism. This technique is particularly interesting as it offers a multi-level and separate exploration of: (a) olfactory and trigeminal stimulation: benzyl carbinol (Kobal and Hummel, 1988) activates the olfactory nerve [associated with the sense of smell (Evans et al., 1993)], while CO_2 activates the trigeminal nerve, associated with somatosensory sensations (e.g. burning, irritation); (b) primary and secondary odor processing: primary stages, indexed by N1 component [peaking around 320–450 ms after stimulus onset (Hummel and Kobal, 2002)], reflect the exogenous cortical activity directly related to chemosensory input processing. Secondary stages, indexed by P2 component [peaking around 520–800 ms after stimulus onset (Pause et al., 1996)], reflect endogenous cortical activity. In addition to offering the first exploration of olfaction cerebral correlates impairments in alcoholism, chemosensory ERP will thus allow to explore whether this deficit is (a) general for chemosensory processing (olfactory and trigeminal abilities) or specific for olfactory ones, and (b) affecting the whole processing stream (i.e. starting at primary stages) or specific for late processing stages.

2. Methods and materials

2.1. Participants

Ten inpatients (seven men), diagnosed with alcohol dependence according to DSM-IV criteria, were recruited during the third week of their detoxification treatment (St Luc Hospital, Brussels, Belgium). They were free of any other psychiatric diagnosis (as assessed by an exhaustive psychiatric examination), were all right-handed and were matched for age, gender and education level with a control group composed of 10 volunteers who were free of any history of psychiatric disorder or drug/substance abuse. Exclusion criteria for both groups included major medical and neurological impairments, olfactory loss/disorder and polysubstance abuse. Groups' characteristics are presented in Table 1. Although all control participants were free of any medication, six alcoholic individuals still received low doses of benzodiazepines (14.04 ± 14.87 mg/day). Participants were provided with full details regarding the aims of the study and gave their informed consent. The study was approved by the Ethical Committee of the Medical School.

2.2. Task and procedure

2.2.1. Control measures

Questionnaires were used to evaluate sub-clinical comorbid psychopathologies: state and trait anxiety [State and Trait Anxiety Inventory, form A and B (Spielberger et al., 1983)], depression [Beck

Table 1
Alcoholic and control individuals' characteristics: mean (S.D.)..

	Controls ($N = 10$)	Alcoholics ($N = 10$)
Gender (women/men)^{NS}	3/7	3/7
Age (in years)^{NS}	48.6 (7.07)	50.6 (12.6)
Education level (in years since starting primary school)^{NS}	16.1 (2.54)	15.8 (3.91)
Number of standard drinks per day (before detoxification)*	0.81 (0.34)	16.5 (13.6)
Number of days since last drink	4.34 (1.21)	16.47 (3.79)
Number of anterior detoxification treatments	NA	1.8 (1.98)
Mean disease duration (in years)	NA	14.7 (14.53)
Presence of smoking habits (yes/no)^{NS}	5/5	5/5
Mean number of cigarettes per week^{NS}	98.5 (104.5)	70 (79.12)
Mean duration of smoking habits (in years)^{NS}	9.5 (10.62)	5.67 (5.96)
BDI[a]$^{/NS}$	3 (3.53)	8.25 (9.49)
STAI A[b]$^{/NS}$	40.6 (10.84)	38.25 (14.42)
STAI B[b]$^{/NS}$	40.3 (9.87)	48.5 (13.36)
IIP[c]$^{/NS}$	1.88 (0.79)	1.41 (0.34)
TAS-20[d]$^{/NS}$	42.7 (8.89)	49.63 (8.37)

NS, non-significant.
[a] Beck Depression Inventory (Beck and Steer, 1987).
[b] State and Trait Anxiety Inventory (Spielberger et al., 1983).
[c] Inventory of Interpersonal Problems (Horowitz et al., 1988).
[d] Twenty-item Toronto Alexithymia Scale–II (Bagby et al., 1994).
* $p < .01$.

Depression Inventory (Beck and Steer, 1987)], interpersonal problems [Inventory of Interpersonal Problems (Horowitz et al., 1988)] and alexithymia [20-item Toronto Alexithymia Scale (Bagby et al., 1994)].

2.2.2. Experimental measures

2.2.2.1. Psychophysical testing of olfactory function.

2.2.2.1.1. Orthonasal testing. Orthonasal olfactory function was assessed by means of the standardized "Sniffin' Sticks" test (Kobal et al., 2000). In this evaluation, odors are presented using felt-tip pens containing a tampon filled with 4 ml of liquid odorants. During odor presentation, the experimenter removes pen's cap and place the pen for 3 s approximately 2 cm in front of both nostrils. This test evaluates olfactory acuity on the basis of three subtests: (1) odor threshold, assessed with N-butanol using stepwise dilutions in a row of 16 felt-tip pens. The task was a triple-forced choice: Three pens were presented in a randomized order (two containing the solvent and the third the odorant at a certain dilution), and the participant had to identify the odor-containing pen. The odor threshold score ranged from 0 to 16; (2) odor discrimination, in which 16 triplets of pens (two containing the same odorant and the third the target odorant) were presented in a randomized order. Subjects had to identify which odor-containing pen smelled different from the two others. The odor discrimination score ranged from 0 to 16; (3) odor identification, evaluated by means of 16 common odors. Participants were asked to identify each odor using multiple-choice lists of four items. The odor identification score ranged from 0 to 16. Finally, results for odor threshold (T), odor discrimination (D), and odor identification (I) were summarized in a composite threshold–discrimination–identification (TDI) score, ranging from 0 to 48.

2.2.2.1.2. Retronasal testing. Retronasal olfactory function was evaluated using a standardized and validated testing (Heilmann et al., 2002) based on the identification of odorized powders or granules presented in the oral cavity. Twenty stimuli were selected (namely coffee, vanilla, cinnamon, cocoa, raspberry, orange, garlic, strawberry, cloves, nutmeg, onion, cheese, curry, milk, banana, mushroom, coconut, lemon, paprika and celery). Stimulants were applied to the midline of the tongue. For each item, participants were asked to perform a forced choice from a list of four items. Participants rinsed with water after administration of each powder.

2.2.2.2. Chemosensory ERP. The ERP were recorded in response to olfactory and trigeminal stimulations with a validated paradigm (see Rombaux et al., 2006a) using a computer-controlled stimulator based on air-dilution olfactometry (Olfactometer OM2S; Burghart Medical Technology, Wedel, Germany). This olfactometer allows delivery of the chemical stimuli without altering mechanical or thermal conditions in the nasal cavity. Stimuli reach the nasal cavity through Teflon tubing placed into a nostril with its opening beyond the nasal valve, pointing toward the olfactory cleft. The total flow rate was 8 l/min (36 °C; 80% relative humidity; stimulus duration, 200 ms; stimulus rise time, <20 ms). To avoid auditory evoked responses due to possible switching clicks associated with the presentation of the chemical stimuli, participants received white noise of 60–70 dB sound pressure level through headphones. Participants sat in a well-ventilated room and were asked to reduce their eye movements or blinks and to breathe through their mouth for the duration of the recording session. Stimulation was presented monorhinally while patients were sitting in a well-ventilated room. Benzyl carbinol (50%, v/v), which has a positive floral odor, was used for olfactory stimulation, and carbon dioxide (50%, v/v) was used for trigeminal stimulation. The two stimuli were presented 20 times each in a randomized sequence with an inter-stimulus interval of 30 s.

Electroencephalogram (EEG) was recorded at a 256 Hz sampling rate from three scalp midline electrode positions (Fz, Cz, Pz) using a SAM 32EP EEG amplifier and digitizer (Micromed, Mogliano Veneto, Italy). Linked earlobes (A1/A2) were used as reference. The impedance of all electrodes was always kept below 10 kΩ. Epochs were created starting 500 ms prior to stimulus onset and lasting for 2000 ms. After baseline correction (reference interval: 500–0 ms), epochs were band-pass filtered (0.3–12 Hz FFT filter). Trials containing eye links and/or showing an activity higher than 50 μV on Fz were rejected before averaging. A minimum of 60% of artifact-free recording was considered as the limit allowing any further interpretation of the CSERP (12 of 20 trials). All offline signal-processing procedures were performed using the Letswave EEG toolbox (Mouraux, 2005). Average waveforms for each stimulation type (olfactory or trigeminal) and each electrode channel were computed for each subject. A general time window was determined globally for the identification of each ERP component on the basis of the ERP literature (290–490 ms for N1, 460–820 ms for P2). Peak selection was then conducted: For each participant, electrode and component of interest, individual peak amplitudes and maximum peak latencies were obtained for the ERP resulting from the waveforms evoked by olfactory or trigeminal stimulations. While control measures and behavioural data were tested using one-way analysis of variance (ANOVA), ERP values were tested using repeated measures ANOVA (Greenhouse–Geisser correction was applied when appropriate), paired sample *t*-tests and two-tailed Pearson correlations.

3. Results

3.1. Control measures

Alcoholic participants had a significantly higher alcohol consumption before detoxification than controls [$F(1,18) = 13.06$; $p < .01$] but, as described in Table 1, no significant group differences were observed for age [$F(1,18) = 0.19$; *NS*], education level [$F(1,18) = 0.018$; *NS*], number of cigarettes per day [$F(1,8) = 0.35$; *NS*], duration of smoking habits [$F(1,8) = 0.59$; *NS*], depression [$F(1,18) = 2.43$; *NS*], trait [$F(1,18) = 0.16$; *NS*] or state [$F(1,18) = 2.24$; *NS*] anxiety, interpersonal problems [$F(1,18) = 2.74$; *NS*] and alexithymia [$F(1,18) = 2.84$; *NS*].

3.2. Olfactory measures

As shown in Table 2, groups did not differ concerning odor detection threshold [$F(1,18) = 0.68$; *NS*] and discrimination [$F(1,18) = 0.01$; *NS*]. Nevertheless, alcoholics obtained lower scores than controls for odor identification [$F(1,18) = 9.42$; $p < .01$], TDI score [$F(1,18) = 8.67$; $p < .01$] and retronasal score [$F(1,18) = 4.55$; $p < .05$].

3.3. Chemosensory ERP

For each component (N1, P2), 3 × 2 × 2 ANOVAs were computed separately for latencies and amplitudes, with electrode (Fz, Cz, PZ) and stimulus type (olfactory, trigeminal) as within-factor and group (controls, alcoholics) as between-factor. These results are presented in Table 3 and Fig. 1.

- N1
  - *Latencies*. A significant main effect was found for (a) stimulus type [$F(1,18) = 6.06$; $p < .05$]: olfactory stimulations led to shorter latencies than trigeminal ones; (b) group [$F(1,18) = 5.28$; $p < .05$]: N1 latencies were longer among alcoholics. A significant Group × Stimulus type interaction [$F(1,18) = 4.73$; $p < .05$] indicated that alcoholics presented longer N1 latencies than

Table 2
Alcoholic and controls individuals' results for behavioural olfactory measures: mean (S.D.)..

Group	Orthonasal testing				Retronasal testing (% correct)*
	OT[a/NS]	OD[b/NS]	OI[c/**]	TDI[d/**]	
Controls ($N = 10$)	5.65 (0.63)	12.3 (1.76)	12.3 (0.94)	30.5 (1.93)	72.3 (10.21)
Alcoholics ($N = 10$)	5.55 (1.04)	12.4 (2.27)	10.4 (1.71)	27.25 (2.91)	60.66 (13.5)

NS, non-significant.
[a] Odor threshold score (0–16).
[b] Odor discrimination score (0–16).
[c] Odor identification score (0–16).
[d] Threshold–discrimination–identification global score (0–48).
* $p < .05$.
** $p < .01$.

controls only for olfactory stimulations [$t(9) = 3.58$; $p < .01$], as groups did not differ for trigeminal stimulations [$t(9) = 0.68$; *NS*].
- *Amplitudes*. There was neither significant main effect nor significant interaction.

• P2
- *Latencies*. A significant main effect was found for Group [$F(1,18) = 4.49$; $p < .05$]: P2 latencies were longer in the alcoholic group. Moreover, a significant Group × Stimulus type interaction [$F(1,18) = 6.09$; $p < .05$] indicated that alcoholics presented longer P2 latencies than controls only for olfactory stimulations [$t(9) = 3.03$; $p < .05$], as the two groups did not differ for trigeminal stimulations [$t(9) = 0.62$; *NS*].
- *Amplitudes*. A significant main effect was found for (a) Electrode [$F(2,36) = 38.44$; $p < .001$]: P2 amplitude was higher at Fz than Cz [$t(19) = 2.59$; $p < .05$] and Pz [$t(19) = 6.67$; $p < .001$], and higher at Cz than Pz [$t(19) = 8.31$; $p < .001$], and (b) Group [$F(1,18) = 4.86$; $p < .05$]: P2 amplitudes were smaller in the alcoholic group. Moreover, a significant Group × Stimulus type interaction [$F(1,18) = 7.66$; $p < .05$] indicated that alcoholic individuals presented smaller P2 amplitudes than controls only for olfactory stimulations [$t(9) = 3.82$; $p < .01$], as the two groups did not differ for trigeminal stimulations [$t(9) = 0.03$; *NS*].

3.4. Complementary analyses

(a) *Gender effect*: this variable was included as a covariate in our ANOVAs. There was no significant influence of gender on experimental results [$F(1,16) < 2.34$; $p > .15$].
(b) *Influence of psychopathological scores on experimental results*: Pearson's correlations (within each group and across groups) were computed between questionnaires scores and experimental results (behavioural and ERP). No significant correlations were found ($\rho < .34$; $p > .16$).
(c) *Influence of medication on experimental results*: Pearson's correlations (in the alcoholic group) were computed between medication level and experimental results. No significant correlations were found ($\rho < .38$; $p > .31$).
(d) *Influence of nicotine dependence on experimental results*: smoking habits were included as covariate in our ANOVAs. We did not observe any significant influence of smoking on experimental results [$F(1,16) < 1.04$; $p > .32$]. Moreover, Pearson's correlations (within each group and across groups) were computed between smoking habits characteristics and experimental results. No significant correlations were found ($\rho < .49$; $p > .11$).
(e) *Association between experimental measures of olfaction*: Pearson's correlations (calculated across groups) were computed between behavioural and ERP measures. While the correlations between ERP values and orthonasal subscales/retronasal scores did not reach significance, a consistent pattern of correlations was found between TDI score and olfactory ERP. TDI score was significantly correlated with olfactory N1 latency ($\rho = -.57$; $p < .01$) and with olfactory P2 latency ($\rho = -.48$; $p < .05$) and amplitude ($\rho = .62$; $p < .01$), but not with N1 amplitude ($\rho = -.02$; *NS*) neither with any trigeminal measure ($\rho < .24$; $p > .3$). Moreover, these links between TDI score and ERP olfactory data was confirmed by covariate analyses: no significant influence of orthonasal subscales/retronasal scores on ERP results were found [$F(1,16) < 2.24$; $p > .13$], but the TDI score significantly influenced olfactory ERP results in which group differences have been found: N1 latency [$F(1,16) = 4.54$; $p < .05$], P2 latency [$F(1,16) = 7.61$; $p < .01$] and amplitude [$F(1,16) = 9.74$; $p < .01$]. This confirms that behavioural and ERP measures of olfaction evaluated the same olfactory processes and both showed a deficit among alcohol-dependent individuals.

4. Discussion

The present study aimed at exploring for the first time the cerebral correlates of the olfactory impairment in alcoholism, and at determining whether this alteration is (a) specific for olfactory stimulations (vs. trigeminal ones) and (b) present as soon as the early stages of olfactory processing (or appearing at later processing steps).

4.1. Behavioural level

First, alcoholic participants showed a preserved "low-level" olfaction (i.e. no odor detection threshold and discrimination deficit). These results are in line with some earlier ones (Jones et al., 1975, 1978), but in contradiction with more recent results (Rupp et al., 2003, 2006) suggesting an impaired detection threshold–discrimination in alcoholism. A possible reason for these contradictory results is that, while earlier studies did not control for interfering variables, the present one proposed a high control of comorbidities, even at subclinical level (as groups did not differ for depression, anxiety and alexithymia). The deficit observed earlier for low-level olfaction could thus be due to uncontrolled comorbidities rather than to alcoholism itself. This proposition is further reinforced by the fact that: (a) depression, anxiety and alexithymia lead to olfaction impairments (Chen and Dalton, 2005; Clepce et al., 2010; Lombion et al., 2010; Scinska et al., 2008), which supports the notion that these comorbidities could reduce olfaction abilities in alcoholism; (b) earlier studies (Rupp et al., 2006) showed that the low-level olfactory deficit in alcoholism is reduced or even disappears when the influence of comorbidities and medication is controlled for. The strict control of potentially confounding variables thus suggests that alcoholism per se does not lead to low-level olfactory deficit.

Nevertheless, alcoholism clearly led to impairments for more complex olfactory functions (i.e. odor identification and general TDI score), which replicates earlier results (DiTraglia et al., 1991; Rupp et al., 2003, 2006; Shear et al., 1992). Moreover, the present results reinforce the earlier observation (Rupp et al., 2003) that this deficit

Table 3
Electrophysiological results: mean latencies [ms (S.D.)] and amplitudes [μv (S.D.)] for each electrode (Fz, Cz, Pz) and each stimulus type (olfactory, trigeminal) for N1 and P2 components, among control and alcoholic groups.

		N1						P2					
		Olfactory			Trigeminal			Olfactory			Trigeminal		
		Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
Controls ($N = 10$)	*Latency*	374 (48.2)	372 (48.8)	372 (37.5)	440 (49.4)	448 (46.5)	444 (53.9)	545 (64.1)	577 (62.8)	558 (78.7)	627 (79.4)	622 (65.5)	621 (66.8)
	Amplitude	−2.55 (3.16)	−2.28 (2.55)	−2.21 (2.16)	−1.98 (2.79)	−2.66 (2.42)	−2.29 (1.21)	13.64 (6.16)	11.6 (4.23)	5.97 (3.47)	9.83 (5.22)	7.35 (2.94)	3.91 (2.01)
Alcoholics ($N = 10$)	*Latency*	454 (68.1)	455 (69.5)	464 (64.1)	458 (87.2)	465 (78.5)	464 (87.1)	662 (84.3)	659 (83.4)	658 (81.2)	649 (87.9)	655 (88.6)	637 (79.4)
	Amplitude	−4.56 (3.32)	−4.21 (2)	−2.05 (1.33)	−3.08 (3.01)	−2.99 (2.19)	−3.32 (2.62)	6.03 (3.05)	5.6 (1.58)	3.45 (2.02)	9.57 (8.41)	7.9 (4.31)	3.44 (3.41)

is not due to smoking habits or medication (absence of correlation between these variables and any olfaction measure) and show that the odor identification deficit is still present when comorbidities are controlled for. While future studies would have to confirm this absence of influence of other addictions (particularly nicotine dependence), it can thus be concluded that alcoholism is associated with high-level olfactory dysfunctions.

Finally, alcoholism was associated with retronasal olfactory impairment. Retronasal abilities had never been explored among psychopathological population, except Parkinson's disease (Landis et al., 2009). This result sheds new light on the behavioural olfactory impairment among alcoholic participants, as orthonasal and retronasal abilities appear to rely on separate processes (Hummel, 2008). This first description of a retronasal deficit in alcoholism thus: (a) complements the clinical picture of olfactory dysfunction in alcoholism, by showing that previously unexplored olfaction abilities are also impaired; (b) supports the proposition that olfactory impairments are implied in alcoholics' nutritional problems (Carey, 1989; Leevy et al., 1970) as retronasal perception is crucial for food's perception; (c) urges future studies to explore taste abilities, as retronasal processing is central in taste–odor interactions (Hornung and Enns, 1987; Murphy and Cain, 1980) and as taste has not been explored yet in alcoholism.

4.2. ERP level

The main result of this study is the first description of olfactory ERP deficit in alcoholism. Indeed, alcoholic participants presented delayed olfactory N1–P2 latencies and reduced P2 amplitude. This complements the few earlier studies showing olfactory ERP impairments in other psychopathological states (Barz et al., 1997; Kayser et al., 2010; Krüger et al., 2006; Turetsky et al., 2003; Welge-Lüssen et al., 2009). These ERP impairments are consistent with behavioural results, as significant correlations were found between global TDI score and impaired olfactory ERP. This is in line with earlier results, obtained among healthy and clinical populations, showing a strong correlation between ERP and behavioural measures of olfaction (Rombaux et al., 2006b, 2009; Roudnitzky et al., 2011). Moreover, the recording of N1–P2 components during olfactory and trigeminal stimulations allows going further than this general description by exploring two complementary propositions:

(a) *Specificity of the deficit for olfactory ERP*. Our results clearly show that the chemosensory deficit in alcoholic individuals is specific for olfaction, as trigeminal chemosensory processing was preserved among alcoholic individuals. This olfactory–trigeminal dissociation shows that the olfactory ERP deficit in alcoholism is not just part of a more general alteration, like for example a global brain activation reduction or impaired nervous transmission (which would also impair trigeminal processing), but is indeed a genuine olfactory impairment. Moreover, at the theoretical level, this dissociation reinforces the proposition that olfactory and trigeminal systems, while presenting some mutual influences and activating similar cortical areas (Frasnelli and Hummel, 2007; Livermore and Hummel, 2004), rely on distinct brain networks (Nordin et al., 2003; Rombaux et al., 2006a).

(b) *Origin of the deficit on the cognitive stream*. Olfactory processing can be separated in two major steps (Martzke et al., 1997; Rombaux et al., 2006a): a primary "sensory" level (indexed by N1) associated with the exogenous brain activity directly provoked by the stimulation in the primary olfactory cortex (Kettenmann et al., 1997); a secondary "cognitive" level (indexed by P2) reflecting endogenous cortical activity influenced by the stimulus novelty and significance. The present results showed that the olfactory deficit in alcoholism is par-

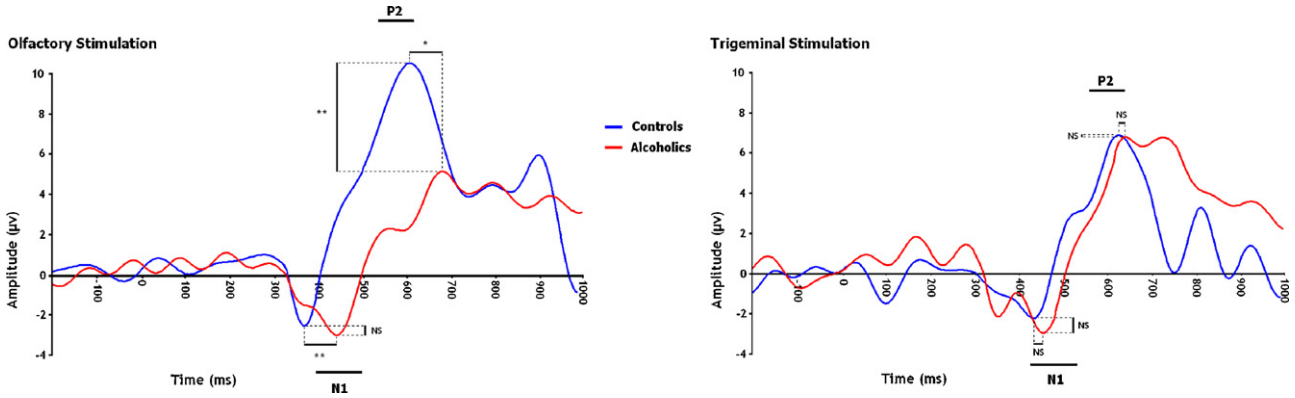

Fig. 1. Electroencephalographic results. Event-related potentials among controls (in blue) and alcoholics (in red) for olfactory (left) and trigeminal (right) stimulations. The waveforms are based on the collapsing of the ERP data across electrodes (Fz, Cz, Pz) and show the specific deficit observed in alcoholism for olfactory stimulation (delayed N1 and P2 latencies, reduced P2 amplitude) as compared to trigeminal ones (no group differences). NS, non-significant; $^{*}p < .05$; $^{**}p < .01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tially detectable as soon as the N1 (delayed latency), but is more pronounced for the later P2 component (delayed latency and reduced amplitude). ERP latency reflects the processing speed while ERP amplitude indexes the processing intensity, i.e. the neuronal population implied in this processing stage (Rugg and Coles, 1995). These results thus suggest that the primary processing stage (N1) is preserved in intensity but delayed, while the secondary cognitive step (P2) is simultaneously delayed and impaired. In other words, alcoholic individuals present a slower but preserved olfactory sensory processing, followed by a delayed and impaired cognitive level. N1 and P2 latency delays could be due to a general slowing down in peripheral sensory transmission (e.g. olfactory nerve and olfactory bulb dysfunction). But more centrally, the amplitude impairments pattern (preserved N1 and impaired P2) support the hypothesis (Rupp et al., 2003; Shear et al., 1992) that olfactory impairment in alcoholism is not mainly due to primary olfactory cortex deficits, but rather to an impairment in the subcortical and cortical areas associated with cognitive olfactory processing (particularly the fronto-temporal areas responsible for high-level olfactory processing): alcoholism is associated with structural and functional alterations in these brain structures (i.e. reduced number of functional neurons, lower neuronal firing synchrony). Importantly, this proposition is strengthened by behavioural results: the odor detection threshold, considered as a primary sensory processing measure (Martzke et al., 1997) is preserved, while the secondary processing level, reflected by identification tasks, is impaired among alcoholic participants. Future studies will thus have to confirm this hypothesis of a specific high-level olfactory impairment in alcoholism.

Finally, it is worth noting that these olfactory ERP alterations are not due to confounding variables, as (a) our groups did not differ for age, gender or educational level; (b) our selection procedure excluded participants with any Axis I–II diagnostic; (c) ERP deficit was not influenced by gender, smoking habits, medication or subclinical comorbidities.

4.3. Implications and conclusions

At the theoretical level, the present results show that olfactory ERP constitute an innovative tool to explore olfactory deficits in alcoholism, and more generally among psychiatric populations. The simultaneous use of olfactory and trigeminal stimulations allows exploring the specificity of the deficit for olfactory functions. Moreover, the possible identification of different ERP components specifically associated with an odor processing stage, permits to identify the origin of the deficit and its latter evolution throughout the olfactory stream.

These first data showing that the olfactory deficit in alcoholism is associated with functional brain impairments have also some implications for the neuroimaging studies exploring craving among alcoholic participants. As underlined above, alcohol odors are highly implicated in the development of alcohol dependence, and many studies used olfactory cues to determine the brain correlates of craving. Nevertheless, these studies were based on the assumption that alcoholics and controls did not differ concerning the general olfactory abilities (i.e. for non-alcoholic odors). Our results show that the olfactory abnormalities in alcoholism, at behavioural and cerebral levels, are not restricted to alcohol odors but constitute a more general impairment also present for non-alcoholic odors. It could thus be that the cerebral modifications observed in earlier studies among alcoholic participants, and considered as the brain correlates of craving, are in fact the consequence of this global olfactory impairment. The absence of a control experimental condition with non-alcoholic cues prevents to draw any strong conclusion from these studies. Future researches using olfactory cues to explore the brain correlates of craving should thus consider this general impairment of the brain areas associated with olfactory processing.

Moreover, the cerebral correlates of impaired olfactory processing (P2 component alterations) are also central concerning the connections between olfaction and high-level cognitive functions. Particularly, executive and emotional deficits are known to be essential in alcoholism and have been extensively explored using visual and auditory stimuli. Nevertheless, olfaction is the only sensorial modality to possess straightforward connections (Price, 1987; Tanabe et al., 1975) with the brain areas processing these emotional and executive stimulations (e.g. amygdala, prefrontal cortex). More specifically, the orbitofrontal cortex constitutes a critical structure concerning this link between olfaction and high-level cognitive functions, as it is simultaneously highly implicated in the processing of olfactory and emotional/executive stimulations (Crews and Boettiger, 2009; Royet et al., 2001). The high-level olfactory processing impairments described here reinforce the hypothesis (Rupp et al., 2006) that a better understanding of olfactory impairment in alcohol dependence could constitute an innovative way to freshen up the exploration of emotion–cognition deficits in alcoholism, as it has been done recently in schizophrenia (Turetsky et al., 2009). Nevertheless, future neuroimaging studies are needed to specify the role played by each cortical area in this olfactory deficit.

A central question concerns the causal link between these olfactory ERP deficits and alcohol dependence. On one hand, the impairment pattern observed among alcoholics is similar to the one observed in neurological states in which high-level olfactory cerebral areas are deteriorated (Barz et al., 1997; Collet et al., 2009; Rombaux et al., 2006b, 2009). This reinforces the proposition (Rupp et al., 2003, 2006) that the olfactory impairment in alcoholism is due to excessive alcohol consumption, which acts as a neurotoxic progressively disrupting the brain areas associated with olfactory processing. Nevertheless, this proposition is still hypothetical, as on the other hand, it could be that the olfactory deficits are at least partly present before the appearance of alcohol dependence. This is supported by genetic animal studies identifying genes simultaneously implied in alcohol preference and olfaction (Saba et al., 2006; Tabakoff et al., 2008, 2009). Moreover, olfactory deficits have been observed among healthy persons at high-risk for developing schizophrenia (Roalf et al., 2006; Turetsky et al., 2008; Ugur et al., 2005) and olfaction is now considered as a vulnerability marker of schizophrenia (Rupp, 2010; Turetsky et al., 2003). Future studies (notably exploring chemosensory ERP among individuals with high-risk of alcoholism) are thus needed to test the hypothesis that olfactory impairments could be a vulnerability marker of alcoholism.

At the clinical level, the present study confirms that alcoholism leads to a behavioural olfactory impairment, extends this observation to other olfactory abilities (i.e. retronasal processing) and offers the first description of the cerebral correlates of this impairment. This deficit might play a role in the poor quality of life and nutrition problems frequently observed among alcoholic individuals. While olfaction impairment is currently totally ignored in psychiatry units, our results thus claim for taking into account this impairment in the clinical context, particularly by developing standard evaluation of these abilities as well as olfaction rehabilitation programs.

In view of the relatively small number of participants and of the use of only one type of olfactory stimulation, the present results are to be considered as preliminary and will have to be replicated in future studies. Moreover, the small number of electrodes used here limits the conclusions that can be drawn from our results, and future studies should be based on a higher number of recording sites (notably to explore the lateralization effects associated with olfactory ERP). The potential influence of comorbidities (e.g. other addictions, depression) on this olfactory deficit in alcohol-dependence should also be further explored. Finally and importantly, the alcohol-dependent population selected in this study presented low abstinence duration (around 15–20 days). It can thus not be excluded that the olfactory deficit described here could be influenced by the early effects of detoxification and modified or reduced with mid- and long-term abstinence. Further data are thus needed to explore the evolution of this deficit during the course of abstinence. Despite these limits, this first observation of an olfactory ERP impairment among alcoholic individuals underlines the importance of exploring olfaction to obtain a better understanding of alcoholism. Knowledge about the behavioural and cerebral correlates of olfactory abilities are indeed tremendously lacking in this pathology, particularly in view of its role in the development and maintenance of alcohol dependence, and of its strong links with cognitive abilities (e.g. executive and emotional processing) considered as crucial in alcoholism.

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All authors declare that they have neither any biomedical financial interests nor any actual or potential conflict of interest.

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