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Research report

The neural network sustaining crossmodal integration is impaired in alcohol-dependence: An fMRI study

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ABSTRACT

Introduction: Crossmodality (i.e., the integration of stimulations coming from different sensory modalities) is a crucial ability in everyday life and has been extensively explored in healthy adults. Still, it has not yet received much attention in psychiatry, and particularly in alcohol-dependence. The present study investigates the cerebral correlates of crossmodal integration deficits in alcohol-dependence to assess whether these deficits are due to the mere accumulation of unimodal impairments or rather to specific alterations in crossmodal areas.
Methods: Twenty-eight subjects [14 alcohol-dependent subjects (ADS), 14 paired controls] were scanned using fMRI while performing a categorization task on faces (F), voices (V) and face–voice pairs (FV). A subtraction contrast [FV−(F+V)] and a conjunction analysis [(FV−F) ∩ (FV−V)] isolated the brain areas specifically involved in crossmodal face–voice integration. The functional connectivity between unimodal and crossmodal areas was explored using psycho–physiological interactions (PPI).
Results: ADS presented only moderate alterations during unimodal processing. More centrally, in the subtraction contrast and conjunction analysis, they did not show any specific crossmodal brain activation while controls presented activations in specific crossmodal areas (inferior occipital gyrus, middle frontal gyrus, superior parietal lobule). Moreover, PPI analyses showed reduced connectivity between unimodal and crossmodal areas in alcohol-dependence.
Conclusions: This first fMRI exploration of crossmodal processing in alcohol-dependence showed a specific face–voice integration deficit indexed by reduced activation of crossmodal areas and reduced connectivity in the crossmodal integration network. Using crossmodal paradigms is thus crucial to correctly evaluate the deficits presented by ADS in real-life situations.

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1. Introduction

Crossmodal processing is the ability to construct a unified representation on the basis of stimuli coming from distinct sensorial modalities (Driver and Spence, 2000). As stimulations are most often integrated in a multi-sensorial flow, this ability is ubiquitous and important for human daily adaptive behaviors like social interactions, spatial attention or perceptuo-motor coordination (Campanella and Belin, 2007; Lalanne and Lorenceau, 2004). While only explored recently, crossmodal mechanisms constitute a blooming research field in neuroscience (Amedi et al., 2005; Calvert et al., 2001; De Gelder and Bertelson, 2003), and several brain areas specifically dedicated to multisensory integration (mainly the superior parietal lobule, inferior occipital, middle frontal and superior temporal sulci) have been identified (Joassin et al., 2011a, 2011b; Love et al., 2011).

Nevertheless, while the brain correlates of crossmodal integration among healthy individuals are well established, few data exist on impaired multimodal integration, particularly among psychiatric populations. Recent results in schizophrenia (De Gelder et al., 2005; Ross et al., 2007; de Jong et al., 2009; Pearl et al., 2009; Szycik et al., 2009; Seubert et al., 2010a; Van den Stock et al., 2011), autism (Foss-Feig et al., 2010; Kwakye et al., 2011; Mongillo et al., 2008; van der Smagt et al., 2007) and Alzheimer's disease (Delbeuck et al., 2007) have suggested large-scale crossmodal deficits in these populations. As crossmodal integration is crucial in daily life, these impairments could be partly responsible for cognitive and social alterations observed in psychiatric states. These preliminary data should thus be extended to offer a more ecological and valid evaluation of psychiatric populations' deficits (Campanella and Belin, 2007), and to better understand healthy crossmodal integration, as exploring an impaired processing among clinical populations can shed new light on normal functioning (Laurienti et al., 2005). The urgency to explore crossmodal abilities in psychiatric states is particularly patent for alcohol-dependence, which is the most wide spread psychiatric disorder (Harper and Matsumoto, 2005). Indeed, the consequences of alcohol-dependence have been extensively investigated at the cognitive and cerebral levels (Bechara et al., 2001; Bülher and Mann, 2011; Harper, 2009; Noël et al., 2001), but previous studies were based on unimodal paradigms, thus preventing any conclusion on the deficits presented by alcohol-dependent subjects (ADS) in real-life situations. Using crossmodal paradigms could thus improve the understanding of alcohol-related impairments (Campanella et al., 2010). The usefulness of crossmodal paradigms in addiction has also been recently underlined in the field of cue-reactivity studies, as a recent review (Yalachkov et al., 2012a) showed that using crossmodal cues (instead of the unimodal visual ones classically used) highly improves the ecological validity of these cues and strongly enhances the induced cue-reactivity. This observation thus further stresses the urgency to switch towards crossmodal stimulations in addiction research and to explore the brain correlates of crossmodality in addictive states.

We recently conducted the two first studies exploring crossmodal integration in alcohol-dependence. As alcohol-dependence leads to social disturbances (Uekermann and Daum, 2008; Uekermann et al., 2005) and as social information is multimodal by essence (Ethofer et al., 2006; Kreifelts et al., 2007), complex social stimuli (faces and voices) were used to increase the ecological value of the paradigm. A first behavioral exploration (Maurage et al., 2007a) showed that the crossmodal facilitation effect [i.e., increased performance for congruent bimodal stimulations as compared to unimodal ones (Latinus et al., 2010; Ngo and Spence, 2010)], indexing successful crossmodal integration (Calvert et al., 2001), is impaired in alcohol-dependence. A second event-related potentials study (Maurage et al., 2008) showed massive impairment of the specific electrophysiological components associated with audio–visual integration in alcohol-dependence, confirming this crossmodal deficit. Nevertheless, the low spatial resolution of event-related potentials did not allow localizing the areas involved in this deficit. Centrally, these preliminary studies did not confirm the specificity of this deficit, namely whether the crossmodal impairment in alcohol-dependence is due to real alterations in brain areas dedicated to crossmodal integration or rather to the simple addition of unimodal impairments provoked by global brain alterations.

The present study thus aimed at determining the brain correlates of crossmodal integration in alcohol-dependence. In line with previous findings on alcohol-dependence, we predicted that alcohol-dependence will lead to specific crossmodal impairment. Namely, we thus hypothesized that ADS will present impaired behavioral facilitation effect and specific cerebral alterations during audiovisual integration. If so, the specific crossmodal activations (resulting from the comparison between crossmodal and unimodal conditions) should be markedly altered in alcohol-dependence, particularly in crossmodal areas (inferior occipital gyrus, middle frontal gyrus, superior parietal lobule). Alternatively, if the crossmodal deficit is just the consequence of more global brain alterations and corresponds to the accumulation of unimodal deficits (i.e., the addition of the brain alterations for faces and voices), the specific crossmodal activations should be globally preserved in alcohol-dependence. Finally, as alcohol-dependence leads to white matter impairments (Pfefferbaum et al., 2005; Yeh et al., 2009) and as crossmodal processing relies on efficient connections between unimodal and crossmodal areas, reduced crossmodal areas activations could be due to impaired connectivity with unimodal ones. Psychophysiological interactions (PPI) exploring functional connectivity between unimodal and crossmodal areas were used to test this hypothesis.

2. Methods and materials

2.1. Participants

Fourteen alcohol-dependent male adults were recruited during their third week of detoxification (Saint-Luc Hospital, Brussels, Belgium). They had all abstained from alcohol for at least 15 days, were right-handed as attested by the Edinburgh inventory questionnaire (Oldfield et al., 1971), and were free of

medication and of any other psychiatric diagnosis except tobacco dependence. Their mean alcohol consumption before detoxification was 16.9 standard alcohol units per day (SD = 5.11), an alcohol unit corresponding to 10 g of pure ethanol. The mean number of previous detoxification treatments was 3.6 (SD = 2.1), and the mean duration of alcohol dependence was 13.7 years (SD = 8.4). They were matched for age, gender and education with 14 male volunteers who were free of any personal or family history of psychiatric disorder and substance abuse, and whose alcohol consumption was lower than 10 standard alcohol units per week. Control subjects (CS) abstained from any alcohol consumption at least three days before testing. Exclusion criteria for both groups included major medical-neurological impairments, past head trauma and polysubstance abuse. Each subject had normal/corrected-to-normal vision and normal hearing. Education level represented the number of education years since primary school. Subjects were assessed for control measures of depression (Beck and Steer, 1987) and anxiety (Spielberger et al., 1983). They were provided with full details regarding the study and gave their written informed consent. The study was approved by the biomedical ethics committee of Catholic University of Louvain and carried out according to the Declaration of Helsinki.

2.2. Task and procedure

In line with earlier studies (Maurage et al., 2007a, 2008), subjects were confronted with faces and/or voices presented separately (unimodal conditions) or simultaneously (crossmodal condition). Two emotional valences were used (anger/happiness), and subjects performed an emotional categorization task.

Visual stimuli were selected from a standardized pictures set (Ekman and Friesen, 1976): Two actors (one male), each displaying two emotions (anger/happiness) were chosen. Facial emotional characteristics are recognized more rapidly than vocal ones (Ellis et al., 1997; Joassin et al., 2004; Schweinberger et al., 1997), but increasing the perceptual complexity of faces can make them as difficult to recognize as voices (Hanley and Turner, 2000). Following an earlier procedure (Maurage et al., 2007a, 2008), visual stimuli were morphed to obtain similar performance levels in vision and audition, leading to a facilitation effect in crossmodal conditions (Maurage et al., 2007a). Four visual stimuli (2 actors × 2 dominant emotions) were used, each depicting 40% of one emotion and 60% of the other. Auditory stimuli were audiotapes enunciating a semantically neutral word ("paper") with an emotional prosody (Maurage et al., 2007b). Four auditory stimuli were selected (2 actors × 2 emotions). Four audio–visual (crossmodal) stimuli were also created, combining visual and auditory stimuli (congruent for emotion and gender). The study comprised 12 stimuli: 2 actors (male 'M', female 'W') × 2 emotions (anger 'A', happiness 'H') × 3 conditions (faces 'F', voices 'V', face–voice 'FV'). Visual stimuli had a 350 × 350 pixels size. Auditory stimuli (Mono, 44,100 Hz, 32bit) were standardized for duration (700 msec) and amplitude (70 dB).

Before the experiment, each subject underwent a training session outside the magnet room to be familiar with the task and to reach a stable performance level. This session comprised three blocks (one per condition) of 12 stimuli (6 per emotion) presented in a random order. Blood Oxygenation Level-Dependent (BOLD) signal changes were then measured while subjects performed the task in the 3 experimental conditions. Subjects answered by pressing a 2-button response pad with right index or middle finger. Response keys were counterbalanced across subjects. Reaction times (RTs) and error rates were recorded. Only correct responses were considered for RTs analysis. Each subject underwent 4 acquisition runs in a counterbalanced order. Each run comprised 9 blocks (3/condition) of 12 trials (WA-WH-MA-MH, each repeated 3 times in a random order). All trials inside each block were related to the same experimental condition and each trial lasted for 2500 msec, comprising the stimulus (700 msec) and an empty interval (black screen, 1800 msec). Subjects had 2500 msec to answer. The blocks were randomized inside each run with the limit that two blocks from the same condition could not appear successively. Each block lasted for 30 sec (12 trials × 2.5 sec/trial) and blocks were interleaved with 15 sec fixation periods (white cross on black background). Each run lasted for 420 sec and comprised 10 fixation periods (total duration:150 sec) and 9 experimental blocks (total duration:270 sec). 36 trials (12 per block × 3 blocks) were recorded in each run for each condition, and a total of 144 trials were recorded (36 per run × 4 runs). Stimulus presentation and response recording were controlled using E-Prime software (Schneider et al., 2002). Back-projected images were viewed through a titled mirror mounted on the head coil.

2.3. Imaging procedure

Functional images were acquired with a 3T magnetic resonance imager and an 8-channel phased array head coil (Achieva, Philips) as series of blood-oxygen-sensitive T2*-weighted echo-planar image volumes (GRE-EPI, TE = 32 msec, TR = 2500 msec, Flip angle = 90°, FOV = 220 × 220 mm, slice thickness = 3.5 mm, SENSE factor = 2.5). Each image volume comprised 36 axial slices acquired in ascending interleaved sequence. Each functional run comprised 168 volumes, 60 corresponding to fixation periods (6 volumes/period × 10 periods) and 108 corresponding to experimental blocks (12 volumes/period × 9 periods, 36 volumes/condition/run). High-resolution anatomical images were also acquired using T1-weighted 3D turbo fast field echo sequence with an inversion recovery prepulse (150 contiguous 1 mm axial slices, TE = 4.6 msec, TR = 9.1 msec, flip angle = 8°, FOV = 220 × 197 mm, voxel size = .81 × .95 × 1 mm^3, SENSE factor = 1.4).

2.4. fMRI data analysis

Data were analyzed using Statistical Parametric Mapping (SPM8, Welcome Department of Cognitive Neurology), implemented in Matlab 7.1 (The Mathworks, Inc.). Functional images were corrected for slice acquisition delays; realigned to the first scan of the first run to correct for within- and between-run motion; coregistered with the anatomical scan; normalized to the MNI template using an affine fourth degree

β-spline interpolation transformation (voxel size = 2 × 2 × 2 mm^3) after the skull and bones had been removed with a mask based on the individual anatomical images; spatially smoothed with 10-mm FWHM Gaussian kernel.

Condition-related changes in regional brain activity were estimated for each subject by a general linear model in which the responses evoked by each condition of interest were modeled by a standard hemodynamic response function. The contrasts of interest were computed at the individual level to identify the cerebral areas activated by faces (F-fix), voices (V-fix) and face–voice associations (FV-fix) relative to the fixation periods used as baseline. Two complementary contrasts were computed to determine the regions specifically responding to one modality and not to the other one [namely (F–V) and (V–F)]. In order to isolate the cerebral areas specifically involved in the associative processes between faces and voices, and in line with most earlier fMRI crossmodal studies, the super-additive criterion (Love et al., 2011) was used, based on the [FV–(F+V)] contrast (Joassin et al., 2011a, 2011b). Significant cerebral activations were then examined at the group level in random-effect analyses using one-sample *t*-tests, with statistical threshold set to $p < .05$ Familywise Error (FWE) corrected for multiple comparisons using cluster size and extending to at least 20 voxels. Between-groups comparisons were conducted using two-samples *t*-tests with the same statistical threshold. A complementary exploration of the specific crossmodal activations was performed using the maximum criterion (Love et al., 2011). In this analysis, a full-factorial Analysis of Variance (ANOVA) with group (CS,ADS) and condition (F,V,FV) as factors was first computed, then (FV–F) and (FV–V) contrasts were computed for each group, as well as group comparisons (CS–ADS and ADS–CS) for these contrasts. Finally the conjunction analysis [(FV–F) ∩ (FV–V)] with a conjunction null hypothesis (Nichols et al., 2005) was performed for each group and for group comparison contrasts. A statistical threshold set to $p < .05$ FWE corrected for multiple comparisons using cluster size and extending to at least 20 voxels was used.

Four PPI analyses (Friston, 2004; Friston et al., 1997) were conducted to determine the areas functionally connected with unimodal areas (left-right fusiform and superior temporal gyri) in the [FV–(F+V)] contrast. For each PPI and each subject, a region of interest (ROI) was determined (5 mm-radius sphere centered on group maximum activity peak in the unimodal area), and the deconvolved activity time course in this ROI was extracted. Activity time course was corrected for the effect of interest. The product of this activation time course was calculated with a condition-specific regressor probing the face–voice integration [FV–(F+V)] to create PPI terms (Joassin et al., 2011a, 2011b). PPI analyses were conducted for each subject and entered into a random-effects analysis for each group with one-sample *t*-tests, using a statistical threshold of $p < .001$ uncorrected with a cluster threshold of 50 voxels. Between-groups comparisons were conducted using two-sample *t*-tests with the same statistical threshold. Finally, the overlap between the significant brain activations found in group comparison for crossmodal integration and for functional connectivity was determined by: (1) performing a global conjunction analysis on the activations found for group comparison (CS-ADS) in each of the four PPI analyses; (2) superimposing the results of this PPI global conjunction analysis with those obtained for the group comparison on [FV–(F+V)] contrast. As no emotional effect was observed in any of our fMRI data, these emotional results will not be described.

3. Results

3.1. Demographic and psychopathological measures

One-way ANOVAs showed that groups did not significantly differ for age [$F(1,26) = .2$,NS], education [$F(1,26) = .66$,NS] and state-anxiety [$F(1,26) = 2.1$,NS], but ADS presented higher depression [$F(1,26) = 9.14, p < .01$] and trait-anxiety scores [$F(1,26) = 8.41, p < .01$] (see Table 1). However, these group differences did not influence the results as no significant Pearson's correlations were found between psychopathological measures and behavioral-fMRI data ($p > .05$ for each correlation). Moreover, once added as covariates in behavioral-fMRI analyses, depression and anxiety scores did not significantly modify the results observed in both groups and group comparisons.

3.2. Behavioral data

A 3 × 2 ANOVA with condition (F,V, FV) as within-factor and group (ADS, CS) as between-factor was conducted separately for accuracy and RTs, with post-hoc paired-samples *t*-tests.

For accuracy, a main effect of group was found [$F(1,26) = 13.46, p < .001$], ADS presenting lower accuracy than CS. A main effect of condition [$F(2,26) = 22.88, p < .001$] was also found: There were more errors in visual than auditory

Table 1 – Results for demographic, psychopathological [mean (SD)] and behavioral measures [RTs: ms (SD)/ accuracy: % of correct responses (SD)] among control (CS) and alcohol-dependent (ADS) subjects.

	CS ($N = 14$)	ADS ($N = 14$)
Demographic and control measures		
Age^{NS}	43 (8.46)	43.5 (10.38)
Educational level^{NS}	14.79 (2.83)	14 (2.25)
BDI**	3.79 (2.06)	7.8 (4.49)
STAI-A^{NS}	38.14 (11.26)	44.29 (11.14)
STAI-B**	39.4 (9.5)	50.57 (12.91)
Behavioral measures		
Accuracy		
F*	81.5 (11.9)	69.4 (13.9)
V**	95.0 (7.9)	81.0 (14.7)
FV***	94.6 (6.2)	78.2 (13.8)
RTs		
F^{NS}	869 (77)	896 (136)
V*	829 (118)	938 (140)
FV***	769 (106)	932 (122)

BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory (A = State-Anxiety; B = Trait-Anxiety).
F = Faces; V = Voices; FV = Face–voice associations.
NS = non-significant; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

[$t(27) = 5.16, p < .001$] and audio–visual [$t(27) = 5.27, p < .001$] conditions.

For RTs, a main effect of group was found [$F(1,26) = 6.62, p < .05$] as ADS had longer RTs than CS. Centrally, an interaction was also found between group and condition [$F(2,26) = 6.02, p < .01$]: ADS showed no significant differences between modalities, while in the control group audio–visual condition led to shorter RTs than auditory [$t(13) = 2.99, p < .01$] and visual [$t(13) = 4.34, p < .01$] ones, thus showing a facilitation effect (see Table 1 – Fig. 1).

3.3. *fMRI data*

3.3.1. *Faces*

Compared to fixation (F-fix contrast), faces elicited the following significant activations (see Table 2A, part 1):

- CS: activations were found in the right superior frontal gyrus and bilaterally in the fusiform gyrus, inferior frontal gyrus, inferior parietal lobule and thalamus.
- ADS: activations were found in the left fusiform gyrus, postcentral gyrus and thalamus, in the right superior frontal gyrus and superior parietal lobule, and bilaterally in the inferior frontal gyrus.
- Group comparison: ADS presented reduced activation in the right middle frontal gyrus. Group comparison results are described in Table 3.

Compared to voices (F-V contrast), faces elicited the following significant activations (see Table 2A, part 2):

- CS: activations were found bilaterally in the fusiform gyrus, inferior frontal gyrus and inferior parietal lobule.
- ADS: activations were found in the right inferior frontal gyrus, in the left precentral gyrus and left thalamus, and bilaterally in the fusiform gyrus.
- Group comparison: ADS presented reduced activation in the right superior frontal gyrus.

3.3.2. *Voices*

Compared to fixation (V-fix contrast), voices elicited the following significant activations (see Table 2B, part 1):

- CS: activations were found in the left calcarine sulcus, in the right superior frontal gyrus, and bilaterally in the superior temporal gyrus.
- ADS: activations were found in the left inferior parietal lobule and bilaterally in the superior temporal gyrus and middle frontal gyrus.
- Group comparison: ADS presented reduced activation in the left middle frontal gyrus and increased activation in the posterior cingulate cortex.

Compared to faces (V-F contrast), voices elicited the following significant activations (see Table 2B, part 2):

- CS: activations were found in the left precuneus and bilaterally in the superior temporal gyrus.
- ADS: activations were found bilaterally in the superior temporal gyrus.
- Group comparison: ADS reduced activation in the left cingulate cortex.

3.3.3. *Face–voice associations*

Compared to fixation (FV-fix contrast), face–voice associations elicited the following significant activations (see Table 2c):

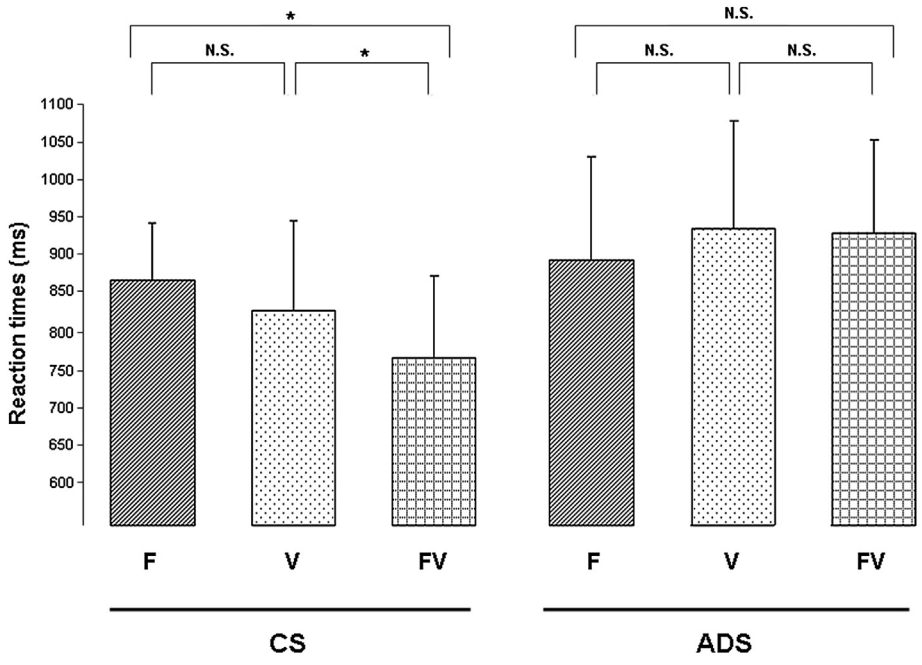

Fig. 1 – Reaction times for control (CS, on the left) and alcohol-dependant subjects (ADS, on the right) in the three experimental conditions (F = Face, V = Voice, FV = Face–Voice), showing the facilitation effect which is present among controls (i.e., shorter reaction times for FV than F and V), but absent in alcohol-dependence (*$p < .01$).

Table 2 – Brain areas showing significant activation among control (CS) and alcohol-dependent (ADS) subjects for: (A.1.) the comparison to baseline (fix) for faces (F-fix); (A.2.) the subtraction between faces and voices (F – V); (B.1.) the comparison to baseline (fix) for voices (V-fix); (B.2.) the subtraction between voices and faces (V – F); (C) The comparison to baseline (fix) for face–voice associations (FV-fix); (D) The super-additive criterion [FV – (F + V)]; (E) The maximum criterion [(FV – F) ∩ (FV – V)].

Contrast	Group	Brain regions	x	y	z	BA	L/R	k	t-statistic
(A.1.) F-fix	CS	Fusiform gyrus	−34	−82	−20	19	L	4032	12.78
		Fusiform gyrus	36	−77	−18	19	R	3833	13.25
		Inferior frontal gyrus	−50	18	24	9	L	275	8.12
		Inferior frontal gyrus	54	14	22	9	R	3284	10.68
		Inferior parietal lobule	−46	−36	48	40	L	931	9.65
		Inferior parietal lobule	38	−46	48	40	R	1728	11.67
		Superior frontal gyrus	10	8	70	6	R	696	5.6
		Thalamus	−16	−14	6	/	L	194	6.61
		Thalamus	18	−12	8	/	R	187	5.66
	ADS	Fusiform gyrus	−44	−55	−20	37	L	2859	9.37
		Inferior frontal gyrus	−42	10	28	45	L	232	8.24
		Inferior frontal gyrus	38	24	2	47	R	1825	9.46
		Postcentral gyrus	−40	−24	64	4	L	1181	6.3
		Superior frontal gyrus	10	12	64	6	R	1132	7.69
		Superior parietal lobule	34	−62	52	7	R	189	5.64
		Thalamus	−18	−26	−4	/	L	299	14.75
(A.2.) F - V	CS	Fusiform gyrus	−40	−66	−20	19	L	2927	13.98
		Fusiform gyrus	42	−64	−20	37	R	3301	12.79
		Inferior frontal gyrus	45	18	14	45	R	530	6.14
		Inferior frontal gyrus	−44	2	31	9	L	23	5.35
		Inferior parietal lobule	38	−48	28	40	R	1724	8.15
		Inferior parietal lobule	−35	−54	54	40	L	235	7.3
	ADS	Fusiform gyrus	33	−68	−16	19	R	3680	9.5
		Fusiform gyrus	−44	−64	−20	19	L	1853	6.83
		Inferior frontal gyrus	40	24	8	47	R	157	5.71
		Precentral gyrus	−40	−10	54	6	L	70	5.45
		Thalamus	−16	−18	−2	/	L	165	6.55
(B.1.) V - fix	CS	Calcarine sulcus	−2	−78	8	23	L	123	4.69
		Superior frontal gyrus	4	14	58	6	R	179	6.9
		Superior temporal gyrus	−50	−32	10	41	L	17154	13.55
		Superior temporal gyrus	48	−24	4	41	R	7249	17.08
	ADS	Inferior parietal lobule	−42	−48	50	40	L	905	11.95
		Middle frontal gyrus	−50	32	34	9	L	530	9.07
		Middle frontal gyrus	46	4	56	6	R	780	7.46
		Superior temporal gyrus	−62	−18	−2	21	L	2385	13.6
		Superior temporal gyrus	46	−20	0	22	R	4403	19.81
(B.2.) V - F	CS	Precuneus	−12	−52	44	7	L	532	6.03
		Superior temporal gyrus	46	−28	6	41	R	6933	15.45
		Superior temporal gyrus	−54	−24	8	41	L	7083	12.9
	ADS	Superior temporal gyrus	−62	−20	−2	21	L	2425	12.76
		Superior temporal gyrus	52	−22	0	21	R	2032	12.57
(C) FV - fix	CS	Fusiform gyrus	−38	−54	−24	37	L	11924	16.23
		Fusiform gyrus	41	−50	−22	37	R	13931	19.17
		Precuneus	8	−72	46	7	R	101	5.34
		Superior frontal gyrus	−8	16	50	8	L	581	8.66
		Superior frontal gyrus	4	16	52	8	R	438	7.89
		Superior parietal lobule	−30	−54	49	7	L	4090	7.73
		Superior parietal lobule	34	−58	50	7	R	1381	11.11
		Superior temporal gyrus-sulcus	−63	−6	−2	21	L	834	7.87
		Superior temporal gyrus-sulcus	60	−9	−3	21	R	1523	9.02
		Thalamus	18	−10	10	/	R	227	7.65
	ADS	Fusiform gyrus	−48	−46	−18	37	L	1159	8.88
		Fusiform gyrus	40	−54	−16	37	R	1307	12.65
		Inferior frontal gyrus	50	20	−6	47	R	5360	21.59
		Superior temporal gyrus	−50	−12	2	22	L	2825	19.85
		Superior temporal gyrus	65	−14	2	22	R	879	12.39

(continued on next page)

Table 2 – (*continued*)

Contrast	Group	Brain regions	x	y	z	BA	L/R	k	t-statistic
(D) FV – (F+V)	CS	Fusiform gyrus	−44	−58	−22	37	L	2084	10.71
		Fusiform gyrus	42	−56	−22	37	R	2467	11.49
		Middle frontal gyrus	−40	8	60	6	L	115	6.29
		Superior parietal lobule	−26	−62	64	7	L	298	5.79
		Superior parietal lobule	32	−54	51	7	R	183	6.01
		Superior temporal gyrus-sulcus	−66	−22	2	22	L	3134	14.21
		Superior temporal gyrus-sulcus	62	−24	4	22	R	2722	17.99
	ADS	Fusiform gyrus	44	−54	−21	37	R	412	7.86
		Superior temporal gyrus	−62	−14	0	22	L	1431	13.59
		Superior temporal gyrus	52	−32	12	41	R	1396	14.32
(E) (FV–F) ∩ (FV–V)	CS	Middle frontal gyrus	−46	10	56	6	L	159	6.23
		Superior parietal lobule	−32	−63	48	7	L	38	5.51
	ADS	Superior temporal gyrus	−52	−27	−1	22	L	113	5.89

x, y and z are stereotaxic coordinates of peak-height voxels.
BA = Broadmann's area, L = Left hemisphere, R = Right hemisphere, *k* = cluster size.
Threshold set at $p < .05$ FWE corrected for multiple comparisons using cluster size.

Table 3 – Brain regions showing significant activation in group comparison between controls (CS) and alcohol-dependent (ADS) subjects for faces alone (F-fix), faces compared to voices (F−V), voices alone (V-fix), voices compared to faces (V−F), face–voice associations (FV-fix), super-additive criterion [FV−(F+V)] and mean criterion [(FV−F) ∩ (FV−V)].

Condition	Contrast	Brain regions	x	y	z	BA	L/R	k	t-statistic
F-fix	CS > ADS	Middle frontal gyrus	44	38	24	10	R	30	4.56
	ADS > CS	No significant activation							
F–V	CS > ADS	Superior frontal Gyrus	46	36	36	9	R	63	5.52
	ADS > CS	No significant activation							
V-fix	CS > ADS	Middle frontal gyrus	−50	34	32	46	L	137	5.84
	ADS > CS	Posterior cingulate	−2	−46	18	29	L	486	4.9
V–F	CS > ADS	Cingulate gyrus	−12	−42	28	31	L	32	7.74
	ADS > CS	No significant activation							
FV-fix	CS > ADS	Fusiform gyrus	−38	−64	−20	37	L	533	4.81
		Fusiform gyrus	42	−65	−20	37	R	145	5.06
		Middle frontal gyrus	44	16	42	9	R	157	4.88
		Middle occipital gyrus	−32	−90	6	19	L	218	4.28
		Middle temporal gyrus	−48	−2	−16	21	L	119	5.11
		Middle temporal gyrus	52	8	−28	21	R	137	4.15
		Precentral gyrus	34	−2	48	6	R	121	3.98
		Precuneus	18	−72	38	7	R	712	4.81
	ADS > CS	No significant activation							
FV-(F+V)	CS > ADS	Fusiform gyrus	−39	−62	−19	37	L	199	3.94
		Fusiform gyrus	30	−67	−14	37	R	67	3.54
		Inferior occipital gyrus	34	−90	−12	18	R	626	4.22
		Middle frontal gyrus	−44	6	60	6	L	120	3.61
		Middle frontal gyrus	46	12	46	8	R	50	3.57
		Superior parietal lobule	32	−58	53	7	R	71	3.43
		Superior temporal gyrus/sulcus	−52	−24	2	22	L	82	4.11
		Superior temporal gyrus/sulcus	68	−34	14	22	R	91	3.81
	ADS > CS	No significant activation							
(FV–F) ∩ (FV–V)	CS > ADS	Fusiform gyrus	−32	−72	−20	19	L	209	3.55
		Inferior occipital gyrus	37	−84	−8	18	R	109	4.51
		Middle frontal gyrus	−22	10	64	6	L	89	4.65
		Middle frontal gyrus	32	10	52	6	R	65	4.11
		Superior parietal lobule	27	−63	45	7	R	41	4.28
	ADS > CS	No significant activation							

x, y and z are stereotaxic coordinates of peak-height voxels.
L = Left hemisphere, R = Right hemisphere, *k* = cluster size.
Threshold set at $p < .05$ FWE corrected for multiple comparisons using cluster size.

- CS: activations were found in the right precuneus and thalamus, and bilaterally in the fusiform gyrus, superior frontal gyrus, superior parietal lobule and superior temporal gyrus-superior temporal sulcus.
- ADS: activations were found in the right inferior frontal gyrus and bilaterally in the fusiform gyrus and superior temporal gyrus.
- Group comparison: ADS presented reduced activations in the right middle frontal gyrus, precentral gyrus and precuneus, in the left middle occipital gyrus, and bilaterally in the fusiform gyrus and middle temporal gyrus.

3.3.4. *Face–voice integration*

The [FV−(F+V)] contrast (i.e., the super-additive criterion) was computed in both groups to isolate the cerebral areas specifically involved in face–voice associative processes (see Table 2d – Fig. 2):

- CS: activations were found in the left middle frontal gyrus and bilaterally in the fusiform gyrus, superior parietal lobule and superior temporal gyrus-superior temporal sulcus.
- ADS: activations were found in the right fusiform gyrus and bilaterally in the superior temporal gyrus.
- Group comparison: ADS presented reduced activations in the right inferior occipital gyrus and superior parietal lobule, and bilaterally in the fusiform gyrus, middle frontal gyrus and superior temporal gyrus-superior temporal sulcus (see Fig. 3).

A complementary exploration of the specific crossmodal activations was performed using a conjunction analysis [(FV−F) ∩ (FV-V)] with a conjunction null hypothesis (i.e., the maximum criterion):

- CS: activations were found in the left middle frontal gyrus and left superior parietal lobule.
- ADS: activations were found in the left superior temporal gyrus.
- Group comparison: ADS presented reduced activations in the right inferior occipital gyrus and superior parietal lobule, in the left fusiform gyrus, and bilaterally in the middle frontal gyrus.

3.3.5. *PPI analyses*

PPI analysis explored the brain areas presenting significant functional connectivity with four unimodal areas in the [FV−(F+V)] contrast (see Table 4 – Fig. 4).

3.3.5.1. Left fusiform gyrus

- CS: Connectivity was found with left cuneus, right fusiform gyrus, middle frontal gyrus, superior frontal gyrus, and superior parieral lobule, and bilateral superior temporal gyrus.
- ADS: Connectivity was found with bilateral superior frontal gyrus and superior temporal gyrus.
- Group comparison: Compared to CS, the connectivity of the left fusiform gyrus among ADS was increased with right cuneus and left superior frontal gyrus, and reduced with right precentral gyrus and superior frontal gyrus, and bilateral middle frontal gyrus.

3.3.5.2. Right fusiform gyrus

- CS: Connectivity was found with left cuneus, right inferior occipital gyrus, middle frontal gyrus, precentral gyrus, superior frontal gyrus and superior parietal lobule, and bilateral superior temporal gyrus.
- ADS: Connectivity was found with left inferior parietal lobule, right precuneus, and bilateral superior temporal gyrus.

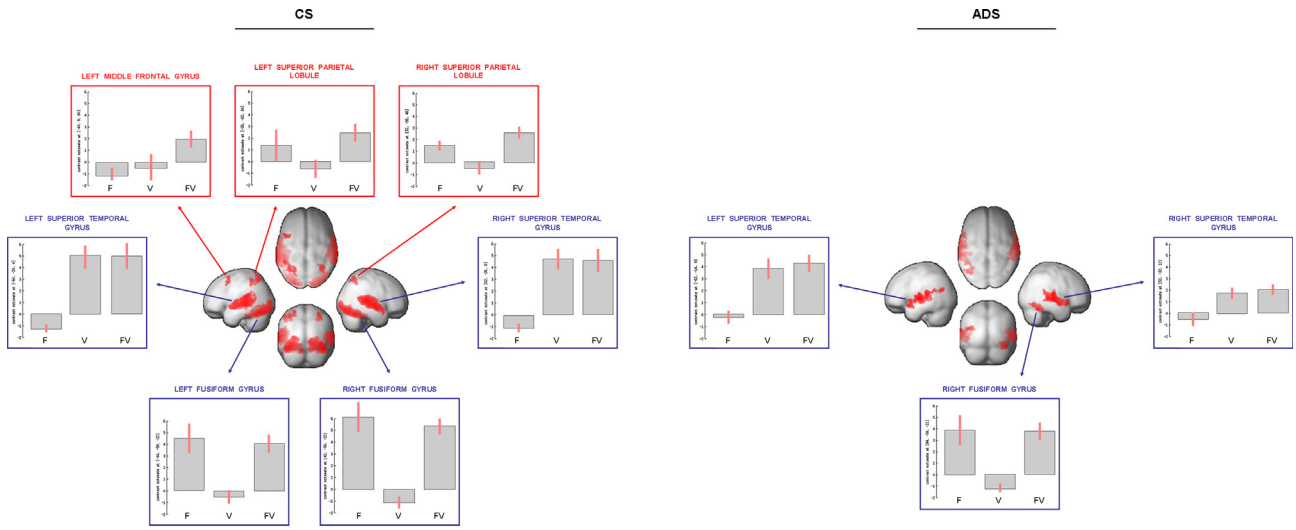

Fig. 2 – [FV−(F+V)] contrast results for the control (CS, on the left) and alcohol-dependant subjects (ADS, on the right). The central figures represent the brain areas significantly activated in the [FV−(F+V)] contrast in each group, by means of the statistical parametric maps superimposed on MRI surface renders. They are surrounded by activation changes (i.e., beta-values) for each condition (F = Face, V = Voice, FV = Face–Voice association) in the activated areas. Classical unimodal areas are in blue, specific crossmodal areas in red. $p < .05$ corrected for multiple comparisons at cluster size. Error bars indicate standard deviations.

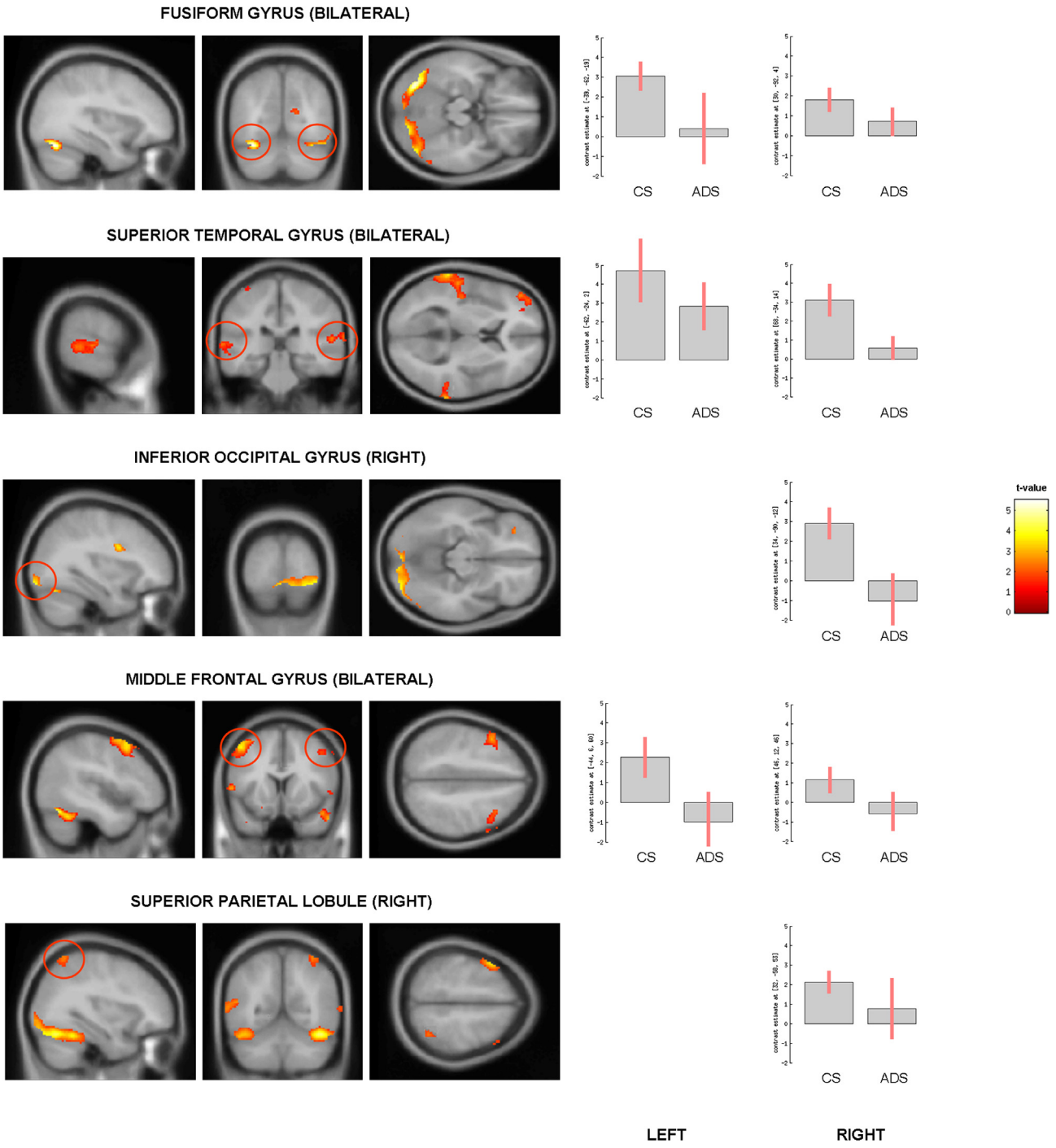

Fig. 3 – Group comparison showing the brain areas presenting significantly reduced activations among alcohol-dependent subjects (ADS) when compared to controls (CS) for the [FV−(F + V)] contrast. Brain sections of the activations for each area are presented on the left, and activation changes (i.e., beta-values) related to this contrast for each group are proposed on the right. $p < .05$ corrected for multiple comparisons at cluster size. Error bars indicate standard deviations.

- Group comparison: Compared to CS, the connectivity of the right fusiform gyrus among ADS was reduced with left fusiform gyrus, and right inferior occipital gyrus, middle frontal gyrus, superior frontal gyrus and superior parietal lobule.

3.3.5.3. Left superior temporal gyrus

- CS: Connectivity was found with left superior parietal lobule, right inferior parietal lobule and middle frontal gyrus, and bilateral fusiform gyrus.

Table 4 – PPI analyses showing the brain areas which present significant functional connectivity with unimodal areas [i.e., left fusiform gyrus (a), right fusiform gyrus (b), left superior temporal gyrus (c), right superior temporal gyrus (d)] during FV – (F + V) contrast. Upper part of each table shows group results [control (CS) and alcohol-dependent (ADS) subjects], lower part shows group comparison.

	Group	Brain area	x	y	z	BA	L/R	k	t-statistic	p-value
(a) Left Fusiform Gyrus										
Group results	CS	Cuneus	−4	−84	3	17	L	353	4.56	<.0001
		Fusiform gyrus	28	−69	−12	19	R	617	5.54	<.0001
		Middle frontal gyrus	4	−28	69	6	R	1865	5.74	<.0001
		Superior frontal gyrus	34	64	−2	10	R	96	4.15	<.001
		Superior parietal lobule	40	−64	50	7	R	229	4.56	<.0001
		Superior temporal gyrus	−60	−32	7	22	L	1590	6.02	<.00001
		Superior temporal gyrus	60	−28	4	22	R	1404	5.53	<.0001
	ADS	Superior frontal gyrus	−32	35	38	9	L	294	7.93	<.00001
		Superior frontal gyrus	8	4	58	6	R	186	4.07	<.001
		Superior temporal gyrus	−57	−12	0	22	L	514	4.31	<.0001
		Superior temporal gyrus	60	−28	4	22	R	789	4.15	<.001
Group comparison	CS > ADS	Middle frontal gyrus	−54	26	40	9	L	110	5.35	<.0001
		Middle frontal gyrus	56	22	36	9	R	875	5.56	<.0001
		Precentral gyrus	18	−30	64	4	R	484	5.25	<.0001
		Superior frontal gyrus	24	67	7	10	R	129	5.5	<.0001
	ADS > CS	Cuneus	20	−84	10	17	R	54	5.25	<.00001
		Superior frontal gyrus	−28	51	37	9	L	121	5.5	<.00001
(b) Right Fusiform Gyrus										
Group results	CS	Cuneus	−4	−84	4	17	L	474	4.92	<.0001
		Inferior occipital gyrus	34	−86	−12	18	R	1079	6.54	<.00001
		Middle frontal gyrus	40	−1	45	6	R	211	3.2	<.001
		Precentral gyrus	20	−36	62	3	R	421	4.35	<.001
		Superior frontal gyrus	14	9	72	6	R	77	3.64	<.001
		Superior parietal lobule	34	−52	50	7	R	54	3.48	<.001
		Superior temporal gyrus	−66	−24	10	42	L	1976	7.08	<.00001
		Superior temporal gyrus	66	−16	2	22	R	2356	8.05	<.00001
	ADS	Inferior parietal lobule	−40	−48	52	40	L	296	6.29	<.00001
		Precuneus	10	−74	40	7	R	107	4.26	<.001
		Superior temporal gyrus	−55	−48	10	22	L	174	6.88	<.00001
		Superior temporal gyrus	57	−26	10	41	R	998	6.93	<.00001
Group comparison	CS > ADS	Fusiform gyrus	−40	−36	−24	20	L	408	3.86	<.001
		Inferior occipital gyrus	34	−88	−14	18	R	408	3.86	<.001
		Middle frontal gyrus	38	42	39	9	R	61	3.91	<.001
		Superior frontal gyrus	34	60	0	10	R	341	5.44	<.0001
		Superior parietal lobule	34	−52	66	7	R	231	4.11	<.001
	ADS > CS	No significant activation								
(c) Left Superior Temporal Gyrus										
Group results	CS	Fusiform gyrus	−30	−69	−16	19	L	158	5.83	<.0001
		Fusiform gyrus	33	−70	−14	19	R	87	5.08	<.0001
		Inferior parietal lobule	36	−47	54	40	R	65	3.54	<.001
		Middle frontal gyrus	18	−12	66	6	R	316	6.32	<.00001
		Middle frontal gyrus	50	14	32	9	R	252	7.04	<.00001
		Superior parietal lobule	−36	−73	44	7	L	180	5.2	<.0001
	ADS	Cingulate gyrus	4	−38	38	31	R	190	6.46	<.00001
		Inferior frontal gyrus	−48	14	37	9	L	52	6.01	<.0001
Group comparison	CS > ADS	Insula	34	−34	20	13	R	97	3.69	<.001
		Middle frontal gyrus	14	−12	58	6	R	68	3.58	<.001
		Middle frontal gyrus	58	34	18	46	R	120	4.32	<.001
		Superior temporal gyrus	50	−44	10	22	R	85	3.68	<.001
	ADS > CS	Cuneus	22	−84	26	31	R	151	5.34	<.0001
(d) Right Superior Temporal Gyrus										
Group results	CS	Cingulate gyrus	16	−10	36	24	R	68	4.25	<.0001
		Fusiform gyrus	−36	−56	−19	37	L	152	4.03	<.001
		Fusiform gyrus	42	−61	−18	37	R	635	5.52	<.0001
		Inferior frontal gyrus	−48	10	32	9	L	219	5.92	<.00001
		Inferior occipital gyrus	42	−79	−11	19	R	3826	6.33	<.00001
		Insula	42	−2	−2	13	R	108	5.28	<.0001
		Middle frontal gyrus	−48	48	14	10	L	83	5.04	<.0001
		Middle frontal gyrus	48	21	26	46	R	699	5.23	<.0001

(continued on next page)

Table 4 – (*continued*)

	Group	Brain area	x	y	z	BA	L/R	k	t-statistic	p-value
		Postcentral gyrus	22	−30	58	3	R	62	3.42	<.001
		Precentral gyrus	−38	−18	60	4	L	325	5.24	<.0001
		Superior parietal lobule	−36	−70	43	7	L	677	5.13	<.0001
		Superior temporal gyrus	−48	−35	14	41	L	52	3.49	<.001
	ADS	Inferior frontal gyrus	49	36	−4	47	R	177	8.21	<.00001
		Inferior parietal lobule	38	−50	42	40	R	70	5.29	<.0001
		Posterior cingulate cortex	−10	−58	21	31	L	289	6.17	<.00001
		Posterior cingulate cortex	10	−58	22	31	R	235	6.44	<.00001
Group comparison	CS > ADS	Inferior occipital gyrus	44	−86	−10	19	R	105	4.1	<.001
		Superior frontal gyrus	−22	44	27	10	L	104	3.67	<.001
		Superior parietal lobule	34	−68	48	7	R	227	4.31	<.0001
		Superior temporal gyrus	−47	−43	18	13	L	100	3.66	<.001
	ADS > CS	Precuneus	8	−72	36	7	R	62	4.53	<.0001

x, y and z are stereotaxic coordinates of peak-height voxels.
BA = Broadmann's area, L = Left hemisphere, R = Right hemisphere, k = cluster size.
Threshold set at $p < .001$ uncorrected with a minimum cluster size of 50 voxels.

- ADS: Connectivity was found with left inferior frontal gyrus and right cingulate gyrus.
- Group comparison: Compared to CS, the connectivity of the left superior temporal gyrus among ADS was increased with right cuneus, and reduced with right insula, middle frontal gyrus and superior temporal gyrus.

3.3.5.4. Right superior temporal gyrus

- CS: Connectivity was found with the left inferior frontal gyrus, precentral gyrus, superior parietal lobule and superior temporal gyrus, right cingulate gyrus, inferior occipital gyrus, insula and postcentral gyrus, and bilaterally in the fusiform gyrus and middle frontal gyrus.
- ADS: Connectivity was found with right inferior frontal gyrus and inferior parietal lobule, and bilaterally in the posterior cingulate cortex.
- Group comparison: As compared to CS, the connectivity of the right superior temporal gyrus among ADS was increased with right precuneus, and reduced with left superior frontal gyrus and superior temporal gyrus, and right inferior occipital gyrus and superior parietal lobule.

3.3.6. *Congruency between crossmodal and functional connectivity deficits*

The overlap between the ADS alterations for crossmodal integration and functional connectivity was determined by superimposing the brain activations found in group comparison (CS minus ADS) for (1) [FV−(F+V)] contrast (Fig. 3); (2) functional connectivity contrasts (Fig. 4), determined by a global conjunction of the activations found for each of the four PPI analyses. These results (Fig. 5) isolated the brain areas simultaneously showing a reduced activation in [FV−(F+V)] contrast and a reduced connectivity with unimodal areas among ADS. An overlap between these two alterations related to alcohol-dependence was found in the right middle frontal gyrus, inferior occipital cortex and superior parietal lobule, and bilaterally in the fusiform gyri and superior temporal gyri.

4. Discussion

On the basis of our earlier studies (Maurage et al., 2007a, 2008) suggesting an impaired crossmodal processing in alcohol-dependence, fMRI was used to investigate the cerebral correlates of this deficit and to determine whether it is specifically accounted for by impaired functioning in crossmodal areas, or rather by more general cerebral alterations also affecting unimodal processing.

First, behavioral results confirmed that the paradigm elicited crossmodal processing as CS presented a crossmodal facilitation effect (Amedi et al., 2005; Diaconescu et al., 2011; Dolan et al., 2001) indexed by faster RTs for the crossmodal condition than for the unimodal ones. ADS had a global behavioral impairment (lower accuracy, longer RTs), confirming perceptual deficits observed earlier (Beatty et al., 1996; Maurage et al., 2007c; Verma et al., 2006). More centrally, and contrary to CS, ADS presented no crossmodal facilitation effect. As this effect indexes efficient face–voice integration, the behavioral results show a specific crossmodal processing impairment in alcohol-dependence, confirming our earlier results (Maurage et al., 2007a, 2008).

Concerning the neuroimaging results, CS first presented classical unimodal activations: Faces alone activated the areas usually involved in face processing (Haxby et al., 2002; Kanwisher et al., 1997; Rhodes et al., 2004), namely bilaterally the fusiform gyri, inferior frontal gyri, inferior parietal lobules and thalami. Voices alone mainly activated the superior temporal gyrus, a critical area for human voice processing (Beaucousin et al., 2007; Belin et al., 2004; Giraud et al., 2004). The direct comparison between unimodal conditions (i.e., F–V and V–F contrasts) confirmed these specific activations of fusiform gyri for faces and superior temporal gyri for voices. Moreover, the [FV−(F+V)] contrast showed that crossmodal processing led to two activation patterns: (1) Activations were found in the areas associated with unimodal processing (i.e., fusiform and superior temporal gyri). This enhanced activation of unimodal areas in crossmodal condition has been repeatedly described (Calvert et al., 1999; Joassin et al., 2011a,

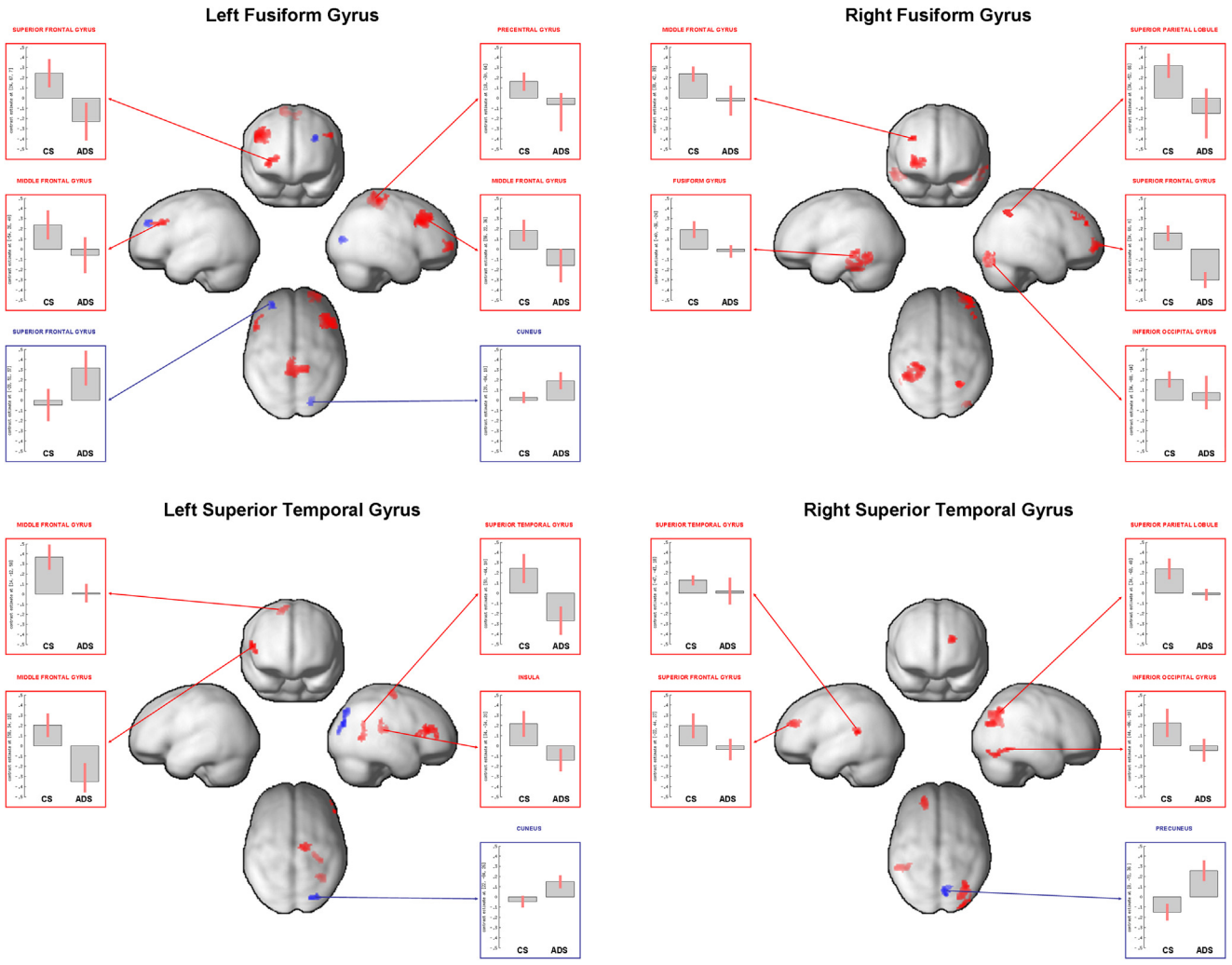

Fig. 4 – Group comparison for the PPI analysis evaluating the functional connectivity with the unimodal areas (left-right fusiform gyri and superior temporal gyri) for the [FV−(F+V)] contrast. This figure shows the brain areas presenting significantly increased (in blue) or reduced (in red) functional connectivity with each unimodal area among alcohol-dependent subjects (ADS) as compared to controls (CS). $p < .001$ uncorrected with a minimum cluster size of 50 voxels. Beta-values for each group in each brain area are presented in graphs around the figure, error bars indicate standard deviations.

2011b; von Kriegstein et al., 2005) and is due to increased connectivity between unimodal areas during crossmodal processing (von Kriegstein and Giraud, 2006). Moreover, the superior temporal gyrus, and particularly the superior temporal sulcus, besides its role in auditory processing, is considered as a key area for audiovisual integration (Campanella and Belin, 2007; Stevenson et al., 2011). As the activations observed here in the superior temporal gyrus are partly located in the superior temporal sulcus, these results confirm the implication of this area in crossmodal integration; (2) Activations were found in specific crossmodal areas (not involved in unimodal conditions), namely the inferior occipital gyrus, middle frontal gyrus and superior parietal lobule. These areas are known to be integrative areas receiving inputs from unimodal sensory regions (Bernstein et al., 2008; Joassin et al., 2011a, 2011b; Rämä and Courtney, 2005; Seubert et al., 2010b). These crossmodal activations were also found in the complementary conjunction analysis, confirming the specific involvement of the middle frontal gyrus and superior parietal lobule during crossmodal integration. The crossmodal activations shown by CS are thus very consistent with the classically described face–voice integration network.

Our main objective was to specify the brain areas responsible for crossmodal impairment in alcohol-dependence. First, ADS, while presenting some reduced unimodal activations (in the middle frontal gyrus), showed a preserved activation of the unimodal areas processing faces (fusiform gyrus) and voices (superior temporal gyrus) in the classical unimodal contrasts (F-fix and V-fix) as well as in the contrasts directly comparing unimodal conditions (F-V and V-F). This confirms earlier results showing a preserved activation of unimodal areas during social stimuli processing in alcohol-dependence (Chanraud-Guillermo et al., 2009; Heinz et al., 2007; Salloum et al., 2007). More centrally, the main result is the reduced specific crossmodal activations in alcohol-dependence: while CS presented activations of specific crossmodal areas in

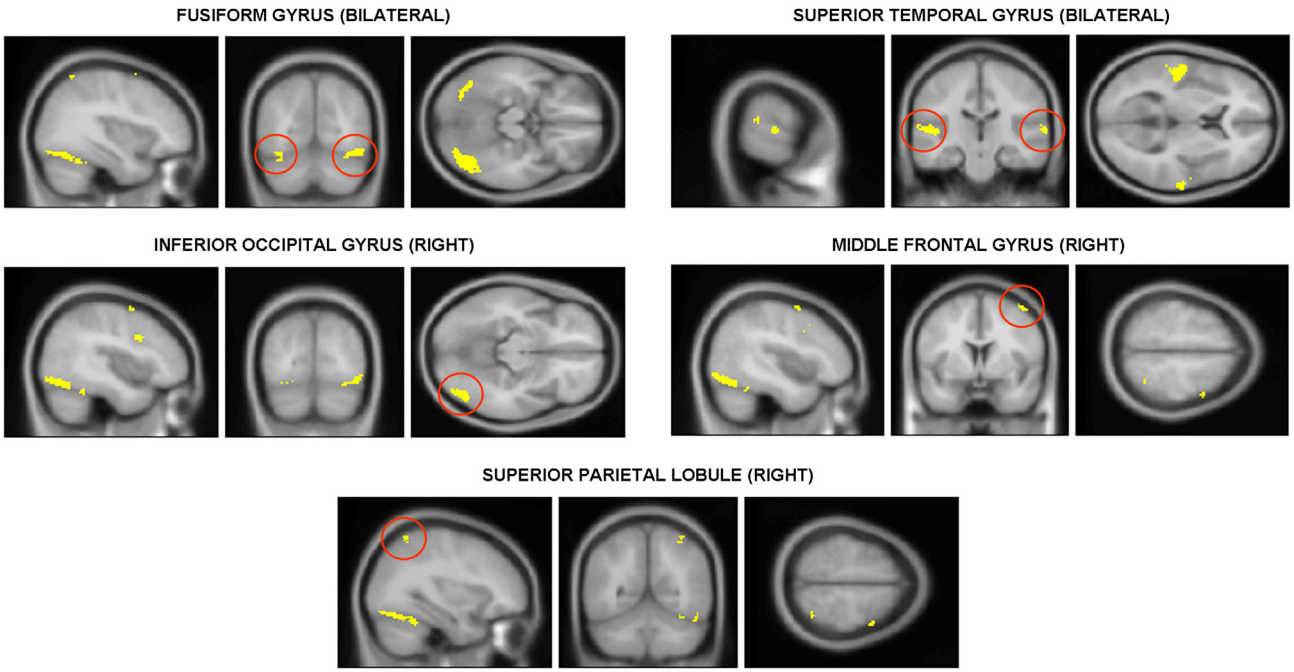

Fig. 5 – Representation of the overlap between cerebral areas showing crossmodal integration deficit and functional connectivity alterations among alcohol-dependent subjects as compared to controls. This figure shows the brain areas simultaneously presenting significantly reduced: (1) activations among alcohol-dependent subjects when compared to controls for the [FV−(F+V)] contrast, and (2) functional connectivity with unimodal areas among alcohol-dependent subjects (ADS) as compared to controls (CS).

[FV−(F+V)] and [(FV−F) ∩ (FV−V)] contrasts, ADS only presented activations of unimodal areas, without any significant activation in associative areas. Group comparison for these contrasts reinforced this result. Compared to CS, ADS showed reduced activations for all areas classically implicated in crossmodal activations: the unimodal areas over-activated among CS in crossmodal conditions (fusiform gyrus and superior temporal gyrus in the [FV−(F+V)] contrast), and the specific crossmodal areas (inferior occipital gyrus, middle frontal gyrus, superior parietal lobule in both [FV−(F+V)] and [(FV−F) ∩ (FV−V)] contrasts). Moreover, the group differences observed in the superior temporal gyrus are partly located in the superior temporal sulcus, which is a key region for crossmodal integration. This result reinforces the proposal of a generalized crossmodal integration impairment in alcohol-dependence. ADS thus present a global hypo-activation of the brain areas involved in face–voice integration. Nevertheless, it should be noted that while the reduced activations in the inferior occipital gyrus and the superior parietal lobule are specifically related to crossmodal integration impairments, reduced middle frontal gyrus activations were already present for the unimodal conditions. It could thus be that this reduced middle frontal gyrus activity is not specific to crossmodal integration but rather indexes a more general frontal hypo-activation. In view of the limited deficit for unimodal conditions, this hypo-activation in crossmodal integration areas cannot be explained by a general reduction of brain activations or by global anatomical modifications related to alcohol-dependence (Harper, 2007; McIntosh and Chick, 2004). Moreover, these results appear linked to alcohol-dependence itself, as depression and anxiety did not influence experimental results.

PPI analyses completed these results by exploring the functional connectivity between unimodal and crossmodal areas during face–voice integration. CS presented a coherent connectivity pattern with (1) increased connectivity within unimodal regions (bilateral fusiform and superior temporal gyri), which confirms the enhanced unimodal connections in crossmodality (von Kriegstein and Giraud, 2006), and (2) increased connectivity between unimodal and crossmodal areas (inferior occipital gyrus, middle frontal gyrus, superior parietal lobule), underlining the efficient functioning of the crossmodal cerebral network. Conversely, ADS did not present this coherent pattern as unimodal areas were partially inter-connected but were not connected with crossmodal ones. Group comparison confirmed the disrupted functional connectivity in the crossmodal network among ADS: as compared to CS, ADS showed highly reduced connectivity between unimodal and crossmodal areas, particularly with the middle frontal gyrus (while, as underlined above, the middle frontal gyrus hypo-activations might be not specific to crossmodal integration). This first use of PPI analyses in alcohol-dependence thus suggests that the crossmodal deficit observed among ADS could be partly due to disrupted connectivity within the crossmodal network, reducing the connections between unimodal and crossmodal areas. This proposal is further reinforced by the complementary analysis showing a strong overlap between the brain areas involved in crossmodal integration deficit and in functional connectivity alterations. Indeed, bilateral fusiform and superior temporal

gyri, as well as right middle frontal gyrus, inferior occipital gyrus and superior parietal lobule, simultaneously presented reduced activations during crossmodal integration and impaired connectivity with unimodal areas among ADS. This makes sense in view of the white matter alterations described in alcohol-dependence (Pfefferbaum and Sullivan, 2005; Yeh et al., 2009), and the crossmodal impairment of ADS could result from a combination of anatomical changes in connectivity and impaired functioning of integrative areas. This "disconnection hypothesis" to explain the crossmodal integration deficits in alcohol-dependence makes sense in view of recent observations in Alzheimer's disease, as a recent study based on the McGurk effect suggested that the disconnection syndrome described in this pathology leads to impaired audio–visual integration (Delbeuck et al., 2007).

This coherent pattern of cerebral impairment during audiovisual integration constitutes the first description of the brain correlates of crossmodal processing in alcohol-dependence. More globally, only two studies explored the cerebral correlates of crossmodality in psychiatry, among schizophrenic subjects (Surguladze et al., 2001; Szycik et al., 2009). Interestingly, our results are coherent with these previous ones, as schizophrenia was associated to preserved unimodal processing but impaired crossmodal integration (particularly in the middle frontal and superior temporal gyri). This similarity between results obtained among different populations suggests that crossmodal impairments might constitute a core deficit in several psychopathological conditions. Nevertheless, while some studies have now explored crossmodal impairments in schizophrenia (De Gelder et al., 2005; Ross et al., 2007; de Jong et al., 2009; Pearl et al., 2009; Seubert et al., 2010a; Van den Stock et al., 2011), autism (Foss-Feig et al., 2010; Kwakye et al., 2011; Mongillo et al., 2008; van der Smagt et al., 2007) and Alzheimer's disease (Delbeuck et al., 2007) at the behavioral level, complementary explorations are needed to confirm these observations among other psychiatric states and to clearly determine the cerebral correlates of impaired integration by means of neuroimaging tools.

Several limitations have to be underlined. First, as our design focused on the simple comparison between crossmodal and unimodal conditions, the cerebral activations observed, which have been interpreted as selectively indexing crossmodal integration, could also be partly due to more general effects. The activations found in the [FV−(F+V)] contrast could indeed be to some extent due to increased perceptual load in crossmodal condition or to a task-related strategy change in link with the need to attend two stimuli simultaneously. Future studies will thus have to explore the specificity of these integration processes by means of paradigms allowing the isolation of crossmodal integration, notably on the basis of congruency manipulation of semantic, spatial or emotional aspects (e.g., Hsiao et al., 2012; Müller et al., 2011; Sarmiento et al., 2012). Second, as we exclusively used emotional stimuli without proposing a control non-emotional condition (based on more basic stimulations), it is impossible to definitely conclude that the crossmodal deficits observed here among ADS exclusively reflects a global impairment for crossmodal processing. While we do not believe that the crossmodal integration deficit observed here can be totally explained by the emotional nature of the stimulations (as ADS presented a preserved processing of unimodal stimulations, which were also emotional), it could indeed be that this deficit is partly due to the use of emotional stimulations, and would be less marked with non-emotional stimuli. The precise influence of the emotional valence of the stimuli on this crossmodal integration deficit in alcohol-dependence will thus have to be determined by including non-emotional control conditions in future experimental designs. Third, the present study used static visual pictures, which limits its ecological validity as real-life situations are based on dynamic facial expressions. Using movies presenting lips movements instead of static pictures, as it has been done in several studies on healthy populations (Collignon et al., 2008; Kreifelts et al., 2007), would strongly increase the ecological validity of future crossmodal explorations in psychiatry.

While these results will thus have to be confirmed and extended in future studies, they already bear some important implications. At the experimental level, the crossmodal integration deficit suggests that the unimodal paradigms used earlier to explore cognitive deficits in psychiatry might have underestimated the deficits presented in real-life situations (which are often crossmodal). Our results claim for using crossmodal paradigms to increase the ecological value of future studies. Moreover, using crossmodal stimulations could also be very useful for cue-reactivity studies in addiction. Indeed, it has been recently underlined that multisensory cues strongly increase the ecological validity of these studies and lead to an enhanced provocation of the drug-seeking behavior, as real-life exposure to drug cues often occurs in several modalities simultaneously (Yalachkov et al., 2012a). Exploring crossmodal processing in psychiatry could also complement the knowledge on normal crossmodal integration. Indeed, by showing specifically reduced activity in inferior occipital gyrus and superior parietal lobule during crossmodal processing among ADS, our results show that these areas are crucial for efficient face–voice integration among healthy subjects. As underlined earlier (Laurienti et al., 2005), establishing connections between studies on healthy and pathological populations could improve the understanding of crossmodality. Finally, at a therapeutic level, the present results showing crossmodal impairments in alcohol-dependence reinforce the proposal (Campanella and Belin, 2007) that they could have deleterious consequences on everyday life. Crossmodal deficits should thus be taken into account in clinical settings, as the reduced ability to integrate social stimulations coming from different sensorial modalities could notably contribute to the interpersonal impairments described among ADS, and thus increase the relapse risk. Moreover, while this study focused on emotional stimulations which were not related to alcohol, it would be interesting to explore whether ADS are also impaired for the crossmodal processing of alcohol-related stimulations. Indeed, an increased processing of unimodal alcohol-related stimuli has been repeatedly shown in alcohol-dependence (i.e., Myrick et al., 2004; Tapert et al., 2004), and enhanced crossmodal integration of cigarette-related stimuli has been recently shown in nicotine dependence (Yalachkov et al., 2012b). The crossmodal processing of alcohol-related cues could thus be preserved or even increased among ADS as compared to controls.

In conclusion, the main result of this study is that ADS have a specific and marked impairment in audiovisual processing. This crossmodal deficit is indexed by an absence of facilitation effect, and more importantly by an extensive reduction of the brain activations dedicated to face–voice integration. Indeed, superior temporal sulcus, inferior occipital gyrus, middle frontal gyrus and superior parietal lobule, which are known to be crucial associative areas, are significantly less activated among ADS than CS when isolating crossmodal activations. Moreover, PPI analyses indicated that this marked reduction of brain activations dedicated to crossmodal integration could be partly explained by reduced functional connectivity between unimodal and crossmodal areas among ADS, leading to a reduced efficiency of the brain network involved in crossmodal processing. These results, together with a global preservation of the areas involved in unimodal processing, offers the first cerebral insights concerning the specific impairment of this crucial ability in alcohol-dependence, and claim for the development of crossmodal studies in psychiatry.

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