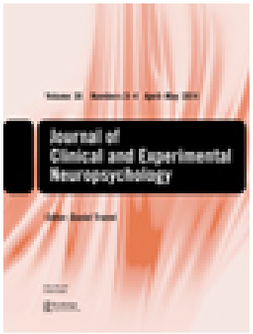

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Imbalance between cognitive systems in alcohol-dependence and Korsakoff syndrome: An exploration using the Alcohol Flanker Task

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ABSTRACT

Background: Alcohol-dependent individuals (ALC) simultaneously present decreased inhibitory control and increased attention towards alcohol-related cues. The dual-process models have proposed that these symptoms reflect an imbalance between prefrontal/reflective and limbic/automatic systems, respectively leading to cognitive dysfunctions in executive processes and to alcohol-related bias. However, most previous research has focused on a separate exploration of these systems among ALC, and the direct measure of their interactions remains to be conducted. Moreover, no study has explored the evolution of this imbalance across the successive stages of alcohol-related disorders, and particularly in Korsakoff syndrome (KS), the most frequent neurological complication of alcohol-dependence.

Method: Ten KS, 14 ALC, and 14 matched control participants performed a modified Flanker task, the "Alcohol Flanker Task," based on congruent, incongruent, and neutral conditions with alcohol-related stimuli. This task required inhibitory processing on alcohol-related stimuli and evaluated, through a behavioral approach, the interaction between reflective and automatic systems, as well as its evolution between ALC and KS.

Results: ALC and KS both presented high reactivity towards alcohol-related stimuli, confirming the presence of alcohol-related bias. KS showed increased omission rates (related to distractor interference) while ALC showed higher false-alarm rates (related to prepotent response inhibition). These results suggest that different inhibitory subcomponents might be altered at the successive stages of the pathology, and experimentally confirms the crucial role of the interaction between reflective and automatic processes in alcohol-use disorders.

Conclusion: The present results reinforce the proposal that alcohol-related cues significantly impact inhibitory control in alcohol-related disorders. However, ALC and KS present different patterns of deficits depending on task complexity (i.e., executive load), thus suggesting a dissociation in inhibitory functions when processing alcohol-related cues.

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Alcohol-related disorders; attentional bias; dual-process model; inhibition

Dual-process models (Bechara, 2005; Bechara & Damasio, 2005; Mukherjee, 2010; Noël, Bechara, Brevers, Verbanck, & Campanella, 2010; Wiers et al., 2007), which are currently the dominant models in addictive disorders, centrally propose that addictive behaviors emerge from the imbalance between two separate but interacting neural systems: a reflective system (mediated by prefrontal regions) using memory and executive functions to initiate controlled–deliberate responses (response–consequences link) and an automatic–motivational system (mediated by limbic regions) driven by appetitive processes triggering spontaneous responses based on associative learning (stimulus–response link). Alcohol-use disorders are thus simultaneously characterized by weak executive functioning (e.g., a reduced ability to inhibit drinking behavior) due to dysfunctional reflective system and by powerful substance-approach impulsions (e.g., a strong appetitive impulse toward alcohol) related to inadequate automatic–motivational activations (Brand, 2005; Brevers et al., 2014; Field, Wiers, Christiansen, Fillmore, & Verster, 2010; Noël et al., 2010).

A large amount of empirical data have validated the impairments found in each brain system. Regarding the reflective system, studies have repeatedly shown, centrally by means of go/no-go, stop signal, or Stroop tasks (Glass et al., 2009; Joos et al., 2013; Kamarajan et al., 2005; Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009; Noël et al., 2012; Pitel et al., 2007), that inhibition deficits are a core characteristic of alcohol-dependent individuals (ALC), involved in the development and

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maintenance of the pathology (Smith, Mattick, Jamadar, & Iredale, 2014). Neuroimaging data have reinforced these observations by reporting cortical gray matter atrophy in prefrontal and parietal regions associated with executive dysfunction, as well as reduced activations of these regions during inhibitory tasks in ALC (Fein et al., 2002; Mason et al., 2005; Meyerhoff et al., 2005). Regarding the automatic–motivational system, previous research has identified, mostly by using attentional bias paradigms (Leménager et al., 2014; Noël et al., 2006), a strong automatic trend towards alcohol cues in ALC, inducing craving (Field, Mogg, Mann, Bennett, & Bradley, 2013) as well as compulsive consumption behaviors (Cox, Klinger, & Fadardi, 2015; Field, Munafò, & Franken, 2009), and directly proportional to actual alcohol consumption (Cox, Fadardi, & Pothos, 2006). This attentional bias is associated with increased activations in the reward network (Hester & Luijten, 2014; Myrick et al., 2004). While constituting a strong validation of both systems' impairment, these previous data present at least two main limits.

First, they nearly exclusively proposed a disjoint exploration of reflective and automatic systems, and thus did not directly explore the main assumption of dual-process models, namely that addiction is related to impaired systems' interactions, characterized by an imbalance with simultaneously underactivated reflective (leading to executive dysfunctions) and overactivated automatic (leading to alcohol-related bias) systems. An effective way to directly test this imbalance is to use behavioral paradigms assessing inhibition response towards alcohol-related stimuli (e.g., addiction Stroop test; Cox et al., 2006). Studies on non-alcohol-dependent social drinkers have shown increased inhibition impairments in Stroop (Field, Christiansen, Cole, & Goudie, 2007), Flanker (Nikolaou, Field, & Duka, 2013), or go/no-go (Petit, Kornreich, Noël, Verbanck, & Campanella, 2012a) tasks when confronted with background alcohol-related stimuli, thus directly documenting systems' imbalance. However, to our knowledge, only very few studies (Czapla et al., 2017; Noël et al., 2007) have documented such imbalance in ALC, showing a performance worsening in go/no-go tasks when confronted with alcohol-related stimuli.

Second, earlier studies focused on recently detoxified ALC without neurological complications, thus totally ignoring the evolution of cognitive systems' deficits within the potential successive stages of alcohol-related disorders, and centrally in Korsakoff syndrome (KS, the most frequent neurological complication of alcohol-dependence). KS usually follows a Wernicke's encephalopathy and is mainly characterized by permanent anterograde and retrograde memory deficits (Pitel et al., 2008) induced by the combination of thiamine deficiency and alcohol neurotoxicity (Butters & Cermak, 1980; Fama, Pitel, & Sullivan, 2012; Sechi & Serra, 2007). KS is thus a relatively rare disorder, the combined effect of thiamine deficiency and alcohol neurotoxicity being much more detrimental than their separated effects (Thomson, Guerrini, & Marshall, 2009). The continuity hypothesis (Bowden, 1990; Ryback, 1971) suggests a linear cognitive decline and worsening of brain impairments between ALC and KS. The suggestion that KS represents a possible outcome situated at the end of a single spectrum of cognitive impairments related to alcohol-use disorders currently remains under debate. Actually, the term "Korsakoff syndrome" has a long history of association with alcohol use because of the high incidence of thiamine deficiency in alcohol-dependent individuals (for a review, see Isenberg-Grzeda, Rahane, DeRosa, Ellis, & Nicolson, 2016). However, it should be pointed out that KS may also originate from various non-alcohol-related conditions such as malnutrition, gastrointestinal surgery, or cancer (e.g., Hargrave, Schroeder, Heinrichs, & Baade, 2015; Nikolakaros et al., 2016; for a review, see Sechi & Serra, 2007). The use of the term thiamine-related encephalopathy has even been proposed to distinguish non-alcohol-related KS from KS associated with alcohol use (Isenberg-Grzeda et al., 2016). Beyond these debates, similarities between the two populations of alcohol-related disorders (i.e., ALC and KS) have been demonstrated in diverse neuropsychological studies (e.g., Butters & Cermak, 1980; Oscar-Berman, Kirkley, Gansler, & Couture, 2004; Pitel et al., 2008), mostly assessing memory processes. KS appeared specifically characterized by a disproportionate episodic deficit compared to ALC, this deficit being manifested by severe amnesia. Consistent with the continuity hypothesis, KS patients would evidence the most severe cognitive impairments and brain damages while ALC would display performance gradually falling between those of KS and healthy individuals. In view of the continuity hypothesis and of the fronto-limbic damages observed in KS (Jacobson & Lishman, 1990; Jauhar & Montaldi, 2000; Kopelman, 1991; Mimura, Kinsbourne, & O'Connor, 2000), it might be hypothesized that KS is characterized by a strong systems' imbalance when considering dual-process models. This hypothesis is reinforced by studies showing that the reflective system associated with executive functions is globally impaired in KS patients, as they present compromised shifting (Beaunieux et al., 2013; Brokate et al., 2003; Shoqeirat, Mayes, MacDonald, Meudell, & Pickering, 1990), updating (Hildebrandt, Brokate, Eling, & Lanz, 2004; Pitel et al., 2008), and inhibition (Beaunieux et al.,

2013; Fujiwara, Brand, Borsutzky, Steingass, & Markowitsch, 2008; Kessels, Kortrijk, Wester, & Nys, 2008; Van Geldorp, Bergmann, Robertson, Wester, & Kessels, 2012) abilities. However, as no study explored the automatic system in KS and as the imbalance between systems has not been directly tested, the validity of dual-process models in KS and the evolution between ALC and KS regarding brain systems' interactions remain to be investigated.

In order to overcome these two limits, the present study directly measured inhibition towards alcohol-related stimuli among ALC and KS, by means of the Alcohol Flanker Task, a modified Flanker task (B. A. Eriksen & Eriksen, 1974) integrating go/no-go components. In its original form, the Flanker task centrally measures the ability to inhibit the processing of irrelevant and incongruent flankers (C. W. Eriksen, 1995) while the go/no-go paradigm evaluates the ability to inhibit a dominant response in no-go trials (Goldstein & Nagliery, 2014). The combined task proposed here thus simultaneously measures two inhibitory processes impaired in alcohol-related disorders—namely, distractor's interference (i.e., conflict processing related to flankers; Padilla et al., 2011) and prepotent response inhibition (i.e., executive control during no-go trials; Goldstein & Nagliery, 2014), and compares these inhibitory abilities when processing closely matched neutral (soft drinks or gray cans) or alcohol-related (beer cans) stimuli. The current study is thus the first to directly explore the imbalance between reflective (inhibitory processes) and automatic (alcohol cue reactivity) systems among ALC and KS. We predicted that alcohol cue reactivity would be increased in ALC and even more in KS compared to healthy control participants (CP), which should lead to: (a) increased performance in ALC and KS when reacting to alcohol-related stimuli compared to neutral ones, despite the global slowdown generally reported in these populations; (b) increased reaction times (RTs) and omission errors when processing non-alcohol-related cues flanked by alcohol-related ones, as participants would need to exert a sustained focus on the central non-alcohol-related target and inhibit automatic bias towards no-go distractors (i.e., beer cans).

Method

Participants

Three groups of participants, 10 KS, 14 ALC, and 14 CP, took part in the study. They were matched for gender, χ^2 (1, N = 38) = 3.73, p = .155, age, $F(2, 35) = 0.96$, p = .390, and education, $F(2, 35) = 2.03$, p = .146, assessed by the number of years of education completed since starting primary school. KS participants were diagnosed with "alcohol-induced persisting amnestic disorder" according to *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* (*DSM–IV*, American Psychiatric Association, 2000) criteria and were recruited during their long-term stay at the Neuropsychiatric Hospitals of Saint-Martin and Beau-Vallon (Belgium). All KS participants had a history of alcohol-dependence and presented severe verbal episodic memory disorders. They were all abstinent (mean abstinence duration = 682 days, SD = 867) and were given adapted nutrition and vitamin supplementation. ALC participants were diagnosed with alcohol-dependence according to DSM–IV criteria and were recruited at the end of their detoxification treatment. They had all been abstinent for at least two weeks (mean abstinence duration = 37.07 days, SD = 44.27), in order to avoid the effects of withdrawal while exploring the durable cognitive consequences of alcohol before the potential recovery following mid- to long-term abstinence (Pitel et al., 2009; Segobin et al., 2014). Alcohol consumption of CP was under two alcohol units per day for women and three units per day for men (Gache et al., 2005). CP were free of any past or present alcohol abuse or dependence, as measured by the Alcohol Use Disorders Identification Test (AUDIT), and did not drink alcohol during the three days preceding testing.

For all participants, general cognitive assessment was carried out through the Montreal Cognitive Assessment (MoCA) and the Brief Evaluation of Alcohol-Related Neuropsychological Impairments (BEARNI; Ritz et al., 2015). Visual episodic memory was assessed by the Doors test (Baddeley, Emslie, & Nimmo-Smith, 1994), and the Stroop test (Stroop, 1935) was administered to measure general inhibition abilities. Psychopathological comorbidities were controlled for using self-reported questionnaires assessing anxiety (State–Trait Anxiety Inventory, Forms A and B; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) and depression (Beck Depression Inventory; Beck, Steer, Ball, & Ranieri, 1996). The study was approved by the Ethics Committee of the Medical School (Université catholique de Louvain, Belgium) and was conducted according to the principles of the Declaration of Helsinki. All participants provided written informed consent to take part in the study and were tested individually. The testing lasted 120 min, with breaks between tasks. Groups' characteristics are provided in Table 1.

Task and procedure

The experimental task was a modified version of the Flanker task, including go/no-go components and consisting of two blocks: one with alcohol-related targets and one

Table 1. Demographic, psychopathological, and cognitive measures for Korsakoff syndrome, alcohol-dependent, and control participants.

	KS (n = 10)	ALC (n = 14)	CP (n = 14)	Group effect p (F)	Post hoc comparisons p (t)		
					CP–KS	CP–ALC	ALC–KS
Demographic measures							
Age (years)	54.3 (8.6)	49.3 (8.2)	51.8 (9.3)	.390 (0.96)	>.999 (0.69)	>.999 (0.72)	.526 (1.38)
Gender ratio (F/M)	4/6	4/10	9/5	χ^2 = 0.155			
Education level (years)	12.6 (1.7)	12.8 (2.3)	14.1 (2.2)	.146 (2.03)	.266 (1.75)	.301 (1.68)	>.999 (0.21)
Alcohol consumption (units/day)*	12.6 (1.7)	24.9 (13.9)	0.2 (0.2)	**<.001** (17.48)	**<.001** (4.43)	**<.001** (5.51)	>.999 (0.59)
Abstinence (days)*	603.2 (840.9)	37.1 (44.3)	3	**.003** (6.82)	—	—	**.009** (3.19)
AUDIT*	—	—	2.6 (1.7)	—	—	—	—
Psychopathological measures							
Beck Depression Inventory*	6.3 (4.3)	10.1 (6.2)	1.9 (2.4)	**<.001** (35.63)	**.084** (2.28)	**<.001** (4.67)	.168 (1.97)
State Anxiety Inventory	33.7 (12.1)	39.4 (14.0)	29.9 (7.6)	.102 (2.44)	>.999 (0.79)	.104 (2.19)	.704 (1.21)
Trait Anxiety Inventory*	40.2 (7.1)	50.2 (11.1)	34.1 (7.0)	**<.001** (11.95)	.312 (1.66)	**<.001** (4.85)	**.027** (2.75)
Cognitive measures							
MoCA*	22.6 (2.2)	25.4 (2.6)	26.4 (2.3)	**.002** (7.40)	**.002** (3.76)	.944 (1.02)	**.023** (2.83)
BEARNI *	7.1 (3.1)	10.6 (3.1)	13.3 (2.3)	**<.001** (14.53)	**<.001** (5.38)	**.042** (2.58)	**.014** (3.02)
Doors Test Part A*	7.1 (2.0)	8.9 (2.4)	10.2 (1.3)	**.002** (7.45)	**<.001** (3.85)	.222 (1.84)	.109 (2.17)
Doors Test Part B*	4.6 (1.1)	5.9 (2.5)	7.6 (1.9)	**.003** (7.04)	**.001** (3.69)	.086 (2.27)	.347 (1.61)
Stroop Denomination (s)*	54.6 (20.1)	78.1 (12.0)	59.5 (8.1)	**<.001** (10.74)	>.999 (0.87)	**.003** (3.65)	**<.001** (4.21)
Stroop Reading (s)*	47.1 (6.6)	55.1 (7.8)	43.9 (6.6)	**.001** (9.06)	.900 (1.05)	**<.001** (4.16)	**.038** (2.63)
Stroop Interference (s)*	113.0 (21.4)	148.9 (37.2)	111.3 (13.6)	**.001** (9.06)	>.999 (0.15)	**.002** (3.74)	**.010** (3.16)
Stroop Interference (errors)	0.7 (1.0)	2.3 (5.5)	0.9 (1.1)	.505 (0.69)	>.999 (0.21)	>.999 (0.94)	.900 (1.05)

Note. Means; standard deviations in parentheses. KS = Korsakoff syndrome; ALC = alcohol-dependent participants; CP = control participants; F = female; M = male; AUDIT = Alcohol Use Disorders Identification Test; MoCA = Montreal Cognitive Assessment; BEARNI = Brief Evaluation of Alcohol-Related Neuropsychological Impairments. Significant p-values are presented in bold text.
*Significant main group effect (p < .05).

with non-alcohol-related targets. Each block contained 375 trials (i.e., 300 frequent go trials and 75 infrequent no-go trials). Participants were required to identify a central target, regardless of the flanking distractors, and to press the spacebar for go trials while refraining to do so for infrequent no-go trials. In the "alcohol-related" target block, the frequent go central target was a beer can ("B") flanked by congruent beer cans ("BBBBB"), incongruent soda ("S") cans ("SSBSS"), or neutral gray ("N") cans ("NNBNN"). The infrequent no-go central target was a soda can flanked by congruent soda ("SSSSS"), incongruent beer ("BBSBB"), or neutral cans ("NNSNN"). In the "non-alcohol-related" target block, go and no-go central targets were reversed so that the frequent go central target was a soda can, and the infrequent no-go central target was a beer can (see Figure 1 for task design). It is worth noting that while prior studies (e.g., Petit, Kornreigh, Maurage, Noël, Letesson, Verbanck, Campanella, 2012b) did not require an effective processing of stimuli (presented as background) and did not match alcohol-related (e.g., alcohol beverage) and non-alcohol-related (e.g., office supplies) stimuli (thus facilitating stimuli discrimination), the present design ensured that the stimuli were effectively processed and were closely matched for colors and shape. This certifies that differences between alcohol-related and neutral stimuli are specifically related to alcohol-cue reactivity.

Every trial started with a random-duration fixation cross (from 400 to 800 ms) followed by the stimulus for a maximum 900 ms (followed by a 490-ms blank screen if the participant did not press the key response during stimulus presentation). Block order was randomized across participants, and each block started with 10 practice trials (repeated if needed) to ensure a correct task understanding. Participants were instructed to answer as quickly and accurately as possible. Error rates (false alarms and omissions) and correct RTs were recorded.

Statistical analyses

Univariate analyses of variance (ANOVAs) were first computed separately for each demographic, cognitive, and psychopathological characteristic with group as between-subjects factor, followed by post hoc independent samples t tests (presented in Table 1). Then, a repeated measures analysis of covariance (ANCOVA) was computed separately for experimental measures (percentage of false alarms, percentage of omissions, mean RT for correct go answers) with group (KS, ALC, CP) as between-subjects factor, condition (congruent, incongruent, vs. neutral) and stimuli (alcohol vs. non-alcohol related) as within-subject factors, and potentially biasing psychopathological variables (i.e., trait anxiety and depression) as covariates. Violations of sphericity were corrected by the Greenhouse–Geisser correction when needed. Post hoc analyses were

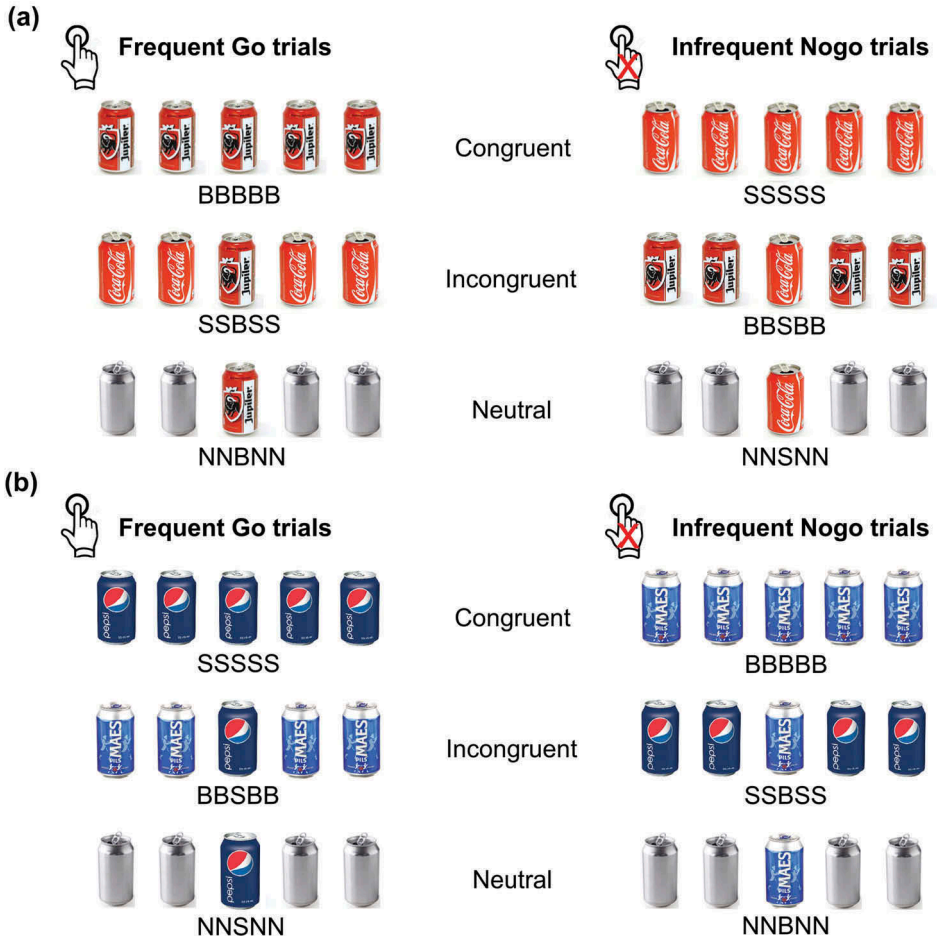

Figure 1. Modified Flanker task. (A) Alcohol-related stimuli block; (B) non-alcohol-related stimuli block. In both blocks, participants have to react to the central target while ignoring congruent, incongruent, or neutral flankers (B = beer can; S = soda can; N = neutral can). To view a color version of this figure, please see the online issue of the Journal.

computed for significant main effects and interactions and were corrected for multiple comparisons using the Bonferroni procedure. For the sake of clarity, we only present the significant main effects and interactions involving groups, as our main aim is to explore the impairments found in ALC and KS. Pearson's correlations finally investigated the links between false alarms, omissions, and RT in incongruent conditions and the Stroop test, to test the relation between the inhibition processes involved in the experimental task and those involved in a classical neuropsychological test.

Results

Experimental measure: Alcohol Flanker Task

As they differed across groups (see Table 1), trait anxiety and depression were included as covariate in the analyses. The main results are presented in Table 2 and Figure 2.

False alarms

A significant effect was found for Group, $F(2, 33) = 5.99$, $p = .006$, ALC presenting more false alarms than CP, $t(26) = 3.37$, $p = .006$, and KS, $t(22) = 2.59$, $p = .042$, which did not differ, $t(22) = 1.16$, $p = .757$. A significant Group × Condition × Stimuli interaction was found, $F(4, 66) = 3.52$, $p = .012$: (a) In the congruent condition with alcohol-related stimuli, ALC had more false alarms than CP, $t(26) = 2.67$, $p = .034$, other comparisons being nonsignificant [CP vs. KS: $t(22) = 1.20$, $p > .999$; ALC vs. KS: $t(22) = 2.50$, $p = .052$]; (b) in the congruent condition with non-alcohol-related stimuli, comparisons were nonsignificant [ALC vs. CP: $t(26) = 2.41$, $p = .063$; CP vs. KS: $t(22) = 1.20$, $p = .716$; ALC vs. KS: $t(22) = 1.50$, $p = .429$]; (c) in the incongruent condition with alcohol-related stimuli, ALC had more false alarms than CP, $t(26) = 3.37$, $p = .006$, other comparisons being nonsignificant [CP vs. KS: $t(22) = 2.27$, $p = .089$; ALC vs. KS: $t(22) = 1.51$, $p = .419$]; (d) in the incongruent condition with non-alcohol-related stimuli, ALC had more false

Table 2. Korsakoff syndrome, alcohol-dependent, and control participants' performance at the Alcohol Flanker Task in congruent, incongruent, and neutral conditions with alcohol- and non-alcohol-related stimuli: False alarms, omissions, and go-RT.

		KS (n = 10)	ALC (n = 14)	CP (n = 14)	Post hoc comparisons (p) CP–KS	CP–ALC	ALC–KS
False alarms (%)							
Alcohol-related stimuli	Congruent	20.00 (17.98)	34.85 (20.30)	19.71 (11.14)	.999	**.034**	.052
	Incongruent	39.20 (23.23)	48.28 (18.66)	23.42 (7.82)	.089	**.006**	.419
	Neutral	23.20 (19.30)	44.28 (18.19)	27.71 (13.07)	.999	**.009**	**.002**
Non-alcohol-related stimuli	Congruent	22.40 (19.43)	31.42 (22.40)	16.85 (9.94)	.716	.063	.429
	Incongruent	29.60 (2.92)	49.42 (17.93)	24.00 (8.15)	.999	**.029**	.074
	Neutral	29.60 (2.58)	43.14 (22.63)	19.42 (6.99)	.750	.083	.506
Omissions (%)							
Alcohol-related stimuli	Congruent	6.70 (9.38)	4.65 (6.36)	2.00 (1.96)	.378	.999	.999
	Incongruent	5.10 (2.33)	4.93 (6.42)	2.93 (2.36)	.999	.999	.999
	Neutral	4.30 (3.23)	4.08 (6.60)	2.58 (3.05)	.783	.999	.999
Non-alcohol-related stimuli	Congruent	1.90 (17.52)	3.93 (5.86)	1.22 (2.08)	.166	.999	.202
	Incongruent	11.30 (11.24)	4.72 (6.89)	1.22 (1.05)	**.014**	.999	.082
	Neutral	8.20 (8.59)	3.29 (5.21)	1.72 (1.68)	**.040**	.999	.101
Go RT							
Alcohol-related stimuli	Congruent	505.98 (55.55)	459.24 (6.09)	464.20 (29.53)	.310	.536	**.011**
	Incongruent	502.60 (56.35)	465.98 (62.29)	482.37 (41.92)	.999	.134	**.023**
	Neutral	485.71 (49.59)	45.49 (6.88)	467.06 (37.91)	.999	.163	**.027**
Non-alcohol-related stimuli	Congruent	506.83 (62.63)	471.59 (45.28)	459.16 (36.65)	.285	.866	**.022**
	Incongruent	515.09 (58.52)	48.12 (44.32)	466.01 (34.76)	.149	.999	**.022**
	Neutral	496.54 (54.29)	463.58 (49.43)	453.13 (35.63)	.367	.730	**.022**

Note. Means; standard deviations in parentheses. KS = Korsakoff syndrome; ALC = alcohol-dependent participants; CP = control participants; RT = reaction time. Significant p-values are presented in bold text.

alarms than CP, $t(26) = 2.74$, $p = .029$, other comparisons being nonsignificant [CP vs. KS: $t(22) = 0.69$, $p > .999$; ALC vs. KS: $t(22) = 2.35$, $p = .074$]; (e) in the neutral condition with alcohol-related stimuli, ALC had more false alarms than CP, $t(26) = 3.21$, $p = .009$, and KS, $t(22) = 3.72$, $p = .002$, which did not differ, $t(22) = 0.16$, $p > .999$; (f) in the neutral condition with non-alcohol-related stimuli, comparisons were nonsignificant [ALC vs. CP: $t(26) = 2.30$, $p = .083$; CP vs. KS: $t(22) = 1.70$, $p = .750$; ALC vs. KS: $t(22) = 1.40$, $p = .506$]. As a whole, ALC presented more false alarms than CP.

Omissions

A significant Group effect was found, $F(2, 33) = 3.69$, $p = .036$, KS presenting more omissions than CP, $t(22) = 2.47$, $p = .019$, other comparisons being nonsignificant [CP vs. ALC: $t(26) = 0.41$, $p = .686$; KS vs. ALC: $t(22) = 1.95$, $p = .059$. A significant Group × Stimuli interaction was found, $F(2,66) = 3.43$, $p = .044$, post hoc t tests showing no group differences for alcohol-related stimuli [CP vs. ALC: $t(26) = 0.48$, $p > .999$; CP vs. KS: $t(22) = 1.49$, $p = .436$; ALC vs. KS: $t(22) = 0.91$, $p > .999$] but significant group differences for non-alcohol-related stimuli: KS presented more omissions than CP, $t(22) = 2.66$, $p = .035$, other comparisons being nonsignificant [CP vs. ALC: $t(26) = 0.29$, $p > .999$; KS vs. ALC: $t(22) = 2.26$, $p = .090$]. As a whole, KS presented more omissions that CP, particularly for non-alcohol-related stimuli.

Go RTs

A significant Group effect was found, $F(2, 33) = 4.70$, $p = .016$, KS presenting longer RTs than ALC, $t(22) = 3.05$, $p = .013$, other comparisons being nonsignificant [CP vs. KS: $t(22) = 1.41$, $p = .497$; CP vs. ALC: $t(26) = 1.51$, $p = .417$]. A significant Group × Condition × Stimuli interaction was found, $F(4, 66) = 4.11$, $p = .006$: (a) In the congruent condition with alcohol-related stimuli, KS had longer RTs than ALC, $t(22) = 3.14$, $p = .011$, other comparisons being nonsignificant [CP vs. ALC: $t(26) = 1.37$, $p = .536$; CP vs. KS: $t(22) = 1.67$, $p = .310$]; (b) in the congruent condition with non-alcohol-related stimuli, KS had longer RTs than ALC, $t(22) = 2.61$, $p = .022$, other comparisons being nonsignificant [CP vs. ALC: $t(26) = 1.03$, $p = .866$; CP vs. KS: $t(22) = 1.71$, $p = .285$]; (c) in the incongruent condition with alcohol-related stimuli, KS had longer RTs than ALC, t

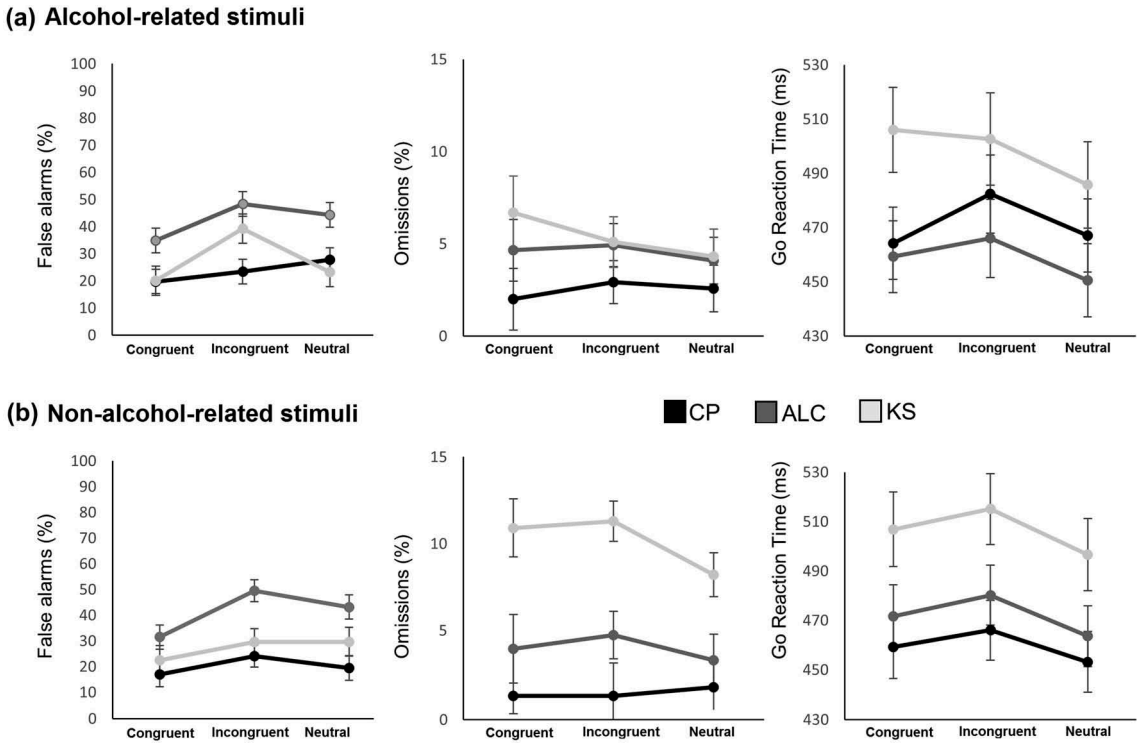

Figure 2. Modified Flanker task performance. (A) No-go false alarms, go omissions, and reaction time (RT) for each group (Korsakoff syndrome, KS; alcohol-dependent, ALC; and control, CP, participants) using the alcohol-related stimuli as target. (B) No-go false alarms, go omissions, and reaction time (RT) for each group (KS, ALC, and CP) using the non-alcohol-related stimuli as target. The presented scores are corrected for State–Trait Anxiety Inventory (STAI) anxiety and Beck Depression Inventory (evaluated at the following value in the model: STAI Trait = 41.66; Beck = 6.08). Error bars represent standard errors of the mean.

(22) = 2.84, p = .023, other comparisons being non-significant [CP vs. ALC: $t(26)$ = 2.08, p = .134; CP vs. KS: $t(27)$ = 0.55, p > .999]; (d) in the incongruent condition with non-alcohol-related stimuli, KS had longer RTs than ALC, $t(22)$ = 2.86, p = .022, other comparisons being nonsignificant [CP vs. ALC: t (22) = 2.03, p = .149; CP vs. KS: $t(26)$ = 0.79, p = .999]; (e) in the neutral condition with alcohol-related stimuli, KS had longer RTs than ALC, t (22) = 2.78, p = .027, other comparisons being non-significant [CP vs. KS: $t(22)$ = 0.59, p > .999; CP vs. ALC: $t(26)$ = 1.99, p = .163]; (f) in the neutral condition with non-alcohol-related stimuli, KS had longer RTs than ALC, $t(22)$ = 2.85, p = .022, other comparisons being nonsignificant [CP vs. KS: $t(22)$ = 1.58, p = .367; CP vs. ALC: $t(26)$ = 1.88, p = .730]. As a whole, KS presented delayed RTs compared to ALC.

Correlational analyses

A significant correlation (r = .46, p = .004) was found in the whole sample between Stroop errors and the percentage of false alarms in the no-go incongruent condition with alcohol-related stimuli. A significant negative correlation (r = −.54, p < .001) was also found between the Stroop speed and the percentage of false alarms for the no-go incongruent condition with non-alcohol-related stimuli. Other correlations were nonsignificant.

Discussion

The dual-process models' assumption (Bechara, 2005; Noël et al., 2010; Wiers et al., 2007) that addictive disorders are centrally underlaid by an imbalance between reflective and automatic–motivational systems has received strong empirical evidence from cognitive psychiatry and neuroscience, as it is now established that ALC simultaneously present decreased inhibitory control and hypersensitivity towards alcohol cues (Fadardi, Cox, & Rahmani, 2016). However, earlier studies proposed a separated measure of these two systems and did not directly measure their interactions. Here, we directly investigated the imbalance between systems by means of a modified Alcohol Flanker Task including go/no-go components. The aim was to determine the extent to which inhibitory control was compromised in the presence of alcohol-related cues in ALC, but also to test for the first time this systems' imbalance in KS, and thus to explore its evolution

during the successive stages of alcohol-related disorders. Besides, this speeded task allowed distinguishing two types of inhibition, respectively related to distractor interference (i.e., the flanking items) and prepotent response inhibition (i.e., false alarms for no-go trials) during the explicit processing of alcohol-related stimuli. ALC globally presented more false alarms than CP, particularly when processing alcohol-related stimuli, which indicates a globally reduced inhibition and increased processing of alcohol-related cues. Moreover, KS presented more omissions for incongruent conditions, indicating stronger sensitivity to distractor interference. These outcomes clearly index an imbalance between reflective and automatic cognitive systems, as postulated by dual-process models.

More specifically, a first main finding is the ALC and KS preserved ability to detect alcohol-related targets in the congruent condition (i.e., "BBBBB"), although KS low omission rate was reached at the expense of speed. This suggests a high reactivity towards alcohol-related items, confirming previous findings (e.g., for reviews, see Christiansen, Schoenmakers, & Field, 2015; Field & Cox, 2008; Garland, Carter, Ropes, & Howard, 2012). Conversely, the higher false-alarm rates of ALC in the no-go congruent trials of the alcohol-related block (i.e., "SSSSS") indicate prepotent response inhibition failure in this group. More specifically, error rates indicated distinct impairment profiles between ALC and KS depending on the executive load: (a) Alcohol-related stimuli specifically affected ALC performance for no-go trials with low executive load measuring prepotent response inhibition (e.g., frequent no-go soda target "SSSSS"), suggesting increased impulsivity in ALC (e.g., Lawrence et al., 2009; Noël et al., 2007). ALC also showed impairments when the condition required high executive load concurrently measuring prepotent response inhibition and distractor interference (i.e., infrequent no-go soda target "BBSBB"); (b) alcohol-related stimuli specifically affected KS performance for trials with low executive load measuring resistance to distractor interference (i.e., frequent go soda target "BBSBB"). Moreover, a significant correlation between the classic Stroop test and the no-go incongruent condition suggested that both tests are underlaid by global inhibitory processes.

These findings are consistent with previous studies showing impulse toward alcohol-related cues and inhibitory control impairments among heavy drinkers and ALC (e.g., Ames et al., 2014; Noël et al., 2010; Petit et al., 2012a). Actually, inhibition is now considered as a multidimensional construct, and three similar yet distinct inhibitory processes arose in the literature (Friedman & Miyake, 2004): prepotent response inhibition, resistance to distractors interference, and resistance to proactive interference. Our study, by showing that KS and ALC display different impairments during inhibitory control of alcohol-related cues, and thus present distinct performance across these components, clearly suggests that inhibition should be considered as encompassing distinct subfunctions that should be separately evaluated.

Our results will have to be confirmed on larger samples with a stricter pairing between ALC and KS regarding abstinence duration. Indeed, the most frequently used abstinence period when exploring the chronic effect of alcohol on cognition ranges from 14 to 21 days (e.g., D'Hondt, de Timary, Bruneau, & Maurage, 2015; Noël et al., 2016; Pitel et al., 2007), in order to explore cognitive functioning after the effects of acute alcohol intoxication and before the development of brain reorganization following midterm abstinence. However, the present sample included three ALC that had been abstinent for a longer period, and KS were also characterized by a strong heterogeneity regarding abstinence duration. The present sample heterogeneity thus prevents us drawing any firm conclusion about the abstinence effect on cognitive performance, and constitutes a limitation of our study. Future studies should include an additional group with long-term detoxified ALC. Besides, the fact that alcohol consumption was assessed only by self-reported measures may have led to potential over- or underestimation. Moreover, these behavioral data need to be confirmed with neuroimaging results, which are essential to bridge the gap between cognitive concepts and brain systems. It should, however, be noted that this experimental design is adapted from event-related potential (ERP) studies (e.g., Sokhadze, Stewart, Hollifield, & Tasman, 2008), which ensured the reliability of the proposed experimental investigation for neuroimaging techniques. The brain correlates of each separated system and of their interactions would constitute valuable complements to the present behavioral findings.

Despite these limits, the present study already has fundamental and clinical implications. At the fundamental level, it reinforces the proposal that alcohol-related cues actively jeopardize inhibitory processes in alcohol-related disorders, but ALC and KS would display a different pattern of impairments when the task requires lower executive process (thus suggesting a dissociation in inhibition functions when processing alcohol-related cues). Our results thus clearly go against the continuity hypothesis (Bowden, 1990; Ryback, 1971), proposing a linear worsening of impairments between ALC and KS: the present findings do not show such linearity but rather demonstrate a

dissociation according to the type of inhibitory process involved, namely a stronger impairment related to prepotent response inhibition in ALC and related to the distractor's interference in KS. Besides, recent studies (Wijnia et al., 2016) have shown that severe infections (e.g., pneumonia, urinal tract infections), which are commonly observed in patients admitted for the acute phase of the Wernicke encephalopathy, may constitute a marker of thiamine deficiency and intensify the extent of KS's long-term neurocognitive impairments. This innovative proposal promotes the emergence of a more complex model than the initial continuity hypothesis, suggesting that the dissociation between ALC and KS observed in the present study (and more globally described in a wide range of cognitive abilities) may result from a combination of layered factors including direct alcohol neurotoxicity and thiamine deficiency, but also the presence of inflammatory/infection factors in the acute phase of Wernicke encephalopathy. At the clinical level, in line with assumptions of dual-process models, rehabilitation programs have been set up to address either the reflective system through inhibitory processes training on neutral stimuli (e.g., Houben, Nederkoorn, Wiers, & Jansen, 2011) or the automatic–motivational system through attentional bias training (e.g., Wiers et al., 2015). The present study, by exploring inhibitory processes on alcohol-related stimuli, rather suggests that simultaneously training both systems by means of rehabilitation tasks improves inhibitory processes when confronted with alcohol-related stimuli, as shown in our Alcohol Flanker Task. Cognitive training to decrease prepotent responses toward alcohol-related stimuli has indeed already appeared to be an effective strategy to prevent relapse (Houben et al., 2011; Schoenmakers et al., 2010), but we highlighted that other inhibitory processes (i.e., resistance to distractor interference) might also serve as a lever to maximize the effectiveness of cognitive training in alcohol-related disorders.

Disclosure statement

No potential conflict of interest was reported by the authors.

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