

Source Memory in Korsakoff Syndrome: Disentangling the Mechanisms of Temporal Confusion

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Background: Korsakoff syndrome (KS), most frequently resulting from alcohol dependence (ALC), is characterized by severe anterograde amnesia. It has been suggested that these deficits may extend to other memory components, and notably source memory deficits involved in the disorientation and temporal confusion frequently observed in KS. However, the extent of this source memory impairment in KS and its usefulness for the differential diagnosis between ALC and KS remain unexplored.

Methods: Nineteen patients with KS were compared with 19 alcohol-dependent individuals and 19 controls in a source memory test exploring temporal context confusions (“continuous recognition task”). Episodic memory and psychopathological comorbidities were controlled for.

Results: While no source memory deficit was observed in ALC, KS was associated with a significant presence of temporal context confusion, even when the influence of comorbidities was taken into account. This source memory impairment did not appear to be related to performances on episodic memory or executive functions.

Conclusions: Patients with KS displayed source memory deficits, as indexed by temporal context confusions. The absence of a relationship with episodic memory performances seems to indicate that source memory impairment is not a mere by-product of amnesia. As ALC was associated with preserved source memory, the presence of temporal context confusion may serve as a complementary tool for the differential diagnosis between ALC and KS.

Key Words: Source Memory, Korsakoff Syndrome, Executive Functions, Alcohol Dependence, Temporal Confusion, Disorientation.

KORSAKOFF SYNDROME (KS), most frequently arising from a combination of alcohol dependence (ALC and thiamine deficiency (Oscar-Berman, 2012), is associated with several cognitive impairments, notably affecting memory, attentional, and executive abilities (Maharasingam et al., 2013; Pitel et al., 2014). However, the core neuropsychological deficit in KS concerns episodic memory, with moderate retrograde but severe anterograde amnesia (Butters and Brandt, 1985; Talland, 1965). Beyond episodic memory, KS might also significantly impair other memory functions, and notably source memory (Kessels et al., 2008), which constitutes a critical memory system as it allows

gathering contextual details related to specific events and retrieving the temporal order of stored information (El Haj et al., 2015). It relies on 2 distinct components: source monitoring (i.e., identifying and attributing the contextual origin of encoded memories) and reality filtering [i.e., discriminating externally (e.g., real events) and internally (e.g., thoughts) generated information (Johnson et al., 1993)]. Source memory deficits, namely the inability to remember contextual and temporal information about encoded memories, have been identified in various neurological disorders (El Haj et al., 2012; Schwartz et al., 2002). It has moreover been suggested that they play a role, together with impaired strategic search (related to frontal lobe dysfunctions) and impaired episodic memory (Moscovitch and Melo, 1997), in temporal disorientation and spontaneous confabulations (Bouzerda-Wahlen et al., 2013; Johnson et al., 1993; Schnider et al., 1996a). Memory distortions and disorientation have been reported since the seminal description of KS (Korsakoff, 1889) and are still frequently described in this population. Therefore, offering a better understanding of the deficits related to the temporal component of source memory in KS might help to disentangle the mechanisms underlying temporal confusions and disorientation.

However, very little is currently known regarding specific source memory deficits in KS. The macrostructural brain profile classically observed in KS combines frontal and subcortical shrinkage centrally involving fronto-cerebellar and

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Papez circuits (and notably medial thalamic and mammillary bodies), as well as corpus callosum (Pitel et al., 2012). This pattern leads to the proposal that source memory may be impaired in KS, as source memory dysfunction usually relies on a combination between temporal/diencephalic and frontal lobe damages (Johnson et al., 1993; Kopelman, 1987; Schnider et al., 2000). Source monitoring deficit has been reported in studies focusing on populations with frontal lobe dysfunctions (Bouzerda-Wahlen et al., 2013; Johnson et al., 1993; Nahum et al., 2012), but as these studies only included very low samples of patients with KS among other neurological populations, they do not offer firm conclusions regarding source memory deficits in KS. Altered performances have also been reported in KS for cognitive functions related to source memory, like implicit contextual learning (Oudman et al., 2011), reality filtering (Bouzerda-Wahlen et al., 2013), or temporal order judgments (Borsutzky et al., 2008; Schnider et al., 1996a). In the same vein, contextual information memory has also been explored in KS, as several studies explored the explicit (Holdstock et al., 1999; Kopelman et al., 1997; Kovner et al., 1988) or implicit (Kopelman et al., 1997; Shoqeirat and Mayes, 1991) memorization of contextual information (e.g., temporal or spatial location) in KS, using tasks in which stimuli (e.g., words, light spots, shapes) were presented and repeated across delayed sessions. These attempts to explore contextual information gave first insights regarding source memory in KS, as they repeatedly reported that KS was associated with a disproportionate impairment at remembering the spatial or temporal context in which an episodic event occurred. Still, direct behavioral observations of source memory deficits are currently lacking to confirm whether these impairments are specifically associated with memory or are explained by joint memory and executive dysfunctions, as contextual memory also relies on frontal lobe functioning (Mayes et al., 1985). Actually, only 2 studies specifically explored source memory in KS (Kessels et al., 2008; Postma et al., 2006). Using an object relocation task in which KS had to indicate either the temporal, spatial, or spatiotemporal order of presented items, Postma and colleagues (2006) revealed memory failure for spatial and temporal information in KS. Moreover, using modified versions of standard memory tests, Kessels and colleagues (2008) showed false detections (namely the erroneous attribution of a stimulus' encoding context) and temporal order confusions in KS, indexing source memory dysfunction. This deficit was mostly present among patients with spontaneous confabulations, reinforcing the proposal that source memory impairment plays a key role in temporal confusion and confabulations. Nevertheless, while constituting a classical method to test temporal context confusion (Johnson et al., 1993; Kane and Engle, 2000), this type of task (i.e., based on the encoding of words' lists) requires explicit memory learning (Schnider et al., 1996a), which may have biased the results in KS, as this population is characterized by severe amnesia. A recent study (El Haj et al., 2016) demonstrated that KS also displays destination memory (i.e., to whom an

information was transmitted) impairments. These findings complemented knowledge on source memory deficit as it was suggested that both deficits would be associated with binding problems (e.g., linking an information to a receiver for destination memory versus linking contextual details to an episodic event for source memory). The use of specific memory tasks directly measuring source memory processes would thus offer a more accurate measure of source memory impairments and of their links with other memory components (Hayes et al., 2012).

An effective task to explore the temporal component of source memory is the "continuous recognition task" (Schnider et al., 1996a,b), which measures false detections resulting from erroneous encoding of temporal context (Schnider, 2008; Schnider et al., 1996a, 2000, 2005). This task consists in the successive presentation of pictures (i.e., simple objects drawings) and comprises 2 runs separated by 1 hour. In each run, participants have to detect pictures' recurrences, namely the repeated appearance of a picture in this specific run. This paradigm thus specifically measures temporal context confusion, namely the inability to determine the context of stimulus encoding (leading to erroneously consider that a picture appearing for the first time in Run 2 has already been presented in this run, while it was actually presented in Run 1). Temporal context confusion has been shown to share common mechanisms with spontaneous confabulations (Bouzerda-Wahlen et al., 2013; Nahum et al., 2012; Schnider et al., 1996a,b). Indeed, temporal context confusion is a failure to update temporal order among stored information (Benton et al., 1964), leading to impaired encoding and recall of memories' temporal and spatial contexts and thus to altered binding between memory traces, reducing the overall cohesion of specific memories. Temporal confusion can thus result in a reduced ability to separate real from imagined memories (Turner and Coltheart, 2010), contributing to the production of confabulations (Berlyne, 1972). In line with this proposal, previous studies, comparing healthy subjects and amnesic patients (including KS), have shown that temporal context confusion (measured by the temporal confusion index [TCC] computed in the continuous recognition task) was strongly correlated with disorientation and the Dalla Barba's (1993) Confabulations Questionnaire. The continuous recognition task has moreover been shown as highly predictive of the clinical course of disorientation (Nahum et al., 2012; Schnider et al., 1996a), which are frequently observed in KS (Kessels and Kopelman, 2012; Kopelman, 1987; Schnider, 2001). This task may thus constitute a useful tool to explore the temporal aspect of source memory deficits. Finally, beyond methodological considerations, a crucial remaining question concerns the evolution of source memory abilities throughout the successive stages of alcohol-related disorders. Indeed, while source memory impairments have been suggested in KS, their presence in ALC before the development of serious neurological complications has barely been explored. Initial studies (Schwartz et al., 2002; Weingartner et al., 1996) have

provided preliminary evidence of dysfunctional source memory and cognitive control in ALC patients performing explicit memory tasks. Using a words-learning task presented at different times and locations, Pitel and colleagues (2007) also reported source memory dysfunction in ALC, which was indexed by a failure at encoding spatial and temporal context of the to-be-remembered information. It has moreover been suggested that ALC patients might exhibit temporal confusion, suggesting source memory impairment that would be associated with orbitofrontal deficits (Maurage et al., 2011). These preliminary findings must be completed by a direct comparison of source memory performances between ALC and KS. An influential proposal regarding the evolution of the deficits between ALC and KS is the continuity theory (Ryback, 1971), which posits a linear worsening of cognitive impairments between ALC and KS patients, the latter presenting more severe behavioral and brain alterations (Sullivan and Pfefferbaum, 2009). This hypothesis has been largely confirmed for several memory subcomponents, as KS displays disproportionate episodic, semantic, perceptual, and procedural memory deficits compared with ALC (Pitel et al., 2014). However, the validity of this continuum hypothesis has not yet been extended to other memory processes and notably to source memory. It thus appears that exploring the temporal context confusion, indexing source memory deficits among ALC and KS, could determine the spread of the continuity theory and specify whether temporal source memory deficits are a specific feature of KS (thus potentially useful as a differential diagnosis criterion between ALC and KS) or are conversely already detectable at previous stages of alcohol-related disorders. Finally, as underlined above, the respective involvements of episodic memory and executive functions in source memory remain to be determined.

The present study thus used the continuous recognition task (Schnider et al., 1996a) to experimentally explore source memory and the mechanisms underlying temporal confusion in ALC and KS, in order to (i) offer a sensitive experimental measure of temporal context confusion, a mechanism associated with source memory; (ii) explore the validity of the continuum hypothesis for the temporal component of source memory, by comparing ALC and KS participants; and (iii) determine the respective roles played by episodic memory and executive functions in these source memory impairments.

MATERIALS AND METHODS

Participants

Three groups of 19 individuals (KS, ALC, and healthy control participants [CP]) matched for gender, $\chi^2(2, n = 57) = 0.14$, $p = 0.93$, and age, $F(2, 54) = 0.81$, $p = 0.44$, took part in the study. Participants were individually interviewed to check that they fulfilled eligibility criteria [i.e., absence of any major medical problem, psychiatric disorder (schizophrenia, bipolar disorder, major depression, or anxiety disorder) as evaluated by the Mini International Neuropsychiatric Interview (Sheehan et al., 1998), neurological impairment including head trauma and epilepsy, and absence of

past or present polysubstance abuse (except tobacco)]. Despite the severity of KS memory impairments, intellectual functions are thought to remain relatively preserved (Butters and Cermak, 1980), with a verbal IQ around the normative mean (Kessels et al., 2008; Kixmiller et al., 2000; Schacter et al., 1998), and premorbid intelligence was thus estimated from the education level, assessed according to the number of years of education completed since starting primary school. Group differences were found for education level, $F(2, 54) = 6.13$, $p < 0.010$: CP had higher education level than KS participants, $t(36) = 3.47$, $p = 0.003$, the other group comparisons being nonsignificant, CP vs. ALC: $t(36) = 1.35$, $p = 0.540$; ALC vs. KS: $t(36) = 2.12$, $p = 0.116$. KS participants were diagnosed with “amnesia due to substance abuse” according to DSM-IV criteria (American Psychiatric Association, 1994), they were recruited during their long-term stay at the Neuropsychiatric Hospitals of Saint-Martin and Beau-Vallon (Belgium), and the diagnosis and participants’ selection was discussed with and confirmed by trained psychiatrist, neurologist, and neuropsychologist working in these hospitals. All KS participants had a history of ALC and presented severe episodic memory disorders [i.e., KS participants presented scores lower than 2 standard deviations (SD) from the mean for the norms of the French version of the Grober–Buschke 16-item free/cued word learning and recall test (Van der Linden et al., 2004) and of the Doors test (Baddeley et al., 1994)]. KS diagnosis was confirmed by a neuropsychological evaluation. All KS participants had been detoxified at testing time (mean abstinence duration: 7.26 months [SD: 5.6]) and were given adapted nutrition and vitamin supplementation. KS participants met the following criteria: The amnesia was consistent with alcohol abuse disorder; symptoms did not occur exclusively during the episode of withdrawal, intoxication, a Wernicke encephalopathy, or a delirium; and the symptoms caused significant impairment in social, occupational, and other areas of functioning.

Besides, there is no epidemiological consensus regarding a distinction between KS and alcohol-related dementia, and most studies consider that alcohol-related dementia is likely to occur after a lifetime history of heavy drinking (Oslin et al., 1998). Hence, neuroimaging studies underline the considerable heterogeneity among KS participants and suggest a continuum rather than a distinction between pure KS and those with the most severe cognitive impairments that might feature alcohol-related dementia (Emsley et al., 1996). It is widely established (Kopelman, 1991; Maharasingam et al., 2013; Pitel et al., 2008) that for most patients with KS, cognitive deficits extend beyond the pure amnesia, the distinction between alcohol-related dementia and pure KS thus being questioned. Given the current uncertainty regarding the nosological distinction between pure KS and alcohol-related dementia, the present study included all patients diagnosed with KS regardless of the extent of their cognitive impairments. Actually, in the present sample, only 2 patients presented a pure amnesic syndrome with relatively preserved (percentiles 10 to 25) executive performances at the Stroop and Trail Making Test (TMT), the others presenting joint memory and executive impairments. Information collected from the neuropsychological assessment performed at the acute phase of the pathology indicated that all patients with KS were temporally disoriented (i.e., patients were questioned about date, month, year, day during medical interviews) and 6 of them also presented spatial disorientation (i.e., patients were questioned about place and city during medical interviews). Most of them were in a stabilized phase of the disease, yet confabulation was still reported by clinical observation for 3 patients. Only 1 patient was diagnosed with Wernicke’s encephalopathy. Regarding other patients with KS, Wernicke’s encephalopathy may have preceded KS. However, the clinical picture was not sufficient for a diagnosis or the KS had developed insidiously (Cutting, 1978). ALC participants were diagnosed for “alcohol dependence” according to DSM-IV criteria and recruited during their third week of detoxification treatment. ALC

participants had been abstinent for at least 14 days and met DSM-IV criteria for ALC for at least 5 years. Alcohol consumption characteristics (before detoxification for ALC and KS) were also obtained from a clinical interview. CP group was composed of volunteers recruited from the investigators' social environment and from the local community. They did not have any personal or familial history of alcohol abuse or dependence, and presented a current weekly alcohol consumption lower than 10 units, without any alcohol consumption during the 3-day preceding testing. Although dual psychiatric diagnosis (e.g., severe depression, anxiety disorder, schizophrenia, personality disorder) constituted an exclusion criterion, psychopathological factors that may affect cognitive functions were also measured with self-reported questionnaires assessing anxiety [State and Trait Anxiety Inventory, forms A and B (Spielberger et al., 1983)] and depression [Beck Depression Inventory (Beck et al., 1996)]. Groups did not significantly differ for state anxiety, $F(2, 54) = 2.98, p = 0.06$. However, differences were observed for (i) Depression, $> F(2, 54) = 7.96, p < 0.001$, CP had lower depression scores than ALC, $t(36) = 3.96, p < 0.001$, other comparisons being nonsignificant, CP vs. KS: $t(36) = 2.40, p = 0.059$; ALC vs. KS: $t(36) = 1.30, p = 0.377$; (ii) Trait anxiety, $F(2, 54) = 8.46, p < 0.001$: CP had lower scores than ALC, $t(36) = 4.11, p < 0.001$, but CP vs. KS, $t(36) = 2.07, p = 0.128$, and ALC vs. KS, $t(36) = 2.04, p = 0.139$, comparisons were nonsignificant. 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 complete evaluation required 75 minutes, and participants were given breaks between tasks. Participants' characteristics are presented in Table 1.

Task and Procedure

Experimental Measures. Source memory was assessed by the continuous recognition task (Schnider et al., 1996a,b), relying on a continuous recognition paradigm divided into 2 runs. As illustrated in Fig. 1, the first run consisted of a recognition task composed of 6 blocks of 20 black-and-white drawings of real objects or animals. In

each block, 8 targets (repeated in each block) and 12 distracters (never repeated within the run) were presented one by one with a total of 120 trials. For each trial, participants had to decide whether or not the picture had already been presented within this run. Each trial consisted in a 700-ms fixation cross followed by the drawing which remained on the screen until the participant answered. A training session using similar pictures preceded this first run. The second run was performed 1 hour after the first one and used the exact same procedure. In this run, however, 8 distracters from the first run became target items, and conversely, target items from the first run became distracters. Instructions remained unchanged, as participants were still asked to decide whether or not the picture had already been presented within this run (i.e., they had to forget the items presented in the first run). Items presented for the first time in the second run (but already presented in the first run) could thus be erroneously considered as targets by the participants. An increase in the false recognition rate (i.e., considering a new item as already seen) during the second run would thus index source memory impairment, namely the inability to distinguish the run in which the item was previously presented. In each run, reaction times (RT), numbers of hits (i.e., correctly identifying an already presented item), and false detections (i.e., considering a new item as already presented) were recorded. The TCC index, constituting the main source memory measure, was defined as the relative increase of false detections in the second run as compared to the first one (for details, see Schnider et al., 1996a). This TCC index was computed using the following formula: $TCC = (FD2/Hits2) - (FD1/Hits1)$, where FD1 and FD2 represent the number of false detections in Runs 1 and 2, respectively, and Hits1 and Hits2 represent the number of hits in Runs 1 and 2, respectively.

Cognitive Measures. Verbal and visual episodic memory, as well as executive functions performances, were collected among 16 patients with KS on the basis of a clinical neuropsychological battery routinely used in the hospitals (data were missing for 3 KS participants who did not complete the battery). For verbal and visual episodic memory, raw scores of the French version of the Grober-Buschke (16-item free/cued word learning and recall test; Van der Linden et al., 2004) and the Doors test (Baddeley et al., 1994) were

Table 1. Demographic and Psychopathological Scores for Control (CP), Alcohol-Dependent (ALC), and Korsakoff Syndrome (KS) Participants: Mean (SD) [Min-Max]

	CP (N = 19)	ALC (N = 19)	KS (N = 19)	Post hoc (p-value)		
				CP-ALC	CP-KS	ALC-KS
Demographic measures						
Age	52.58 (5.43) [42 to 62]	52.37 (6.15) [39 to 64]	54.84 (8.00) [34 to 65]	1	0.890	0.760
Gender ratio (F/M)	9/10	10/9	9/10		0.932 (χ^2)	
Education level (years)	15.52 (2.48) [9 to 19]	14.31 (2.78) [9 to 20]	12.42 (2.96) [9 to 17]	0.540	0.003	0.116
Alcohol use characteristics						
Alcohol consumption (units/day)	1.01 (0.81) [0 to 3]	17.94 (10.51) [3 to 40]	16.55 (5.40) [8 to 25]	<0.001	<0.001	0.533
Disease duration (in years) ^a	–	12.26 (7.56) [1 to 25]	12.68 (12.25) [1 to 36]	–	–	0.910
Number of previous detoxifications ^a	–	3.20 (1.97) [1 to 6]	1.08 (1.62) [0 to 5]	–	–	0.006
Psychopathological measures						
Beck depression inventory	2.42 (2.65) [0 to 6]	6.58 (5.67) [0 to 25]	9.37 (7.36) [0 to 20]	0.001	0.059	0.377
State anxiety inventory	27.79 (7.44) [20 to 49]	37.32 (13.01) [21 to 64]	37.37 (13.17) [20 to 65]	0.119	0.116	0.989
Trait anxiety inventory	37.00 (6.34) [26 to 52]	49.79 (11.25) [27 to 65]	43.74 (8.93) [29 to 59]	<0.001	0.128	0.139

^aData gathered from 15 ALC patients during clinical interview.

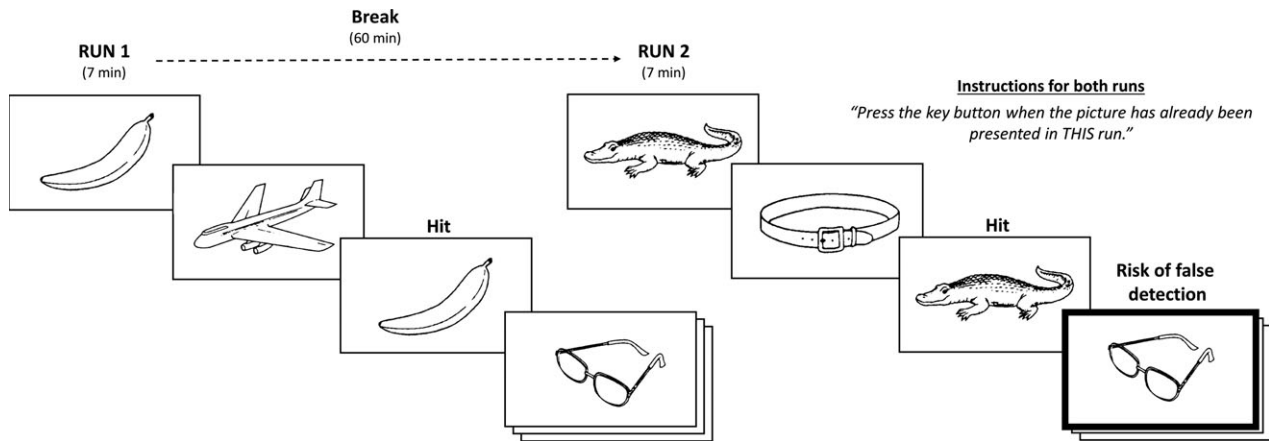


Fig. 1. Continuous recognition task (Schnider et al., 1996a,b). In both runs, participants have to detect items' recurrence (i.e., hit). Items presented for the first time in Run 2 (but already presented in Run 1) can be erroneously considered as targets, leading to false detections. An increase in the false detection rate in Run 2 thus indicates source memory impairment.

recorded. Regarding executive functions, KS raw scores for the Stroop task, TMT, and Fluency tests (Godefroy, 2008) were recorded. These results are presented in Table 2.

Statistical Analyses. Statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL). To compare performances in the continuous recognition task, repeated-measures analyses of variance (ANOVAs) were used for each dependent measure (RT, hits, false detections), with groups (KS, ALC, CP) as between-subjects factor, experimental measure (for Run 1 and Run 2) as within-subjects factors, and the demographic measures and other characteristics of participants presenting significant group differences as

covariates (i.e., educational level, depression, and trait anxiety). Repeated-measures analyses of covariance (ANCOVAs) were also used to explore group differences in the TCC index, with groups (KS, ALC, CP) as between-subjects factor, TCC index as within-subjects factor, and control measures presenting significant group differences as covariates. Bonferroni tests were used for post hoc comparisons. Partial Spearman's correlations within each experimental group were also used to explore the links between experimental variables, demographic/psychopathological measures, and alcohol consumption characteristics (i.e., alcohol consumption before detoxification, number of previous detoxification treatments, and duration of ALC) with educational level as a controlling variable. The alpha level was set at 0.05 for each analysis.

Table 2. Raw Cognitive Scores for Korsakoff Syndrome (KS) Participants (Mean (SD) [Min-Max]) and Percentiles

Cognitive measure	Total (N = 16)	Percentile ¹
Grober-Buschke 16-item test scores		
Immediate recall	13.12 (1.82) [10 to 16]	<5
Free recall 1-2-3	4.27 (1.73) [2 to 8]	<5
Cued recall 1-2-3	10.27 (2.85) [4 to 15]	20
Free delayed recall	3.56 (2.68) [0 to 9]	<5
Cued delayed recall	9.62 (4.03) [2 to 15]	<5
Doors test scores		
Part A	8.75 (1.73) [5 to 12]	5
Part B	4.81 (2.00) [1 to 7]	5
Stroop test (seconds)		
Denomination	75.68 (16.27) [50 to 100]	5
Reading	60.81 (16.57) [32 to 88]	<5
Interference	130.68 (35.70) [85 to 200]	5
Trail Making Test (seconds)		
Part A	59.18 (23.22) [34 to 99]	5 to 10
Part B	171.06 (82.55) [62 to 296]	<5
Fluency test		
Phonemic	16.81 (4.75) [9 to 28]	5 to 10
Semantic	19.00 (9.25) [0 to 34]	<5
Digit span		
Forward	5.06 (1.23) [4 to 8]	50
Backward	3.93 (1.28) [2 to 7]	45
Block tapping test	4.62 (1.08) [3 to 6]	15

¹Normative data from the French adaptation of the *Free and Cued Selective Reminding Test* (Van der Linden et al., 2004; norms established for the age range 50 to 64) for the Grober-Buschke test, and from GRE-FEX (Godefroy, 2008; norms established for the age range 40 to 59, education level 3 [12 years of education]) for the other tests.

Exploratory Analyses. In previous studies (Nahum et al., 2012; Schnider et al., 1996a,b), a TCC cutoff score of 0.3 was used to distinguish healthy from disoriented patients presenting various etiologies leading to amnesia. In order to allow comparison with these earlier studies, this TCC cutoff score was first applied here. The KS group was thus split using the TCC cutoff score of 0.3 to compare the demographic/psychopathological measures, alcohol consumption characteristics, and cognitive performances on neuropsychological evaluation between temporally confused and unconfused KS subgroups. Note that a median split procedure was also performed within the KS group according to this TCC index, but no significant difference between resulting subgroups was found on any psychopathological, consumption, or cognitive measures. Regarding cognitive measures (Grober-Buschke 16-item, Doors, TMT, Stroop, Fluency tests), performances were analyzed by nonparametric Wilcoxon signed-ranks tests. Partial Spearman's correlations were also used to explore the links between experimental variables and cognitive measures with educational level as a controlling variable. The alpha level was set at 0.05. Moreover, to go beyond this classically used cutoff score which might not be totally adapted to the present sample, a receiver operating characteristics (ROC) curve analysis was conducted to select the most accurate TCC threshold for discriminating ALC and KS based on source memory impairment. The ROC curve was also computed for the 2 other possible group comparisons [CP vs. ALC and CP vs. KS] to test whether TCC score would be an efficient tool for distinguishing ALC and KS patients from CP. The most appropriate threshold chosen was the one which optimized sensitivity and specificity on the ROC curve. In order to further explore the heterogeneity of the ALC and KS groups, a single-case approach using the Crawford method

(Crawford and Garthwaite, 2004, 2012) was used to compare the TCC index of each ALC and KS participants with the CP sample. This method differs from the use of a z -score to the extent that it refers to a modified independent samples t -test in which the individual's score is not part of the estimate of the within-group variance (Crawford and Garthwaite, 2004, 2012).

RESULTS

Continuous Recognition Task

Reaction Times. A main Group effect was found, $F(2, 51) = 15.25, p < 0.001$. Post hoc t -tests showed that KS and ALC patients presented longer RT than CP, KS vs. CP: $t(36) = 5.45, p < 0.001$; ALC vs. CP: $t(36) = 2.09, p = 0.044$, and that KS presented longer RT than ALC patients, $t(36) = 3.22, p = 0.007$. No significant Run effect, $F(1, 51) = 0.01, p = 0.891$ or interaction, $F(2, 51) = 0.66, p = 0.517$, were found.

Hits: No significant effect was found for Group, $F(2, 51) = 1.14, p = 0.325$, Run, $F(1, 51) = 0.32, p = 0.572$, and interaction, $F(2, 51) = 1.83, p = 0.170$.

False detections: A main Group effect was found, $F(2, 51) = 21.85, p < 0.001$. Post hoc t -tests showed that patients with KS presented more false detections than CP, $t(36) = 4.79, p < 0.001$, and ALC patients, $t(36) = 6.20, p < 0.001$, who did not differ, $t(36) = 0.83, p = 0.412$. No main Run effect was found, $F(1, 51) = 3.52, p = 0.066$. The interaction was significant, $F(2, 51) = 14.36, p < 0.001$: In Run 1, patients with KS presented more false detections than ALC patients, $t(36) = 3.48, p = 0.003$, the other comparisons being nonsignificant, CP vs. KS: $t(36) = 1.55, p = 0.129$; CP vs. ALC: $t(36) = 1.08, p = 0.285$. In Run 2, patients with KS presented more false detections than ALC patients, $t(36) = 6.68, p < 0.001$, and CP, $t(36) = 5.59, p < 0.001$, who did not differ, $t(36) = 0.46, p = 0.641$.

Taken together, these results underline that KS did not significantly differ from CP for hits and false detection during Run 1, nor for hits during Run 2 which underlines that both KS and ALC participants correctly understood task instructions and were able to perform the task, despite a general slowdown compared with CP.

TCC index: A main Group effect was found, $F(2, 51) = 13.91, p < 0.001$, as patients with KS presented higher TCC index than ALC patients, $t(36) = 4.61, p < 0.001$, and CP, $t(36) = 4.81, p < 0.001$, who did not differ, $t(36) = 0.18, p = 0.855$. These results are presented in Fig. 2, showing the mean TCC index per group (panel A) as well as individual scores (panel B). Importantly, all CP and ALC patients were below the TCC cutoff score of 0.3 for source memory impairment (Schnider et al., 1996a), while the KS group was distributed above and below 0.3, with a mean score higher than this threshold. Experimental measures are presented in Table 3.

Partial Spearman's correlations were also conducted within each group between TCC index, age,

psychopathological measures, and alcohol use characteristics with educational level as a controlling variable. Within the CP group, all correlations were nonsignificant ($\rho < 0.37, p > 0.064$). Within the ALC group, all partial correlations were nonsignificant ($\rho < 0.39, p > 0.083$). Within the KS group, the only significant partial correlation was between TCC index and age ($\rho = 0.913, p < 0.001$).

Exploratory Analyses

As illustrated in Table 4, no significant group differences were found between temporally confused KS (presenting temporal context confusion, that is, a TCC index higher than 0.3) and unconfused KS (presenting TCC scores lower than 0.3) on episodic memory and executive performances (all p -values higher than 0.05). Partial Spearman's correlations were also conducted within the KS group between TCC index and cognitive performances, with educational level as a covariate: All correlations were nonsignificant ($\rho < 0.41, p > 0.070$), except for the TMT part A ($\rho = 0.65, p = 0.006$). As source memory deficit might be influenced by abstinence duration, KS subgroups were compared on this factor: Abstinence duration did not significantly differ between confused (mean: 9 months, SD: 4.6) and unconfused (mean: 6 months, SD: 6.7) KS (Wilcoxon test = 1.05, $p = 0.29$).

As illustrated in Fig. 3, ROC curve analysis reveals that the most accurate cutoff point (89%) to discriminate ALC from patients with KS is a TCC index of 0.13 ($p < 0.001$) while the cutoff point (88%) to discriminate CP from KS is a TCC index of 0.125 ($p < 0.001$). Finally, no TCC cutoff point was able to efficiently discriminate CP from ALC participants ($p = 0.65$).

Besides, a single-case approach using the Crawford method (Crawford and Garthwaite, 2002, 2004, 2012) was computed to compare the TCC index of each ALC and KS participants with the CP sample. Crawford t -tests revealed that 74% (i.e., 14 of 19) of KS had a TCC index which was significantly higher than the one observed in the CP group (all $t(18) > 1.79, p < 0.044$) while 95% (i.e., all but one) ALC group did not significantly differ from the CP group (all $t(18) < 1.22, p > 0.118$), which further confirms that most of the KS participants presented high TCC score (see Fig. 2B).

DISCUSSION

The present study proposed the first specific exploration of source memory deficits in KS by means of the continuous recognition task (Schnider et al., 1996a). We showed that KS is associated with a high rate of temporal context confusions, indexing source memory impairments. Moreover, these source memory deficits were not found in ALC and do not seem to be the mere consequence of the severe episodic memory impairments classically described in KS, nor of the main executive dysfunctions measured with classical tests.

It should first be underlined that both KS and ALC participants showed a global perceptive-motor slowing down

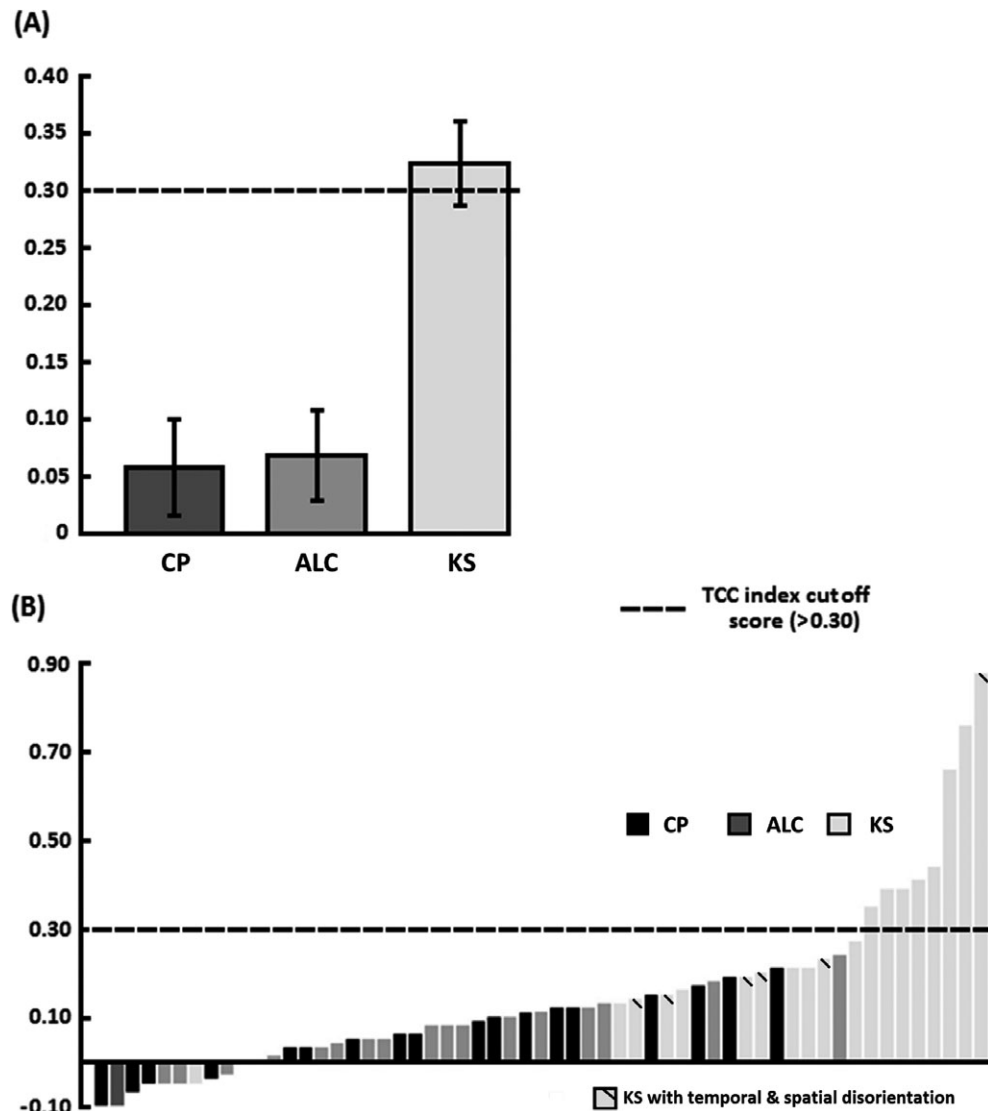


Fig. 2. Results for the Temporal Context Confusion (TCC) index. **(A)** Mean TCC index score for each group (control [CP], alcohol-dependent [ALC], and Korsakoff syndrome [KS] participants). The presented scores are corrected for education level, depression, and trait anxiety using covariance analyses. Covariates appearing in the model are evaluated at the following values: 14.09 for education level, 6.07 for depression, and 43.7 for trait anxiety. Error bars represent standard errors of the mean. **(B)** TCC index score for each participant.

(Butters and Cermak, 1980), as their RT were increased throughout the task compared with CP. This slowing down was more severe among KS participants than ALC ones, which is consistent with previous reports (Butters and Cermak, 1980). More interestingly, KS participants correctly understood task instructions and presented preserved performances for the recognition task: While presenting more false detections than ALC in Run 1, they however did not significantly differ from CP for hits and false detections during Run 1, nor for hits during Run 2. Patients with KS had thus a quite preserved performance in recognizing the already seen pictures, suggesting efficient encoding and storage of the stimuli. However, they showed a dramatic increase in the false detection rate during Run 2 compared with ALC and CP groups. This specifically indexes a difficulty to identify the context and moment (i.e., Run 1 or Run 2) during which

images were encoded, and is thus the behavioral expression of an impairment in the temporal component of source memory (Schnider, 2003). As shown by increased false detection rate in Run 2, KS group clearly failed to suppress intrusion of previously encoded memories, which might result in source memory disturbances related to spontaneous confabulations (Dalla Barba et al., 1999; El Haj and Allain, 2012). Importantly, as the TCC index is computed using a formula $[(FD2/Hits2) - (FD1/Hits1)]$ that controls for the overall recognition performance, this result cannot be explained by an overall increased tendency in KS to consider the item as previously presented (Schnider et al., 1996a). Previous findings among non-KS amnesic patients (Schnider et al., 1996a, b, 2013) have shown that a TCC index higher than 0.3 was tightly associated with source memory impairments and disorientation. On the overall, our KS sample is above this

Table 3. Source Memory Scores for Control (CP), Alcohol-Dependent (ALC), and Korsakoff Syndrome (KS) Participants: Mean (SD) [Min-Max]

					Post hoc comparisons (<i>p</i> -value)		
	CP (<i>N</i> = 19)	ALC (<i>N</i> = 19)	KS (<i>N</i> = 19)	Group effect (<i>p</i> -value)	CP-ALC	CP-KS	ALC-KS
<i>Source memory scores</i>							
Reaction time							
Run 1	760 (115) [604 to 991]	914 (186) [627 to 1,319]	1,079 (172) [735 to 1,375]	<0.001	0.097	<0.001	0.004
Run 2	730 (85) [621 to 989]	880 (178) [598 to 1,195]	1,003 (195) [657 to 1,343]		0.076	<0.001	0.056
Hits							
Run 1	39.36 (0.95) [37 to 40]	38.05 (3.06) [27 to 40]	37.10 (2.90) [30 to 40]	0.325	0.260	0.067	0.513
Run 2	36.73 (2.10) [31 to 40]	36.89 (2.07) [32 to 39]	36.73 (3.31) [26 to 39]		0.933	0.940	0.861
False detections							
Run 1	3.15 (3.07) [0 to 10]	2.52 (2.38) [0 to 8]	6.78 (6.21) [0 to 24]	<0.001	0.285	0.129	0.003
Run 2	5.21 (2.97) [1 to 11]	4.57 (3.27) [0 to 11]	18.42 (8.97) [6 to 35]		0.641	<0.001	<0.001
TCC index	0.064 (0.09) [−0.12 to 0.21]	0.056 (0.08) [−0.10 to 0.24]	0.323 (0.23) [−0.05 to 0.88]	<0.001	0.855	<0.001	<0.001

Table 4. Comparison Between Temporally Confused (i.e., Presenting a TCC Index Higher Than 0.3) and Unconfused Korsakoff Syndrome (KS) Participants Regarding Demographic Measures, Alcohol Use Characteristics, Psychopathological Measures, and Cognitive Performances: Mean (SD) on a Wilcoxon Signed-Ranks Test

	Confused KS (N = 8)	Unconfused KS (N = 11)	Wilcoxon test value	p-Value
<i>Demographic measures</i>				
Age	57.75 (6.13)	52.73 (8.79)	−1.6	0.09
Gender ratio (F/M)	4/4	6/5	0.38	0.84 (χ^2)
Education level (years)	12.12 (3.04)	12.63 (3.04)	−0.17	0.88
<i>Alcohol use characteristics</i>				
Alcohol consumption (units/day)	16.20 (5.13)	16.80 (5.82)	−0.14	0.88
Disease duration (in years)	15.57 (13.69)	10.44 (11.31)	−0.73	0.46
Number of previous detoxifications	0.80 (1.30)	1.28 (1.88)	<0.01	0.99
<i>Psychopathological measures</i>				
Beck Depression Inventory	5.25 (3.88)	7.54 (6.69)	−0.84	0.39
State Anxiety Inventory	31.00 (5.45)	42.00 (15.35)	−0.93	0.35
Trait Anxiety Inventory	42.87 (7.97)	44.36 (9.90)	−0.33	0.73
<i>Cognitive measures</i>				
Grober-Buschke 16-item Test scores	(N = 6)	(N = 10)		
Immediate recall	13.16 (2.04)	13.10 (1.79)	0.67	0.49
Free recall 1-2-3	3.70 (1.58)	4.60 (1.81)	0.94	0.34
Cued recall 1-2-3	9.30 (3.43)	10.80 (2.48)	0.10	0.91
Free delayed recall	2.33 (2.25)	4.30 (2.75)	1.26	0.20
Cued delayed recall	9.00 (4.38)	10.00 (4)	0.10	0.91
<i>Doors test scores</i>				
Part A	9.00 (1.41)	8.60 (1.95)	1.84	0.06
Part B	5.16 (2.31)	4.60 (1.89)	0.81	0.41
<i>Stroop test (seconds)</i>				
Denomination	78.00 (15.86)	74.30 (17.21)	0.10	0.91
Reading	67.50 (20.02)	56.80 (13.69)	1.15	0.24
Interference	134.33 (34.71)	128.50 (37.95)	0.31	0.75
<i>Trail Making Test (seconds)</i>				
Part A	73.50 (24.27)	50.60 (18.79)	1.36	0.17
Part B	173.16 (75.42)	169.66 (91.46)	0.54	0.58
<i>Fluency test</i>				
Phonemic	18.33 (5.81)	15.90 (4.04)	0.95	0.34
Semantic	14.16 (11.40)	21.90 (6.70)	0.84	0.40
<i>Digit span</i>				
Forward	5.66 (1.63)	4.70 (0.82)	−1.08	0.27
Backward	4.10 (1.94)	3.80 (0.78)	−0.10	0.91
Block tapping test	4.66 (1.03)	4.60 (1.17)	−0.37	0.70

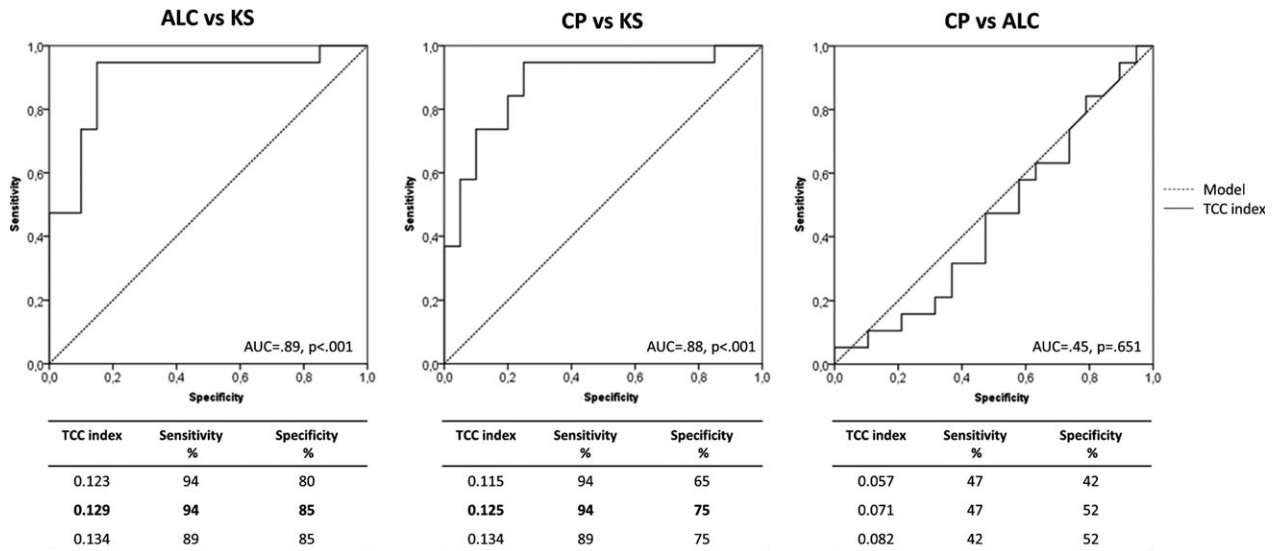


Fig. 3. ROC curves for each comparison between group pairs (control [CP], alcohol-dependent [ALC], and Korsakoff syndrome [KS] participants), showing the discrimination between groups (area under the curve [AUC], p -value) and the evaluation of the best cutoff point for the TCC index, based on sensitivity and specificity.

cutoff score, further underlining the intensity of this impairment. Importantly, and as illustrated in Fig. 2B, the presence of temporal context confusion appears to be exclusively found among patients with KS, as no CP or ALC participant presented a TCC index higher than 0.3. Hence, a high specificity is ensured with a cutoff score of 0.3, as defined earlier (Schnider et al., 1996a, 2013). However, the cutoff's sensitivity is quite low and thus leaves false negatives (i.e., several KS with an index lower than 0.3 would not be detected), thus compromising the accuracy of KS diagnosis. In order to overcome this issue, the ROC analysis illustrated in Fig. 3 enabled to investigate the ideal TCC cutoff score (0.13) that would balance specificity (85%) and sensitivity (94%) of the continuous recognition task, thereby making it a useful complementary tool for the diagnosis of KS. In order to further take into account the potential heterogeneity within the patients, Crawford's single-case approach was used to compare each patient with the control group (Crawford and Garthwaite, 2002, 2004, 2012). This analysis reinforced the proposal of a specific temporal context confusion in KS, as 14 KS participants out of 19 exhibited a significantly increased TCC index compared with CP, this result being observed in only 1 ALC participant.

Regarding the continuum hypothesis between KS and ALC, the present results are in favor of a discontinuity on the temporal component of source memory. Indeed, a qualitative break was found between KS and ALC as no source memory deficits were found for ALC participants, suggesting an absence of continuum across the successive stages of the disease. In a previous study using the same paradigm (Maurage et al., 2011), ALC patients significantly differed from CP for TCC index and RT. A possible explanation for this inconsistency in the results is the heterogeneity of the ALC group in the previous study (see Maurage et al., 2011),

regarding disease duration and alcohol consumption, but also comorbid psychopathologies. Therefore, using a cutoff score specific to alcohol use disorders in previous work would have permitted to obtain a better screening of potentially confused patients with ALC at risk to develop KS after detoxification. It should be noted that in this previous study, the reported average TCC score for ALC participants was below Schnider's (Schnider et al., 1996a, 2013) cutoff score (mean: 0.14, SD: 0.167 for TCC index) and that these results might be at least partly explained by confounding factors (educational level, depression, anxiety, abstinence duration). Thus, chronic and excessive alcohol consumption per se do not seem to lead to temporal context confusion and source memory dysfunctions, although deficits in cognitive functions related to these abilities have been reported in this population (e.g., contextual memory; Pitel et al., 2014). This raises the proposal that, in contrast with other memory mechanisms (such as episodic memory), the continuum hypothesis is not confirmed for source memory, temporal context confusion being specifically found in KS. The continuous recognition task might thus constitute a promising tool to differentiate ALC from KS, as a complement to the classical exploration of episodic memory. It should however be underlined that, while strong temporal context confusion is actually seldom reported in nonamnesic ALC participants, subtle source memory impairments might still already be present. Subclinical source memory impairment, which would not lead to clinical confabulations and would perhaps not be observed in classical clinical settings, could thus also be detected with the TCC index in certain ALC patients and potentially help to identify those at risk to develop KS.

Interestingly, major source memory impairment was not found in all KS participants as more than half of our KS sample did not reach Schnider and colleagues' (1996a) cutoff

score. No difference was found between temporally confused and unconfused KS participants regarding performances in classical tasks of episodic memory (i.e., Grober–Buschke, Doors tests), executive functions (i.e., Stroop, TMT, Fluency tests), and abstinence duration, nor any correlation in the KS group between TCC index and cognitive functions (except for the TMT part A, which is not related to memory-executive functions, but rather to visuospatial and processing speed abilities). These complementary analyses showed that source memory may not be interpreted as being a simple by-product of the severe episodic memory deficits, neither as being closely related to the executive dysfunctions observed in KS. It should be noted however that, due to the small sample size related to these complementary analyses, these results should be confirmed and extended. Upcoming works should also compare the brain damages between temporally confused and unconfused KS, as source memory impairments may result from a particular combination of brain dysfunctions (e.g., massive dorsolateral and ventrolateral prefrontal cortex added to classic subcortical dysfunction). The relationship between working memory (associated with frontal areas), episodic memory (associated with the subcortical areas), and temporal confusion was indeed investigated among KS in a study assessing time intervals estimation, showing impairments when events exceeded KS' working memory capacities (Mimura et al., 2000). Future studies should therefore further explore the “executive-focused” hypothesis, suggesting that source memory impairments in KS, at least regarding their temporal component, are related not only to memory but also to the ability to strategically explore memories in order to efficiently activate encoded memories (Gilboa et al., 2006; Moscovitch and Melo, 1997). Neuroimaging studies have shown that some prefrontal cortex areas (i.e., dorsolateral and ventrolateral regions) were strongly involved in source monitoring (El Haj and Allain, 2012; Mitchell and Johnson, 2009), reinforcing the proposal that executive functions are involved in source memory. However, the only study to date that explored the links between clinically reported spontaneous confabulations, source memory, and executive abilities in KS (Kessels et al., 2008) did not show significant correlations between these factors. The specific role played by executive deficits in source memory should thus be further explored.

Future studies should also go beyond the present exploration of a specific aspect of source memory (i.e., its temporal component) in KS, notably by clarifying the involvement of subprocesses potentially playing a distinct role in the deficit. Particularly, the specific role played by source monitoring (i.e., the ability to identify the emotional, space, and temporal context in which a memory was encoded) and reality filtering (i.e., discriminating self-upcoming memories from external memories of the ongoing reality) in this deficit should be explored, as these 2 processes have been identified as distinct mechanisms both contributing to efficient source memory (Bouzerda-Wahlen et al., 2015). In addition, using

both a valid confabulation questionnaire addressing spontaneous confabulations (Rensen et al., 2015) and a source memory measure would be useful to further explore the link between these mechanisms. Several limitations of the present study should also be taken into account in upcoming works. As it has been established that KS had relatively intact intellectual functions (Butters and Cermak, 1980), premorbid intelligence was estimated from educational level, but IQ measures should be performed to better control for cognitive performances. Moreover, our comparison between the 2 KS subgroups was based on a very limited sample, and these preliminary explorations of the interactions between source memory and episodic/executive impairments should thus be explored on larger populations. The neuropsychological evaluation also presents some limits. Particularly, the absence of validated measure of temporal or spatial orientation abilities in KS prevents us from exploring the link between TCC index and orientation scores. Moreover, no neuropsychological assessment was conducted in CP and ALC, which might have limited the power to detect a significant association between TCC index and cognitive measures, and hampers to draw strong conclusions regarding the cognitive profile of nonamnesic ALC individuals and controls. Furthermore, alcohol consumption characteristics were assessed only by self-report measures, which can lead to imprecisions and biases, particularly in the KS group. Finally, the brain correlates of source memory deficits in KS should also be examined, notably to directly compare the pertinence of “memory-focused” (suggesting a central role of the orbitofrontal cortex combined with the classic subcortical memory circuit) and “executive-focused” (proposing a crucial involvement of the ventromedial prefrontal cortex) hypotheses. Nevertheless, the present study, by offering the first experimental insights regarding the temporal component of source memory from uncomplicated ALC to KS, constitutes an important first step toward a better understanding of source memory impairments in alcohol-related disorders.

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CONFLICT OF INTEREST

All authors report no competing financial interests or potential conflict of interests, and no connection with tobacco, alcohol, pharmaceutical, or gaming industries.

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