Dynamics of the Cognitive Procedural Learning in Alcoholics with Korsakoff's Syndrome

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Background: While procedures acquired before the development of amnesia are likely to be preserved in alcoholic patients with Korsakoff's syndrome, the ability of Korsakoff patients (KS) to learn new cognitive procedures is called in question. According to the Adaptive Control of Thoughts model, learning a new cognitive procedure requires highly controlled processes in the initial cognitive phase, which may be difficult for KS with episodic and working memory deficits. The goals of the present study were to examine the learning dynamics of KS compared with uncomplicated alcoholic patients (AL) and control subjects (CS) and to determine the contribution of episodic and working memory abilities in cognitive procedural learning performance.

Methods: Fourteen KS, 15 AL, and 15 CS were submitted to 40 trials (4 daily learning sessions) of the Tower of Toronto task (disk-transfer task similar to the tower of Hanoi task) as well as episodic and working memory tasks.

Results: The 10 KS who were able to perform the cognitive procedural learning task obtained lower results than both CS and AL. The cognitive phase was longer in the Korsakoff's syndrome group than in the other 2 groups but did not differ between the 3 groups any more when episodic memory abilities were controlled.

Conclusions: Our results indicate that KS have impaired cognitive procedural learning abilities compared with both AL and CS. Episodic memory deficits observed in KS result in a delayed transition from the cognitive learning phase to more advanced learning phases and, as a consequence, in an absence of automation of the procedure within 40 trials.

Key Words: Procedural Memory, Cognitive Skill, Korsakoff's Syndrome, Episodic Memory, Working Memory.

IN ITS MORE frequent form, Korsakoff's syndrome (Korsakoff, 1889) represents the chronic phase of the so-called Wernicke–Korsakoff syndrome, which results from the combination of heavy alcohol consumption and thiamine deficiency. Korsakoff's syndrome is characterized by widespread brain shrinkage (Pitel et al., 2009) affecting more particularly the Papez's circuit and the frontocerebellar loops (Pitel et al., 2012). Korsakoff's syndrome is classically described as a disproportionate impairment of episodic memory (Kopelman, 1995, 2002) associated notably with working memory and executive deficits (Brokate et al., 2003; Jacobson et al., 1990; Joyce and Robbins, 1991; Oscar-Berman et al., 2004; Pitel et al., 2008). Whether other memory systems, such as procedural memory, are preserved in Korsakoff's syndrome is still a matter of debate. While procedures acquired before the development of amnesia are likely to be preserved, the ability of Korsakoff patients (KS) to learn new procedures is called into question.

Procedural memory is defined by Cohen and Squire (1980) as the memory system in charge of encoding, storing, and retrieving the procedures that underlie motor, verbal, and cognitive skills. Procedural learning abilities are thus assessed by means of learning tasks involving motor, verbal, or cognitive procedures. Only a few studies examined procedural learning in KS, some of them showing preserved learning abilities (Beaunieux et al., 1998; Cermak et al., 1973;. Charness et al., 1988; Kessels et al., 2007; Swinnen et al., 2005) while others reported impaired ones (Butters et al., 1985; Nissen et al., 1989; Schmidtke et al., 1996; Xu and Corkin, 2001). When focusing on cognitive procedural learning, previous studies reported deficits of new learning abilities (Butters et al., 1985; Xu and Corkin, 2001) and ascribed them to executive functions (Butters et al., 1985) and episodic memory (Xu and Corkin, 2001) deficits frequently observed in KS. And yet, an investigation of the relationships between nonprocedural cognitive functions and cognitive procedural performance in a group of 20 amnesic patients including 7 with Korsakoff's syndrome did

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not reveal any direct evidence of a role of episodic memory impairment in cognitive procedural learning deficits in amnesia (Schmidtke et al., 1996). In this study, executive functions were involved notably at the initial stage of the learning process when rule-directed behavior, planning, and problem-solving are required. These data suggest that prolonged dependence on intellectual abilities in the amnesic group may indicate a delayed transition to more advanced stages of the skill acquisition. However, the small number of trials (3 learning sessions of 2 trials each) hampered the experimenters to really study the contribution of episodic memory and executive functions to the different learning stages, which reflect the dynamics of the cognitive procedural learning.

Impairments of episodic memory, working memory, and executive functions observed in KS may affect cognitive procedural acquisition. In effect, according to the Adaptive Control of Thoughts model (Anderson, 1992), cognitive procedural learning occurs in 3 qualitatively different phases (cognitive, then associative, and finally autonomous), involving different types of processing (Ackerman and Cianciolo, 2000; Beaunieux et al., 2006). According to this model, learning a new cognitive procedure requires highly controlled processes in the initial cognitive phase and more automatic ones in the final autonomous phase. The associative phase is the transition phase between the cognitive and autonomous phases. The role of episodic memory, working memory, and executive functions in the cognitive phase has been suggested by neuropsychological studies (Baddeley and Wilson, 1994; Butters et al., 1985; Winter et al., 2001; Xu and Corkin, 2001) and confirmed by cognitive (Beaunieux et al., 2006, 2009, 2012) and neuroimaging investigations (Hubert et al., 2007, 2009). The cognitive phase of the cognitive procedural learning requires the involvement of the executive functions and working memory (Saint-Cyr et al., 1988; Welsh et al., 1999; Woltz, 1988) to plan the resolution of the Tower of Toronto (TT) task. Episodic memory, which is assumed to be in charge of error elimination (Baddeley and Wilson, 1994), is also required. Thus, we can hypothesize that episodic memory, working memory, and executive deficits would affect the dynamics of cognitive procedural learning in KS by delaying the transition from the cognitive phase to the associative phase. Furthermore, given that KS differ from uncomplicated alcoholic patients (AL) on episodic memory performances but not on working memory and executive function performances (Pitel et al., 2008), we can hypothesize that the cognitive phase of KS will be longer than that of AL because of more frequent error perseverations in the Korsakoff's syndrome group.

The objectives of the present study were therefore (i) to examine cognitive procedural learning abilities in KS compared with AL and control subjects (CS) using a large number of trials (40 resolutions) of the TT task (disk-transfer task similar to the tower of Hanoi task), (ii) to specify the learning dynamics by comparing the length of the different learning phases in the 3 groups, and (iii) to determine the contribution of episodic and working memory abilities in cognitive procedural learning performance.

MATERIALS AND METHODS

Subjects

Fourteen KS, 15 AL, and 15 healthy CS matched for age and education were included in the present study. KS, some AL, and CS were included in previous studies (Pitel et al., 2007a,b, 2008, 2009). None of the participants were taking psychotropic medication, presented psychiatric problems, had any additional medical history (head injury, coma, epilepsy, depression, etc.), or history of other forms of substance abuse (except tobacco) which might have affected their cognitive functions. All of them gave their informed consent prior to their inclusion in the study, which was approved by the local ethics committee. Demographic information and other characteristics of the research participants are provided in Table 1.

Alcoholics with Korsakoff's Syndrome. Korsakoff's syndrome was diagnosed with reference to the "Alcohol-Induced Persisting Amnestic Disorder" DSM-IV criteria (American Psychiatric Association, 1994). For each patient, the selection was made in accordance with a codified procedure in French officially registered centers by senior neurologists. Each patient's case was examined by a multidisciplinary team made up of specialists in cognitive neuropsychology and behavioral neurology. Background information was provided by family members and by medical records. All KS had a history of very heavy drinking, even though it was difficult to gain an accurate picture of their drinking history. They were unable to recall day-to-day events, and their memory impairments had social repercussions. On the French version of the free and cued selective reminding test (Grober and Buschke, 1987; Grober et al., 1988), all KS were significantly impaired compared with both CS and AL. The vocabulary and the matrix subtests of the Wechsler Adult Intelligence Scale (WAIS III; Weschler, 2001), which evaluate verbal and nonverbal intelligence, respectively, showed that intelligence abilities were impaired to the same extent in KS and AL compared with CS (Brand et al., 2005; Joyce and Robbins, 1991; Oscar-Berman et al., 2004). KS had therefore a profile of disproportionately severe episodic memory disorders compared with a relative preservation of intelligence abilities. A full description of episodic memory, working memory, and executive deficits of these patients is available in Pitel and colleagues (2008).

Clinical and neuroimaging investigations ruled out other possible causes of memory impairment (particularly focal brain damage). The consequences of their cognitive impairments were such that none of the KS were able to go back to their previous jobs, and all of them lived in sheltered accommodation or were inpatients waiting for a place in an institution. According to the criteria of Caine and colleagues (1997), 11 KS had presented Wernicke's encephalopathy prior to their amnesic syndrome. In 2 KS, there was no history of Wernicke's encephalopathy at all, but amnesia had occurred in <8 weeks, indicating that these patients did not present alcohol dementia (Cutting, 1978). The time of onset of amnesia could not accurately be traced in the remaining 2. Most of the KS who were in the early stages of the disease still presented confabulation and false recognition, whereas in other patients with longstanding Korsakoff's syndrome, these symptoms had disappeared.

Non-Korsakoff Alcoholics. Uncomplicated alcoholic patients were recruited by clinicians while they were receiving alcohol withdrawal treatment as inpatients at Caen University Hospital. All of them met the criteria for alcohol dependence according to the DSM-IV (American Psychiatric Association, 1994). We only

Table 1. Main Features of the Participants

	Control subjects (N = 15)	Non-Korsakoff alcoholics (N = 15)	Alcoholics with KS (N = 14)	Statistic	p-Value	Group comparisons
Age	54.19 ± 4.52	50.74 ± 3.69	54.35 ± 6.82	$F(2, 41) = 2.31$	0.11	–
Years of schooling	11.73 ± 2.49	10.26 ± 3.28	11.71 ± 3.96	$F(2, 41) = 0.97$	0.38	–
Vocabulary subtest (WAIS III)	10.26 ± 1.79	6.6 ± 3.04	5.21 ± 2.75	$F(2, 41) = 15.00$	<0.001*	CS > (AL = KS)
Matrix subtest (WAIS III)	11.93 ± 1.57	7.93 ± 2.52	7.64 ± 2.67	$F(2, 41) = 16.06$	<0.001*	CS > (AL = KS)
Free and cued selective reminding test						
Immediate recall	15.8 ± 0.56	15.2 ± 1.14	12 ± 4.03	$F(2, 41) = 10.44$	<0.001*	(CS = AL) > KS
Sum of the 3 free recalls	29.66 ± 6.28	25.8 ± 5.61	7.00 ± 3.94	$F(2, 41) = 72.35$	<0.001*	(CS = AL) > KS
Sum of the 3 total recalls	45.93 ± 2.31	42.46 ± 5.02	25.92 ± 10.91	$F(2, 41) = 33.96$	<0.001*	(CS = AL) > KS
Recognition	15.86 ± 0.35	15.4 ± 1.12	12.00 ± 4.03	$F(2, 41) = 11.31$	<0.001*	(CS = AL) > KS
Delayed total recall	15.33 ± 0.97	15.2 ± 0.77	2.07 ± 1.32	$F(2, 41) = 762.92$	<0.001*	(CS = AL) > KS

*Significant effect of group.
KS, alcoholics with Korsakoff's syndrome; AL, non-Korsakoff alcoholics; CS, control subjects; WAIS, Wechsler Adult Intelligence Scale.
Mean ± standard deviation.

selected patients who had already been physically weaned of alcohol, established by means of the Cushman Score (Cushman et al., 1985), to decrease the likelihood of acute alcohol withdrawal effects. They were early in abstinence (7.73 ± 4.71 days of sobriety before inclusion) because it is now clear that episodic memory and working memory recover and may even normalize with abstinence (Fein et al., 2006; Pitel et al., 2009; Rourke and Grant, 1999). AL were interviewed to specify the age at which they had had their first alcoholic drink (16.62 ± 2.80), their age at the onset of alcoholism (25.23 ± 7.97), the length of time they had drunk in excess (24.57 ± 9.31 years), and their usual daily alcohol consumption (16.73 ± 8.85 standard drinks per day, a standard drink corresponding to any drink that contains about 10 g of pure alcohol).

Control Subjects. CS were interviewed to check that their alcohol consumption did not exceed the recommendations of the World Health Organization (no more than 21 or 14 weekly standard drinks for men or women, respectively, and 4 at the same time).

Neuropsychological Description

Cognitive Procedural Learning. The learning of the TT task was carried out on 4 consecutive days, 1 learning session per day. Subjects were asked to perform 10 trials in each learning session. The TT task consisted of a rectangular base and 3 pegs. Four different-colored disks were used: 1 black, 1 red, 1 yellow, and 1 white. The disks were initially stacked on the leftmost peg, with the darkest one at the bottom and the lightest one on top. The task consisted in rebuilding this configuration on the rightmost peg, obeying the following 2 rules: only 1 disk may be moved at a time, and a darker disk may never be placed on top of a lighter one. The rules were read out to the subjects, and they were then required to solve the puzzle. The subjects' performance on the TT task was assessed in terms of completion time, number of moves needed to complete it (minimum 15), and number of errors (breaking rules, e.g., a darker disk placed on top of a lighter one) per trial. For each variable, learning scores corresponded to the sum of the 10 trials in each session.

Episodic Memory. The Spondee test ("Spon" for spontaneous and "dee" for deep; Pitel et al., 2007b) is a verbal learning test comprising 2 lists of 16 words belonging to 16 different categories. It is derived from the Double Memory Test (Grober and Kawas, 1997). In the first list, words were encoded spontaneously according to the strategies subjects were able to implement on their own. In this condition, subjects had to point to words as they were read out by the experimenter. In the second list, words were deeply encoded, that is, in a semantic mode: subjects had to point to words in response to their semantic category. For each list, a free recall test, a semantic cued recall test, and a recognition task were then carried out. To reduce the number of later correlations, the 6 raw scores were converted into standard units (Z-scores) in reference of the CS data and averaged into 1 composite Z-score.

Working Memory and Executive Functions. The slave systems of working memory were assessed by means of 3 computerized passive storage tasks. The phonological loop and the visuospatial sketchpad were evaluated by verbal span and spatial span tasks, respectively. The episodic buffer was assessed by means of a multimodal span task (Quinette et al., 2006): patients were asked to memorize increasingly long strings of letters (verbal span), locations (spatial span), and letters placed in an array (multimodal span) and had to recall them immediately afterward. The final score corresponded to the number of correctly reported sequences. Executive functions were assessed using the verbal fluency tasks (Cardebat et al., 1990) and the Stroop test (Stroop, 1935) to evaluate the ability to self-generate strategies and inhibition capacity, respectively. These tasks are fully described in Pitel and colleagues (2007a,b). Raw scores were converted into standard units (Z-scores) in reference of the CS data and averaged into a working memory composite Z-score and 1 executive composite Z-score (see Table 2 for details of composite Z-scores).

Statistical Analysis

Comparison of the Cognitive Procedural Learning Results in the 3 Groups. Data were aggregated by block of 10 trials (1 per session) to allow a more stable estimate of performance. Multivariate analyses of variance (MANOVA) were carried out, with performance on the 4 sessions (in terms of completion time, moves, and number of errors as the repeated measure and group as a between-subjects factor). We then used post hoc tests (HSD Tukey) to compare KS, AL, and CS on each learning session.

Comparison of the Learning Dynamics in the 3 Groups. The 3 learning phases (cognitive, associative, and autonomous phases) were delimited using a 3-stage analysis (Hubert et al., 2007) conducted for each individual subject using the number of moves per trial. The subject remained in the cognitive phase until she or he had found the optimum solution (i.e., 15 movements). The length of the cognitive phase therefore corresponded to the number of trials during which the subject failed to find the optimum solution. The autonomous phase started when the subject was able to provide the optimum solution to the TT task 5 times in a row. However, we deemed that the subject was allowed to make 1 error during the autonomous phase, that is, 1 extra move among 75 consecutive moves (=5 trials of 15 moves). The associative phase was defined by default as the transition phase between cognitive and autonomous phase. We carried out 1-way ANOVAs to compare the length of the 3 phases in the 3 groups.

Comparison of Episodic Memory, Working Memory, and Executive Functions in the 3 Groups. We carried out 1-way ANOVA and post hoc tests (HSD Tukey) to compare episodic memory, working memory, and executive functions in the 3 groups.

Contribution of Episodic Memory, Working Memory, and Executive Results to the Cognitive Procedural Learning Dynamics. Pearson's correlations coefficients and linear regression analyses were conducted between the length of each learning phase and episodic and working memory performance using the variability of the 3 groups pooled together. An ANCOVA was then conducted using the predictor(s) highlighted in the previous analysis as covariates to determine whether the 3 groups would still differ on the length of the learning phases when controlled for episodic memory and/or working memory abilities.

RESULTS

Comparison of the Cognitive Procedural Learning Results in the 3 Groups

These analyses were conducted in 10 KS because 4 KS were unable to fully understand the instructions of the TT task and were therefore unable to perform it. With regard to completion time, the repeated-measures ANOVA showed a significant effect of group, $F(1, 37) = 12.61$, $p < 0.001$, session repetition, $F(3, 111) = 71.17$, $p < 0.001$, and interaction, $F(3, 111) = 6.14$, $p < 0.001$. Post hoc analyses showed that both AL and KS were significantly slower than CS in session 1 (KS: $p < 0.001$; AL: $p < 0.001$). KS also differed from AL ($p < 0.05$). In the 3 last sessions, KS were slower than both CS (sessions 2 and 3: $p < 0.001$; session 4: $p < 0.01$) and AL (session 2: $p < 0.001$; session 3: $p < 0.01$; session 4: $p < 0.05$). AL did not differ from CS in the 3 last learning sessions (Fig. 1*A*).

With regard to the number of moves, the repeated-measures ANOVA showed a significant effect of group, $F(1, 37) = 7.68$, $p < 0.01$, and session repetition, $F(3, 111) = 26.91$, $p < 0.001$, but no significant interaction, $F(3, 111) = 1.49$, $p = 0.18$. Post hoc analyses showed that KS needed more moves to solve the TT task than CS in all learning sessions (session 1: $p < 0.05$; session 2: $p < 0.001$; session 3: $p < 0.01$; session 4: $p < 0.05$). KS only differed from AL in session 2 ($p < 0.01$). AL differed from CS only in session 2 ($p > 0.05$; Fig. 1*B*).

With regard to the number of errors, the repeated-measures ANOVA showed a significant effect of group, $F(1, 37) = 7.84$, $p < 0.01$, session repetition, $F(3, 111) = 19.04$, $p < 0.001$, and interaction, $F(3, 111) = 3.09$, $p < 0.01$. Post hoc analyses showed that KS differed significantly from CS in the 3 first sessions (sessions 1 and 2: $p < 0.001$; session 3: $p < 0.05$) and from AL in the 2 first sessions (sessions 1 and 2: $p < 0.01$). AL differed from CS only in session 1 ($p < 0.05$; Fig. 1*C*).

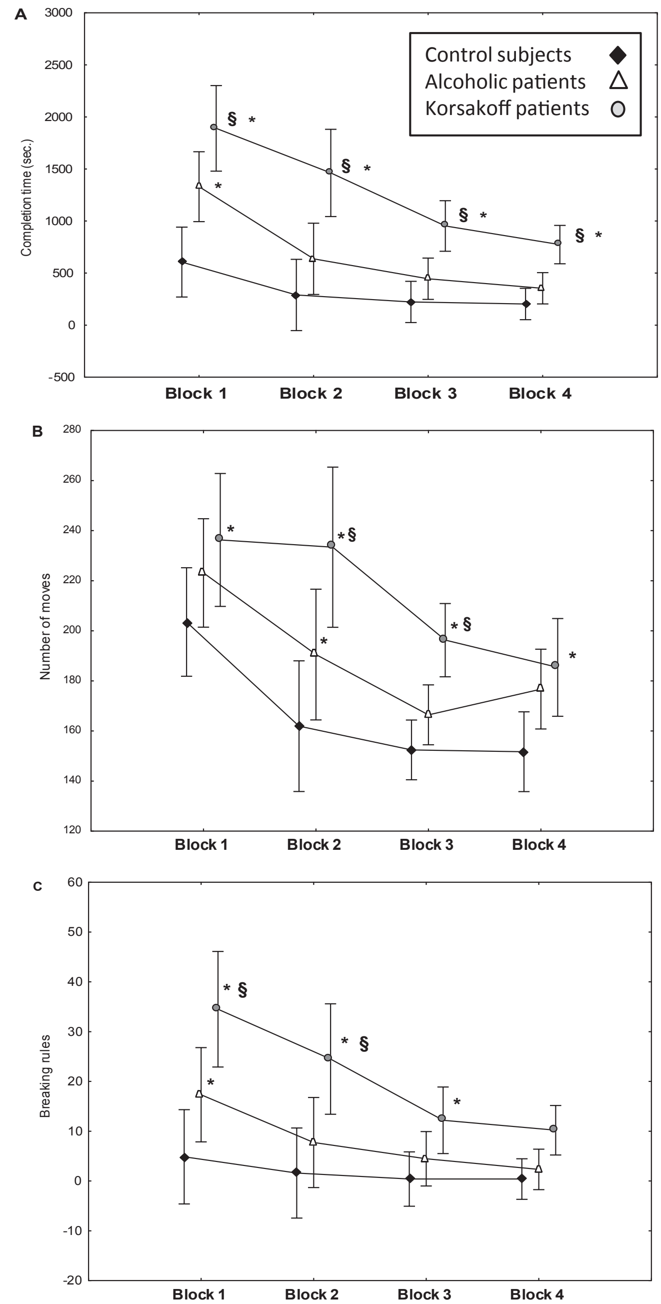

Fig. 1. Cognitive procedural learning in terms of completion time in seconds (**A**), number of moves (**B**), and errors (**C**). *Significant difference compared with control subjects ($p < 0.05$). §Significant difference compared with AL ($p < 0.05$). Data were aggregated by block of 10 trials (1 per session). NC, normal controls; AL, alcoholic patients; KS, Korsakoff patients.

Comparison of the Learning Dynamics in the 3 Groups

Comparison of the length of the cognitive phase in the 3 groups showed a significant group effect, $F(2, 37) = 6.87$, $p < 0.01$. The cognitive phase was significantly longer in the Korsakoff's syndrome group (19.90 ± 16.42; trials 1 to 20) than in the AL (10.13 ± 6.35; trials 1 to 10; $p = 0.02$) and CS (5.66 ± 4.74; trials 1 to 5; $p < 0.001$) groups, who did

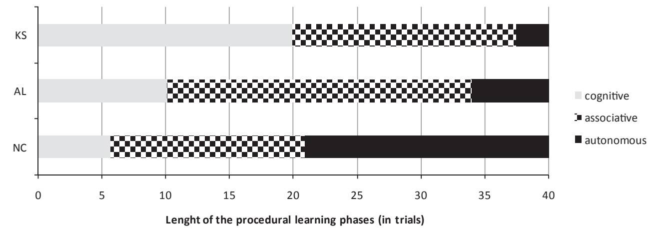

Fig. 2. Length of the 3 procedural learning phases. NC, normal controls; AL, alcoholic patients; KS, Korsakoff patients.

not differ from each other ($p = 0.2$; Fig. 2). The length of the associative phase did not differ among the 3 groups (KS: 17.50 ± 14.56; trials 21 to 38; AL: 23.8 ± 10.91; trials 11 to 34; CS: 15.2 ± 8.31; trials 6 to 21; $F(2, 37) = 2.37$, $p = 0.11$). The length of the autonomous phase was significantly shorter in AL (6.06 ± 10.01; trials 35 to 40) than in CS (19.13 ± 7.61; trials 22 to 40; $F(1, 28) = 16.93$, $p < 0.0001$; Fig. 2). According to our criteria, KS did not reach the autonomous phase even after 40 learning trials.

Comparison of Episodic Memory, Working Memory, and Executive Function in the 3 Groups

There was a group effect on episodic memory results, $F(2, 41) = 35.5$, $p < 0.001$, with AL having significantly lower performance than CS ($p < 0.01$) and KS presenting even worse results than AL ($p < 0.001$; Table 2). Regarding working memory, there was a group effect on the composite Z-scores (slave systems Z-score: $F(2, 41) = 7.3$, $p < 0.01$). Concerning executive functions, 1 KS was unable to perform the inhibition test. There was a group effect on the executive composite Z-score, $F(2, 41) = 10.5$, $p < 0.001$. Compared with CS, AL and KS were impaired to the same extent for working memory and executive functions (Table 2). When the 4 KS who could not perform the TT task were excluded the results remained the same. These patients differed from KS who could perform the TT task only on the executive composite Z-score, $t(12) = 3.09$, $p = 0.009$. Taken together, these findings indicate that episodic memory was more severely impaired in KS than in AL, but working memory was altered to the same extent in the 2 patient groups.

Contribution of Episodic Memory, Working Memory, and Executive Results to the Cognitive Procedural Learning Dynamics

When the 3 groups were pooled together, the length of the cognitive phase significantly and negatively correlated with performance on the tasks evaluating episodic memory ($r = -0.50$; $p < 0.001$), executive functions ($r = -0.38$; $p = 0.016$), and working memory ($r = -0.44$; $p = 0.004$; Fig. 3*A*). Regression analysis identified episodic memory performance as the only predictor of the length of the cognitive phase (23% of the variance, $p < 0.01$; Fig. 3*B*). When episodic memory was entered as a covariate, the 3 groups did not differ from each other anymore on the length of the cognitive phase ($p = 0.37$). Episodic memory, working memory, and executive functions results did not correlate with the length of the associative phase. Finally, the length of the autonomous phase significantly and positively correlated with episodic memory ($r = 0.66$; $p < 0.001$), working memory ($r = 0.60$; $p < 0.001$), and executive performances ($r = 0.65$; $p < 0.001$; Fig. 3*A*). Regression analysis identified episodic memory performance as the only predictor of the

Table 2. Episodic Memory, Working Memory, and Executive Functions Performances of Alcoholic Patients with Korsakoff's Syndrome (KS), Non-Korsakoff Alcoholics (AL), and Control Subjects (CS)

	Control subjects (N = 15)	Non-Korsakoff alcoholics (N = 15)	Alcoholics with KS (N = 14)	Statistic	p-Value	Group comparisons
Episodic memory						
Free recall after spontaneous encoding (%)	47.5 ± 18.86	34.58 ± 16.51	19.19 ± 7.1	$F(2, 41) = 12.57$	<0.001*	CS > AL > KS
Cued recall after spontaneous encoding (%)	59.58 ± 20.02	37.08 ± 20.24	19.18 ± 15.59	$F(2, 41) = 16.81$	<0.001*	CS > AL > KS
Recognition after spontaneous encoding (%)	85.83 ± 12.60	73.75 ± 13.40	37.94 ± 16.52	$F(2, 41) = 43.03$	<0.001*	CS > AL > KS
Free recall after deep encoding (%)	43.33 ± 23.79	35.83 ± 15.92	16.07 ± 7.23	$F(2, 41) = 9.60$	<0.001*	(CS = AL) > KS
Cued recall after deep encoding (%)	79.58 ± 17.90	75.00 ± 24.71	37.5 ± 15.69	$F(2, 41) = 12.74$	<0.001*	(CS = AL) > KS
Recognition after deep encoding (%)	90.41 ± 9.98	82.91 ± 24.43	52.23 ± 17.78	$F(2, 41) = 10.88$	<0.001*	(CS = AL) > KS
Composite Z-score	0 ± 0.5	−1.2 ± 1	−2.9 ± 1	$F(2, 41) = 35.56$	<0.001*	(CS = AL) > KS
Working memory						
Phonological loop	5.66 ± 1.54	4.33 ± 0.81	4.42 ± 1.45	$F(2, 41) = 4.81$	<0.05*	CS > (AL = KS)
Visuospatial sketchpad	5.2 ± 0.77	3.86 ± 0.83	3.64 ± 1.08	$F(2, 41) = 12.85$	<0.001*	CS > (AL = KS)
Episodic buffer	4.2 ± 1.14	3.80 ± 1.01	3.57 ± 1.09	$F(2, 41) = 1.25$	0.29	CS = AL = KS
Composite Z-score	0 ± 0.70	−1 ± 0.60	−1.1 ± 1	$F(2, 41) = 7.28$	<0.01*	CS > (AL = KS)
Executive functions						
Organization	48.40 ± 9.68	37.60 ± 10.98	29.14 ± 10.31	$F(2, 41) = 12.6$	<0.001*	CS > AL > KS
Inhibition	43.00 ± 12.25	30.40 ± 14.36	29.50 ± 16.76	$F(2, 41) = 3.99$	<0.05*	CS > (AL = KS)
Composite Z-score	0 ± 0.7	−1.1 ± 1	−1.5 ± 1.10	$F(2, 41) = 10.48$	<0.001*	CS > (AL = KS)

*Significant effect of group.
Mean ± standard deviation.

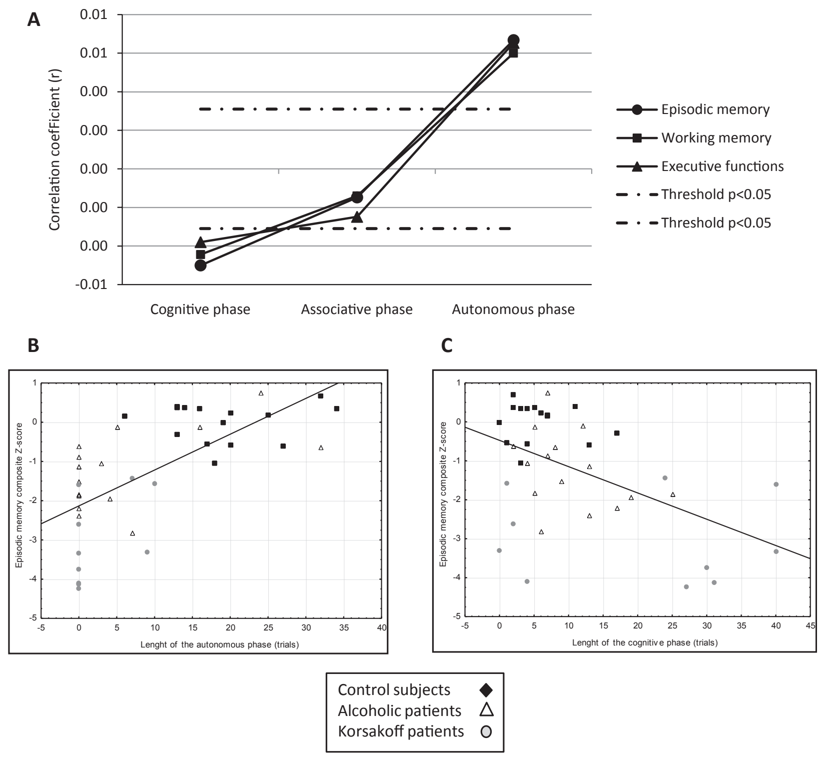

Fig. 3. Contribution of episodic memory, working memory, and executive functions in the cognitive procedural learning dynamics when the 3 groups are pooled together. (**A**) Correlations between the length of the procedural learning phases and episodic memory, working memory, and executive results. The more efficient the episodic memory, working memory, and executive functions are, the shorter the length of the cognitive phase is and the longer the length of the autonomous phase is. (**B**) Relationship between episodic memory results and the length of the cognitive phase. (**C**) Relationship between episodic memory results and the length of the autonomous phase.

length of the autonomous phase (43% of the variance, $p < 0.001$; Fig. 3*C*).

DISCUSSION

The results of the present study confirm previous neuropsychological investigations showing impaired learning of a new cognitive procedure in KS (Beatty et al., 1987; Butters et al., 1985; Wilson et al., 1989; Winter et al., 2001; Xu and Corkin, 2001) and challenge the traditional description of preserved procedural learning in Korsakoff's syndrome. In addition, our findings enable us to deepen our understanding of cognitive procedural learning in Korsakoff's syndrome thanks to the comparison of learning abilities in KS and AL, the analysis of the dynamics of learning in each group, and the study of the relationships between episodic memory, working memory, executive abilities, and cognitive procedural learning performance.

Whatever the learning variable considered (solving time, moves, or errors), KS exhibited lower procedural learning performance than both AL and CS. In accordance with our hypothesis, KS made more errors than AL throughout the cognitive procedural learning process. The differences observed between the 2 patient groups on the learning task can be interpreted taking the results of the neuropsychological examination into account. Given that AL and KS had similar working memory deficits but episodic memory was more severely impaired in KS than in AL, cognitive learning disabilities observed in KS are likely to be related to the severity of amnesia. AL presented a slowdown in the cognitive procedural learning but managed to reach a normal level of performance at the end of the learning process. In another study, we showed that compared with CS, AL implemented less efficient and more cognitively costly learning strategies based on residual working and episodic memory (Pitel et al., 2007a). Because of their severe episodic memory deficits, KS may have been unable to implement such compensatory strategies and remained lower than both controls and AL until the end of the learning sessions. Their severe episodic memory deficits may also hamper them to efficiently correct errors (Baddeley and Wilson, 1994) during the procedural learning.

The observation that episodic memory may have a major contribution to cognitive procedural learning performance was confirmed by the analysis of the learning dynamics, which indicated that contrary to AL and according to our criteria (Hubert et al., 2007), KS were not in the autonomous phase of the learning at the end of the protocol. This absence of automation within the 40 trials of our protocol suggests a selective impairment of the ability to encode a new cognitive procedure into procedural memory in KS. This slowdown in the dynamics of the cognitive procedural learning results from a delayed transition from the cognitive phase to the autonomous phase. In effect, the length of the cognitive phase was longer in KS than in the 2 other groups. Episodic memory was the main predictor of the length of the cognitive phase, and the 3 groups did not differ from each other any-more on the length of the cognitive phase when controlling for episodic memory results. Taken together, these findings enable us to specify that the severe impairments of episodic memory observed in KS may have hampered them to be efficient during the cognitive phase of the cognitive procedural learning (Fig. 4), resulting in a delayed transition to advanced stage of learning. Such effects of episodic memory decline on the cognitive procedural dynamics have also been showed in normal aging (Beaunieux et al., 2009) and Alzheimer's disease (Beaunieux et al., 2012). Interestingly, Swinnen and colleagues (2005) showed that motor procedural learning performance can be improved in KS by providing episodic feedback during learning sessions. Kessels and colleagues (2007) also revealed that KS with better episodic memory exhibited better spatial procedural learning results. These 2 studies suggest a contribution of episodic memory not only to the acquisition of a new cognitive procedure but to procedural learning in general.

It is worthwhile noting that the present conclusions are drawn from a limited number of patients with Korsakoff's syndrome. Even though it is particularly difficult to assemble a larger group of carefully chosen alcoholics with Korsakoff's syndrome, the results have to be interpreted with caution. In effect, there is a considerable variability in learning performance among KS, some of them exhibiting preserved cognitive procedural learning abilities (Beaunieux et al., 1998) while others are not able to perform the task. In the present study, 4 KS did not manage to perform the cognitive procedural task. Executive functions were more severely impaired in those KS than in patients being able to perform the procedural task (data not shown), suggesting a key role of executive functions in the nature and extent of the residual cognitive procedural learning abilities in KS (Butters et al., 1985). Cognitive procedural disabilities in KS may also be explained by the visual-related deficits that are frequently reported in alcoholics (Fama et al., 2004; Sullivan et al., 2000). However, given that AL and KS have similar visuo-spatial deficits (Fama et al., 2006), the differences observed between the 2 patients groups in the cognitive procedural learning results cannot be explained by their visual-related deficits.

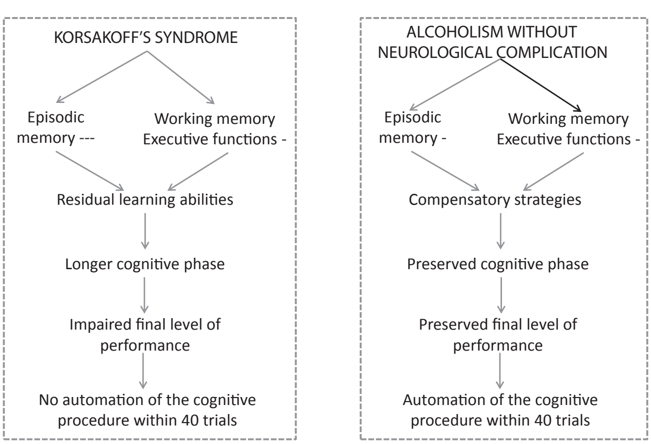

Fig. 4. Summary of the cognitive procedural results in alcoholics without neurological complication (left panel) and in patients with Korsakoff's syndrome (right panel). Alcoholics without neurological complication, who have only mild-to-moderate episodic memory and working memory deficits, seem to implement compensatory strategies (Pitel et al., 2007b), which enable them to exhibit preserved cognitive phase and final level of performance. Uncomplicated alcoholics are therefore able to automate the cognitive procedure within 40 trials. Even though patients with Korsakoff's syndrome have similar working memory deficits, their episodic memory is severely impaired, which seem to hamper them to implement compensatory strategies. Based on residual learning abilities, patients with Korsakoff's syndrome exhibit a longer cognitive phase and impaired final level of performance. Alcoholics with amnesia are therefore unable to automate the cognitive procedure within 40 trials.

To conclude, cognitive procedural acquisition was impaired in KS compared with both CS and AL. The severity of episodic memory deficits in KS may explain the delayed transition from the cognitive phase to the associative phase, which resulted in a slowdown in the dynamics of learning and an absence of automation of the cognitive procedure within the 40 trials of the task. Nonetheless, cognitive procedural learning was not completely eliminated in KS. Residual learning abilities observed in KS are unlikely to be based on explicit memory processes but may rather involve, by default, implicit processes like it was suggested for new semantic learning (Pitel et al., 2009). Further investigations are required to determine whether even more practice would enable KS to automate the cognitive procedure or whether rehabilitation methods (Beaunieux et al., 1998; Cohen et al., 1985) such as errorless learning (Baddeley and Wilson, 1994) are required to bypass the first learning phase which requires relatively efficient episodic memory.

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