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Going for a Walk: An Empirical Study of Route Learning Training and Its Effects on Mental and Physical Fitness in Patients with Korsakoff Syndrome

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Abstract: Korsakoff syndrome (KS) is a chronic neuropsychiatric disorder caused by severe thiamine deficiency. The syndrome is characterized by deficits in explicit memory and executive functions. These impairments severely limit patients with KS in their daily activities like visiting new and familiar places. The aim of the present study was to examine whether patients with KS are still able to learn a route, despite their cognitive impairments. We compared three route learning methods across three groups of patients with KS: passively following the experimenter (PL), trial-and-error learning (TEL), and errorless learning (EL). In the EL group, the participants had to walk towards a landmark that was shown on a tablet by the experimenter, and upon arrival, they had to find and walk towards the next landmark shown by the experimenter. Over 12 training sessions all participants showed improved route retracing performance. There was no difference between the three groups. Moreover, the results indicated positive effects of the walking training on quality of life, physical fitness, and attentional functioning. These promising findings imply that walking training may be beneficial for various aspects of amnestic patients' daily functioning. It is therefore recommended to integrate route training into standard care for patients with KS.

Keywords: Korsakoff syndrome; procedural memory; route learning; amnesia; spatial navigation; errorless learning

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1. Introduction

In our daily life, we often have to learn new locations and destinations. This involves a gradual learning process, in which typically the number of errors declines with each new route reproduction attempt. In the initial stages of learning a new route—the first one or two times you try to make a new route trip—you depend on a more or less fragile spatial episodic memory. Episodic memory allows coding of personal events, which contain complex clusters of information also informing the original context of learning [1]. Initially, route events have to be memorized on the basis of a single experience (e.g., the first route trip). Encoded memory has a conscious format: For example, you realize you have to turn right at the newspaper shop. It is also fragile: It can be incomplete, open to confusion (streets and buildings look similar), and prone to being forgotten the longer the time between the first and the second trip. Episodic memory typically stores unique events [1]. The combination of what happened within a spatiotemporal context makes a

onetime experience. However, in the case of traveling the same new route multiple times, the spatial context can be repeated with only very limited variation. This could afford cumulative strengthening of the route memory trace, turning it into a more semantic memory format or even a semi-procedural memory. The latter can provide a more automatic, partly unconscious memory routine (you turn right at the newspaper store without making a deliberate decision). Hartley et al. [2] emphasize the difference between so called wayfinding (finding novel paths between locations) and processing well-established trajectories from one location to the other. They report distinct neural circuitries to be associated with these two types of navigation: Wayfinding recruits the hippocampus whereas the latter depends on the caudate nucleus (see, however, Claassen et al. [3]).

In the neuropsychological literature, wayfinding—the initial learning of new destinations—has often been investigated. That is, performance is tested after a single or only a few exposures to the target routes [4–6]. In other studies, however, multiple learning and test occasions have been included. Mitolo et al. [7] trained older participants on a route learning test in which routes of different lengths had to be reconstructed within a 5×5 array marked on the floor in an indoor environment. Practice clearly helped the older people. Wiener et al. [8] tested younger and older participants on VR routes that were trained on across 6 sessions. Both groups improved with training, but the older people had more difficulty in retracing the routes (going from end to start). The authors suggested that retracing might depend on a more allocentric hippocampal-dependent strategy that is similar to the wayfinding described above. Older people might suffer hippocampal decline. Claessen et al. [9] specifically trained stroke patients to apply novel navigation strategies, focusing not on learning a specific route but more on acquiring a richer generic navigational ability. Bouwmeester and colleagues reported a highly interesting case report on a stroke patient who suffered a really severe topographical disorientation disorder [10]. The patient was followed for years and was observed to be able to learn routes after extensive dedicated interventions. A requirement was that the routes were highly familiar (traveled frequently). The authors suggest that this might involve a form of implicit route learning.

Assessing the remaining route learning potential in neuropsychological patient groups is very valuable. It gives more insight in how to enhance mobility and autonomy in otherwise restricted individuals. Bouwmeester et al. [10] noted for their topographical disorder patient that their rehabilitation intervention increased quality of life and independence. Claessen et al. [9] pointed out that their patients regarded the navigation strategy training as valuable. One patient group for which higher independence could in particular be important is individuals suffering from Korsakoff syndrome (KS). These individuals stay in long-term care facilities for many years while the disease is not progressive. Innovation in reconstructing cognition and goal-directed activity could therefore be of extreme value.

KS is a chronic neuropsychiatric disorder caused by thiamine (vitamin B1) deficiency. According to Palm et al. [11], the incidence of Wernicke–Korsakoff syndrome is 3.7 per 100,000 person-years in men and 1.2 per 100,000 person-years in women, peaking in those aged 50–59 years, although no direct prevalence figures were provided. Patients with KS have permanent brain damage in the diencephalon, specifically the thalamic region and the mammillary bodies [12–14]. Also, to a lower extent, frontal, cerebellar and hippocampal areas could be affected. Chronic alcoholism and associated malnutrition are two primary factors that contribute to thiamine deficiency, leading to Wernicke's encephalopathy, the precursor stage of KS. As a result of the brain damage, multiple cognitive and behavioral impairments occur. Executive dysfunctioning—limitations in starting, stopping, and organizing activities—has been documented [15,16]. Furthermore, problems with orientation in time and place can occur, just as impaired social cognition and lack of illness insight can [12,17]. However, the most prominent cognitive problems in

patients with KS are seen in the memory domain, particularly including severe anterograde memory loss for declarative knowledge.

Wayfinding and route learning have rarely been examined in patients with KS. Two studies applied a relatively short route of less than 1000 m, showing evidence of some route learning in KS [5,18]. Oudman et al. [5] had patients with KS walk a new route from the long-term care residence and found compromised route knowledge and route reconstruction performance after this single exposure. Interestingly, the patients who did the initial walking while instructed to pay deliberate attention to the route and environment did not differ from the patients who had not received any navigation warning. This may further suggest that patients with KS have limited possibilities to create explicit conscious spatial memories. Of notice though, while the performance of the patients with KS was markedly lower than that of the controls, it was above chance. This signals the possibility that some extent of residual learning capacity is present.

A learning method that has proven highly successful in patients with KS is errorless learning. In this technique, new skills are practiced by slicing them up in a sequence of small steps that are practiced in a way that making errors is avoided. This is done because an error could be stored in memory, either in an implicit or explicit format, and negatively affect subsequent learning and performance [19]. Patients with KS have been demonstrated to profit from errorless learning in mastering a skill such as doing the laundry [20]. Rensen et al. [21] trained on several other instrumental activities and observed errorless learning advantages as well as an increase in subjective quality of life after successful learning. Biemond et al. [22] demonstrated positive errorless learning effects in patients with KS when using video app instructions. If route learning is comparable to skill learning, errorless learning could be beneficial for this activity as well. Lloyd et al. [23] trained patients with acquired brain damage on learning a route in a virtual environment both under full guidance instructions and under trial-and-error conditions. In the errorless learning condition, the experimenter mentioned at each junction which turn should be taken, e.g., "We are approaching [a crossroads/a turn-off to the right/a turn-off to the left]; we need to [turn right/turn left/go straight ahead] here." The route was better learned with full errorless learning guidance. Rivest et al. [24] successfully designed a smartphone-guided errorless learning intervention for a patient with acquired topographic disorientation disorder.

As far as we know, errorless route learning in patients with KS has only been tested yet by Kessels et al. [18]. The researchers did not find a difference between errorless and trial-and-error learning, but the results were suggestive for some residual learning potential in KS. Possible limitations in Kessels et al.'s study were that the route length was relatively short, and the learning took place in a rather familiar environment. This may have caused relatively fast learning with low error rates from the start. It thus could have obscured any learning differences between the two conditions.

Errorless skill learning has been shown to form a very effective memory rehabilitation method for patients with KS. Route learning may be viewed as a type of skill learning that could increase autonomy and quality of life in trainees. However, there is hardly any literature yet on errorless route learning. In light of the foregoing, the aim of the present paper was to further study route learning potential in patients with KS, in particular comparing errorless route learning to trial-and-error learning and passive learning (i.e., following a guide). In the present study, we used a longer route with more turns and a less well-known route environment together with a larger patient group than in the study by Kessels et al. [18]. Moreover, we employed new errorless instructions that emphasized active exploration of the environment during the training. As such, the creation of what is called a cognitive map could also be stimulated. We will return to this in the Discussion

section. Three groups of patients diagnosed with KS, following one out of three learning methods (passive, trial-and-error, and errorless learning) were trained on a specific route over several weeks.

It has already been pointed out a number of times that patients might gain satisfaction, stronger feelings of independence, and a higher subjective quality of life by learning new skills and new routes [9,10,21]. Therefore, a second question of interest was whether any gain in route knowledge also enhanced quality of life in the patient groups. Accordingly, we also collected measures of subjective and proxy-estimated quality of life during the training.

The present setup allowed us to address two further questions of secondary interest. The first question concerned changes in physical fitness in the participants over the course of the training. Patients with KS are not only cognitively affected; they also typically suffer poor physical fitness. This can already be seen in the early stages of the disease. Wijnia et al. [25] reported a case of Wernicke encephalopathy with severe physical and mobility deficits. Knulst-Verlaan et al. [26] found 98% of 64 hospitalized patients with KS to be lower than the control norm on the six-minute walking test (6MWT), indicative of diminished physical fitness. We therefore examined whether the route training caused any physical fitness gains as measured by the 6 min walking test.

The possibility of fitness gains in our training triggered a second question of secondary interest. In the last decades, several neuropsychological lines of research have looked at how physical exercise can affect brain functioning both in terms of neural organization and density and of cognitive functioning. Meta-analyses have demonstrated positive effects of physical activity on cognition in persons with MCI [27], Alzheimer's disease [28], and diverse types of dementia [29]. Other studies and reviews, however, reported no or mixed effects of physical exercise in older people with cognitive decline [30–32]. In the present study, we explored cognitive functioning across a range of domains before and after the route training.

2. Methods

2.1. Participants

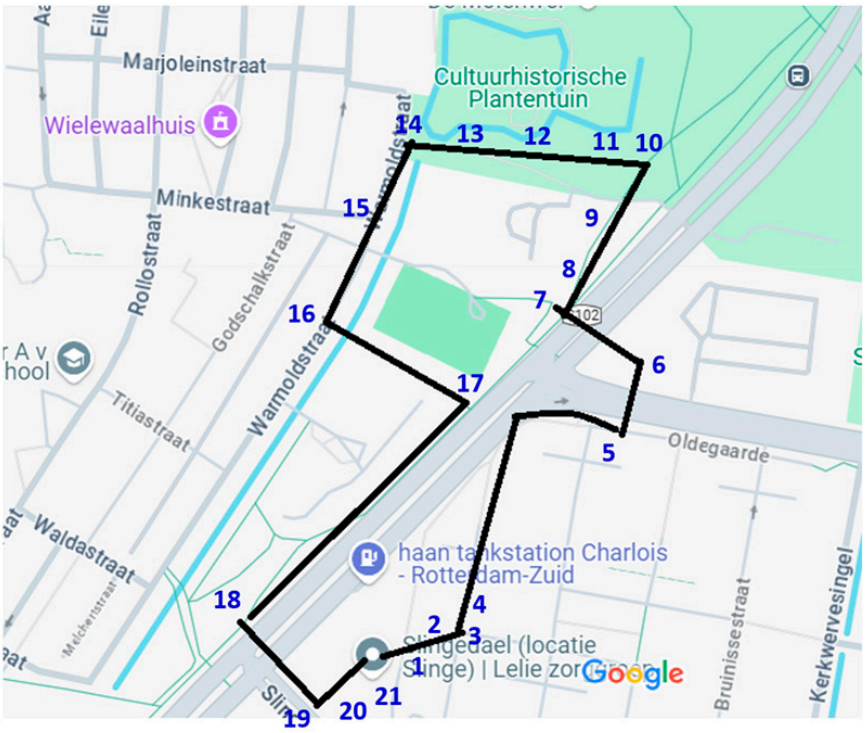
A sample of 26 patients completed the training and was enrolled in the analysis. The patients were inpatients of the Korsakoff Centre of Expertise Slingedael, Rotterdam, The Netherlands or participated in an ambulatory treatment program for KS offered by this center. All patients were diagnosed with alcohol-induced major neurocognitive disorder of the amnestic-confabulatory type, based on the DSM-5 criteria (American Psychiatric Association, 2014). All patients were in the chronic, amnestic stage of the syndrome. None of the patients had confusional Wernicke delirium at the time of testing [12]. The study was approved by the Faculty Ethical Review Committee of Utrecht University, Social Sciences (FETC 20–0706; 17 December 2020; https://ferb.fss.uu.nl/). Written informed consent was obtained from all patients. The study was an empirical, experimental study, in which a preexisting, available sample of patients was randomly divided into three groups that were assigned to one of three learning conditions.

2.2. Measures

2.2.1. Route Learning Test

We created an experimental route learning test (RLT). First, a route was chosen of approximately 1.8 km in length, spanning 21 intersections. This route was walked during every session of the training, and the time to complete the route was tracked for every participant. Depending on the learning condition for their group, the participants were either guided by the experimenter or had to find the route themselves. The experimenter always corrected the participants whenever a wrong turn was taken. See Figure 1 for the

route that the participants had to walk. Route learning performance (RLT) was assessed at three moments during the training: in the first training trial (only for the TEL group) (T0); halfway during the training (T1); and at the end of the training (T2). During the RLT, the participants of all three groups were instructed to complete the route they had learned in the foregoing weeks to the best of their knowledge. In that case, the PL and EL participants did not receive any guidance in making their route choices. An error was scored when a participant took a wrong turn at an intersection. A researcher corrected the participants immediately when they made an error, and errors were recorded on a scoring sheet. To avoid as much as possible that the PL and EL participants could make errors during the training, no RLT was administered for those two groups at T0. If we had started the first walking session with all participants having to find the way by themselves, they would have made multiple errors, which would have very damaging for any subsequent learning, even if that had been guided by the experimenter or by an errorless learning technique.



1. Barrier poles (2)	12. Willows (2)
2. Trees (2)	13. Road demarcation (2)
3. Bicycle shed (2)	14. Dog walking sign (2)
4. Waste container (2)	15. Green transformer (2)
5. Traffic light sign (3)	16. Red door transformer (3)
6. Direction sign (3)	17. Construction board (2)
7. Grey transformer (2)	18. Apartment building (3)
8. Pole with tree (3)	19. 'Slingedael' (3)
9. Bench (2)	20. Tree/ bus shelter (2)
10. Tree with ribbon (2)	21. One footpath pole (2)
11. Tree trunk (2)	

Figure 1. Route followed during the route training. The landmark items that were used in the errorless learning condition are represented in the right table. The number of route continuation alternatives per landmark/decision point is also listed there.

2.2.2. Quality of Life

In order to measure quality of life, the Manchester Short Assessment of Quality of Life (MANSA) and the QUALIDEM were administered. The MANSA is a self-report questionnaire that consists of 16 items, containing four objective questions to be answered with yes or no and 12 subjective questions. Subjective quality of life is rated on a seven-point rating scale (1 = negative extreme; 7 = positive extreme) [33]. The MANSA has been recommended as a tool to assess quality of life in addiction care and long-term psychiatry, making it the most suitable instrument for this population [34].

At the time of testing, no proxy-based instruments to assess quality of life specifically in patients with KS were available. The QUALIDEM was used to measure observed quality of life by the first responsible caregiver. The QUALIDEM was developed as an instrument to measure quality of life for people with dementia in a residential setting. It

is a multidimensional scale with 37 items and nine subscales. The items were rated by professional caregivers. Questions are rated on a four-point scale (0 = never; 3 = often) [35].

2.2.3. Physical Fitness

The Six-Minute Walk Test (6MWT) was administered by a physiotherapist to measure physical fitness. It is a reliable and valid test that measures gait pattern, walking speed, and endurance. The maximum distance that someone was able to comfortably walk in six minutes was registered [36].

2.2.4. Neuropsychological Tests

Multiple neuropsychological tests were administered before the training program (T0), after three weeks (T1), and after six weeks (T2). The test battery included tests for general cognition (screening), working memory, long-term memory, and executive functioning. During the midterm testing (T1), only the screening tool for general cognition was given, because completing the full test battery three times was too straining and time-intensive for patients. When possible, parallel test versions were used at the different test sessions (i.e., MoCA and RAVLT).

General Cognition Screening. To measure general cognition, the Dutch parallel version of the Montreal Cognitive Assessment (MoCA) was given (7.1, 7.2, 7.3) [37]. The MoCa is a short cognitive screening test with high sensitivity and specificity. It is a 30-point test consisting of several short tasks measuring different cognitive domains. The instrument has successfully been applied to detect KS-related cognitive deficits [38].

Working Memory. A lengthened Dutch version of the Digit Span subtest from the Wechsler Adult Intelligence Scale, version III was used to measure verbal working memory [39]. This version consists of two parts in which patients have to remember and repeat a verbally presented digit span. The digit spans increase in length after every three items. During the first part, the participant has to repeat sequences of digits in the same order that is presented to them verbally. In the second part, the participant has to repeat the sequences backwards. The test is finished when the participant is not able to repeat two consecutive sequences of the same length correctly. A higher score represents a better working memory capacity.

Long-term Memory. Verbal long-term memory was measured using the Dutch version of the Rey Auditory Verbal Learning Test; RAVLT-D [40]. In this test, 15 words are verbally presented by the researcher, after which the test subject is prompted to recall as many words as possible. This is repeated five times. Delayed recall is tested after 20 min. A parallel version of the RAVLT was given at the post-training test time, T1.

Attention and Executive Functioning. To assess executive functioning, the Dutch version of the Frontal Assessment Battery (FAB) was presented [41]. The FAB has six subtests: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. Each subtest is scored from zero to three, with a score of three when the participant performs the subtest perfectly and with a score of zero when the participant fails. The total scores were recorded.

The Dutch version of the Stroop Color Word Test was included in order to measure attention and central executive functioning [42]. This test consists of three cards. On the first card, the participant is asked to read 10 rows of the names of colors printed in black ink. On the second card, they are instructed to name the color of multiple-colored rectangles. The time was tracked during the presentation of both cards [43]. A t-score was computed for both cards. In light of low performance on the most complex card of the Stroop Test, we excluded card 3 and did not calculate an interference score.

2.3. Procedure

The patients received a brief explanation about the study, and written informed consent was obtained for those patients who agreed to participate. The patients were assigned into one of three groups matched for sex, age, estimated (premorbid) intelligence, general cognition, and level of education. The neuropsychological tests, quality-of-life questionnaires, and Six-Minute Walking Test were administered as a baseline measurement before the start of the route training (T0). For quality of life and physical fitness, a midterm measurement was administered after three weeks and a final measurement after six weeks as well. The neuropsychological test battery was only administered at baseline and at the end of the training (T2). The exception was the cognitive screening test (MoCA) that was also offered at midterm (T1). An overview of the walking sessions and measurements collected can be found in Table 1.

Table 1. An overview of the training schedule and the different tests and observations that were collected during the training. RLT—the route learning test; TEL group = the trial-and-error group.

Week	Route Learning	Neuropsychological Tests	Quality of Life	Physical Fitness
T0	RLT only in the TEL group	MOCA, WM, LTM, Executive functioning	MANSA, QUALIDEM	6MWT
Week 1	2 training sessions			
Week 2	2 training sessions			
Week 3	1 training session	MoCA	MANSA, QUALIDEM	6MWT
T1	RLT			
Week 4	2 training sessions			
Week 5	2 training sessions			
Week 6	1 training session	MoCA, WM, LTM, Executive functioning	MANSA, QUALIDEM	6MWT
T2	RLT			

Note. T = timepoint, MoCA = Montreal Cognitive Assessment, WM = Working Memory Task, LTM = Long-term Memory Task, 6MWT = Six-Minute Walking Test.

2.4. Learning Conditions

The current study contained three learning conditions: passive learning (PL), trial-and-error learning (TEL), and errorless learning (EL). The participants in the PL condition were asked to follow the researcher along the route without any other instruction. The participants in the TEL group were asked to find the correct route by themselves through trial-and-error exploration. When they made an error by choosing the wrong direction, they were corrected and guided the right way. The participants in the EL group were guided during the route by photos of landmarks on a tablet. These photos were shown by the researcher on the tablet as soon as the forthcoming landmark could be seen from a given position. The participant was instructed to scan the environment and search for the landmark in order to know in which direction the route had to be continued. In this way, they had to search actively for the landmarks, but at the same time it was impossible to make an error, as the landmarks were clearly visible and easy to detect.

Design and Data Analysis

Background characteristics (neuropsychological test scores) were compared for the three groups using nonparametric Kruskal–Wallis tests on the various T0 scores.

The route learning test (RLT) was analyzed using nonparametric statistics because the groups were small and the scores were not normally distributed. The three groups were compared using a Kruskal–Wallis test, assessing whether there was any difference between the learning conditions. In case there was no group difference on the route learning test, we decided to take all the three groups together into a single new group in order to analyze

the other dependent variables. A Friedman test was performed to examine te effects of the route training on route learning.

For self-reported quality of life, a Friedman's test was performed for the pre- and post-measurement of the MANSA questionnaire. For the observed quality of life, a Friedman test was also performed on the pre- and post-measurement of the separate scales of the QUALIDEM.

To investigate the influence of the training on physical fitness, a one-way repeated measures ANOVA test was performed with physical fitness (6MWT) as the dependent variable and the training sessions (T0, T1, T2) as independent variables.

For the neuropsychological tests, nonparametric analyses were performed. The MoCA was analyzed by a Friedman test with test sessions as the independent factor (T0, T1, T2). For the other neuropsychological tests, Friedman tests were performed comparing the scores before and after the training (T0, T2). For the effect on verbal long-term memory, the measurements of the RAVLT-D were used. For verbal working memory, the measurements of the Digit Span subtest were included. Attention was assessed by a composite score of the first and second cards of the Stroop Color Word Test. Lastly, measurements of the FAB and the third card of the Stroop Color Word Test were pooled into a composite score to assess central executive functioning effects. Following Schmand et al. [43], t-scores were computed for the attention, executive functioning, and memory tests.

3. Results

3.1. Background and Neuropsychological Characteristics of Patients

This study started before the COVID-19 lockdown period. We originally planned to test a convenience sample of three groups of 10 patients. These planned sample sizes were comparable to the one used by Kessels et al. [18], and in light of the overall low mobility of these patients and of our previous experience in testing patients for longer training periods [20], we thought it would be very difficult, if not impossible, to include larger group sizes. It should be mentioned here that with this sample size, an alpha of 0.05, and a power of 0.8, an effect size f = 0.3 results [44]. This means that with the current design, a medium effect size is required to obtain significance. Noteworthily, throughout the course of the study, we encountered several obstacles that made it difficult to complete the training protocol for individual patients. One important reason why patients did not start or finish the training were the COVID-19-related restrictions at that time. In the second half of 2022, when the last patients were included and trained, we decided to stop further inclusion and training by the end of that year. Our schedule was to have fully tested 29 patients by then. Unfortunately, three patients dropped out because of motivational issues and/or physical problems during the training protocol. Hence, a total of 26 patients completed the training and were included in the analyses.

The patients were randomly assigned to one of three route learning conditions. In the group that received the passive learning training (PL), eight participants were included (four males; mean age = 59.6 years, SD = 7.5). The trial-and-error learning group (TEL) had nine participants (seven males; mean age = 60.0 years, SD = 8.2). The errorless learning group (EL) contained nine participants (seven males; mean age = 63.3 years, SD = 6.9). The education levels over the whole sample ranged from primary up to two years of low-level secondary education (n = 5), low-level secondary education (n = 9), average-level secondary education (n = 4), high-level secondary education (n = 5), and a university degree (n = 3).

The neuropsychological test scores of the patients with KS can be found in Table 2. The intelligence scores did not statistically significantly differ between the three groups, H(2) = 1.18, p = 0.56. Also, general cognition before the training did not statistically significantly differ between the groups, H(2) = 0.003, p = 0.998; neither did the specific

cognitive domains: verbal working memory H(2) = 1.004, $p = 0.61$, verbal long-term memory H(2) = 0.22, $p = 0.9$, attention H(2) = 1.17, $p = 0.56$, and central executive functioning H(2) = 0.995, $p = 0.61$. Together, these results indicate that the groups did not differ on baseline cognitive abilities.

Table 2. Neuropsychological test scores per group (learning condition) in the pre (T0), midterm (T1), and post (T2) training measurements.

Group (Learning Method)	Estimated IQ		General Cognition Screening (MOCA)		Verbal Working Memory		Verbal Long Term Memory		Attention		Central Executive	
	M	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***
Passive ($n = 8$)												
T0	98	14.3	20.9	3.2	50.7	10.7	27.0	4.4	33.3	9.2	47.0	8.9
T1	-	-	20.8	4.1	-	-	-	-	-	-	-	-
T2	-	-	20.5	2.7	51.5	6.7	24.1	3.1	36.8	11.3	50.3	8.6
Trial-and-Error ($n = 9$)												
T0	104	15.0	20.1	5.4	48.6	7.6	26.6	4.3	29.0	11.5	44.6	7.5
T1	-	-	19.0	6.1	-	-	-	-	-	-	-	-
T2	-	-	19.7	5.7	49.6	10.4	23.8	2.9	37.1	10.5	46.9	9.1
Errorless ($n = 9$)												
T0	103	21.0	20.3	4.8	46.4	9.3	26.4	6.3	35.6	8.1	48.5	6.1
T1	-	-	20.7	4.0	-	-	-	-	-	-	-	-
T2	-	-	19.7	3.4	44.6	11.9	23.4	3.5	40.6	8.8	50.2	5.7

Note: IQ was estimated with the Dutch Adult Reading Test [43]. The general cognition screening outcome is presented by the raw total score on the MoCA [37].

3.2. Effects of Learning Methods on Route Learning

To investigate the effects of the different learning methods on route learning, two Kruskal–Wallis tests were performed comparing the groups on the RLT at T1 and at T2. The tests showed no statistically significant differences between the groups (T1: H(2) = 3, 16, $p = 0.21$; $Eta^2 = 0.05$; T2: H(2) = 2.9, $p = 0.23$; $Eta^2 = 0.04$).

In the absence of these group/ learning methods effects, for all the consecutive analyses, the three groups were taken together. A Friedman test examined whether route performance improved in the patients after training. This effect was significant $\chi^2(1) = 13.8$, $p < 0.001$; Kendall's W = 0.53). As can be seen in Figure 2, the error rates clearly dropped from T1 to T2.

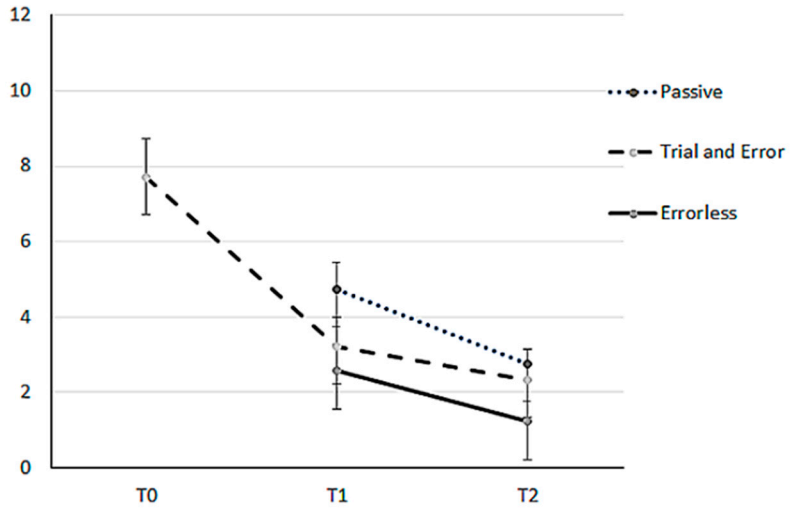


Figure 2. Mean learning test scores (number of incorrect route decisions) and standard errors for the three training methods (groups) over the three training sessions.

3.3. Quality of Life

3.3.1. Self-Reported Quality of Life

Figure 3 shows a scatterplot of MANSA scores—self-reported quality of life—pre- and post-training. First of all, we can see there is a clear correlation between the two scores $r(26) = 0.73$, $p < 0.001$. Even though insight into their functioning and impairments is typically limited in patients with KS, the correlation is a token of the meaningfulness of the MANSA scores. A Friedman test was performed to examine the effect of the walking training on self-reported quality of life in patients with KS on the MANSA questionnaire. Initial quality of life was regarded as reasonable to good based on the total MANSA scores (see Figure 3). Self-reported quality of life before (T0) and after the training (T2) was significantly different ($\chi^2(1) = 4.167$, $p = 0.041$). The mean rank and the mean of the post-measurements were higher than the mean rank and the mean of the pre-measurements, suggesting that the patients with KS had better self-reported quality of life after the walking training. This implies that patients with KS were more satisfied with their current life-situation after the training than before the training (see Figure 3).

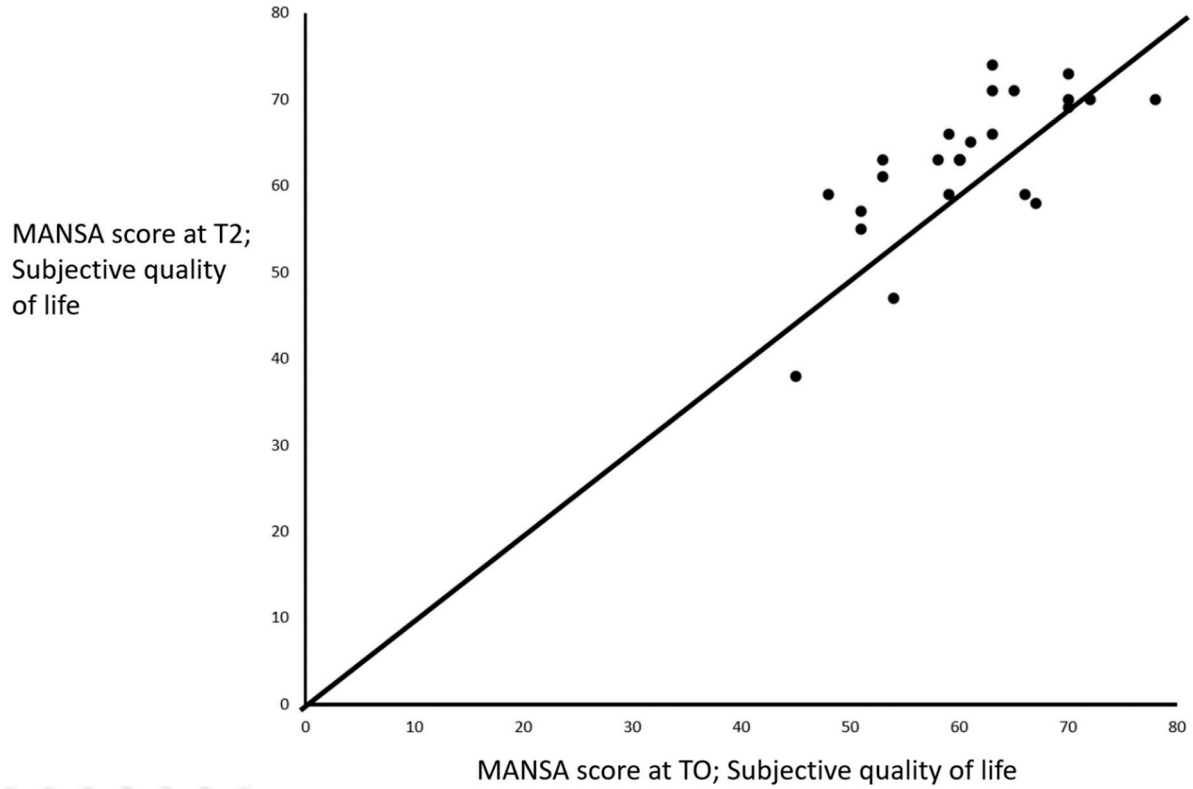


Figure 3. Subjective quality of life before the route training (MANSA at TO) and after the route training (MANSA at T1). Each dot is a single participant. The diagonal line gives the line at which the pre- and post-training scores are equal.

3.3.2. Observed Quality of Life by Nursing Staff

The QUALIDEM has nine scales (Care relationship; Positive Affect; Negative Affect; Restless tense behavior; Positive self- image; Social relations; Social isolation; Feeling at home; and Having something to do). We computed an overall average percentage score ranging from 0 to 100, with a higher score indicating a better quality of life. A Friedman test on the overall average percentage score did not yield a significant difference between the pre-test (72.5; T0) and the post-test (72.6; T2) ($\chi^2(1) = 0.0$, $p = 1$), suggestive of comparable proxy-reported quality of life before and after the training.

3.4. Physical Fitness

A one-way repeated measures analysis of variance (ANOVA) was conducted to evaluate the effects of the walking training on the patients' physical fitness. The results of the ANOVA indicated significant training effects, (F (2, 24) = 9.2, $p < 0.01$, $\eta^2 = 0.27$). As can be seen in Figure 4, physical fitness increased with the route training in the patients with KS.

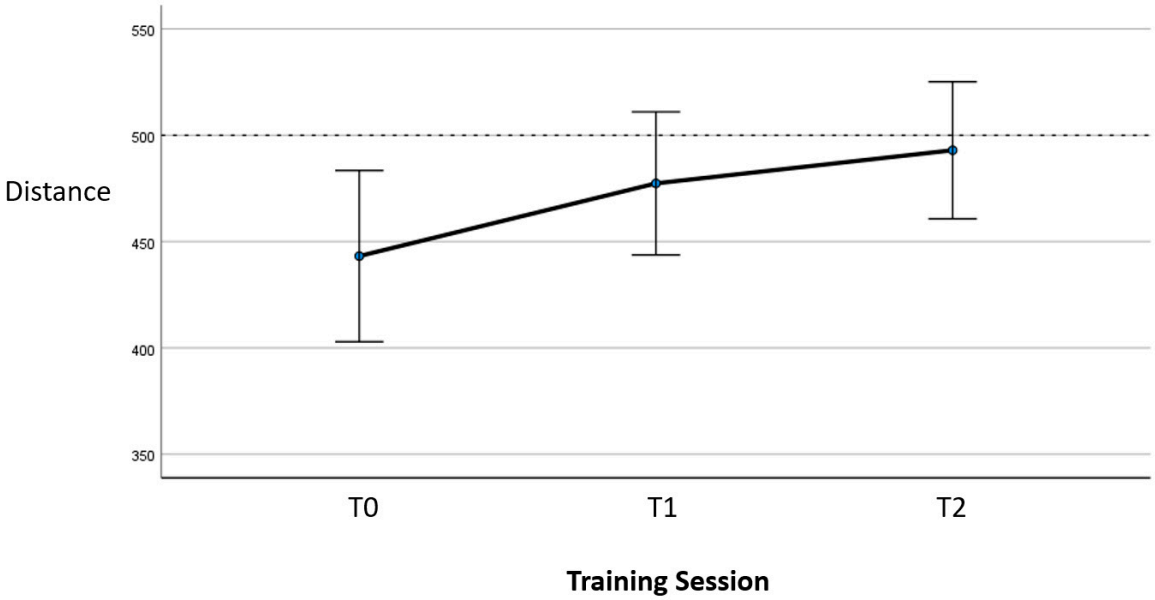


Figure 4. Distance walked (mean and standard error) in meters on the Six-Minute Walking Test at three training sessions. Note: The dotted reference line is based on the scores of healthy older people of 60 years and older [45].

3.5. Neuropsychological Tests

3.5.1. General Cognition Screening

A Friedman test was conducted to evaluate the effect of the walking training on general cognition in the patients with KS. The MoCA was used for this and measured before, halfway, and after the walking training. There were no statistical differences in general cognition between the three measurements, ($\chi^2(2) = 1.56$, $p = 0.46$), suggestive of comparable global cognitive functioning on the screening instrument.

3.5.2. Attention

To investigate the effect of the training on attention, a composite t-score of the t-scores of the first and second Stroop cards was computed. A Friedman test showed a statistically significant difference between the measurement of selective attention before and after the training ($\chi^2(1) = 11.6$, $p < 0.001$). The scores for the post-measurement were higher than for the pre-measurement.

3.5.3. Executive Functioning

The t-scores of the third card of the Stroop Test and of the FAB were combined to obtain a composite t-score for executive functioning. No statistically significant difference between the pre- and post-measurements was shown by a Friedman test ($\chi^2(1) = 2.46$, $p = 0.12$).

3.5.4. Verbal Memory

Verbal working memory. To investigate verbal working memory, a composite t-score was created with all the t-scores of the Digit Span subtest. According to a Friedman test, there

was no significant difference between the pre- and post-performance of verbal working memory ($\chi^2(1) = 0.15$, $p = 0.7$).

Verbal long-term memory. A composite t-score was created for verbal long-term memory, combining the t-scores of the learning phase and the delayed recall phase of the RAVLT-D. A Friedman test showed no statistically significant difference between the pre and post-measurement of verbal long-term memory ($\chi^2(1) = 2.13$, $p = 0.14$).

4. Discussion

Patients with Korsakoff syndrome suffer notable deficits in declarative memory. Hence, they have difficulties remembering a new route after one or two exposures. However, little is known about what will happen after multiple training sessions on the same route. In light of this, the aim of the present study was to further explore route learning potential in patients with KS, in particular focusing on which learning method would work best.

4.1. Effects of Learning Method on Route Memory

A key discovery in this study is that patients with KS could significantly benefit from repeated training sessions on the same route. After 12 training sessions, the error rates dropped to about three mistakes for 21 route decisions points in total (14%). While a single mistake can be enough to completely distance you from your intended target location, this performance seems quite acceptable. Moreover, there is also the possibility that the patients would have engaged in self-corrections if we had let them walk on after a mistake (see [46,47]). This we could not assess in the present setup. A second question of interest was which type of route learning would work best for our group of patients with KS. We compared errorless learning to trial-and-error learning and to passive learning principles. The learning methods did not differ statistically in their effectiveness. The effect sizes in the Kruskal–Wallis tests of group differences were small. The learning method effects are in line with Kessels et al. [18], who did not observe any difference between errorless route learning and trial-and-error learning in patients with KS on a shorter route either.

4.2. Quality of Life

A major reason to study route learning potential in patients with KS was that it could create more mobility and autonomy. If so, it might have a direct impact on quality of life in our participants. We took the three groups together and compared the pre-training quality-of-life scores to the post-training scores. Interestingly, the subjectively experienced quality of life (QoL) was higher after training. This suggests that patients with KS rated their current life situation after the training as higher than before the training. These effects are in line with earlier findings by Rensen et al. [21] that skill learning stimulates quality of life in patients with KS and by Claessen et al. [9] that promoting navigation abilities is highly appreciated by patients with acquired brain damage. Also, in line with earlier research, quality-of-life ratings prior to training were reasonable to good [21]. While subjective estimates were raised, the quality-of-life estimates by caretakers did not differ between pre- and post-training. Although one would expect both a raised self-report and a care staff report of quality of life, it might be that our results are relatively subtle. The use of self-estimations of QoL (like the MANSA) in a patient population can be debated. Patients with KS typically have limited illness insight [12]. This is also due to the psychopathological personality of these patients [48]. This may have affected their QoL self-reports. Notwithstanding this possibility, we would like to point out that the MANSA gives an impression of how patients experience and value their lives at a given moment and is therefore highly relevant. Moreover, as clearly can be seen in Figure 3, the pre- and

post-training MANSA scores were highly correlated, attesting the potential reliability of this measure.

Notably, QoL did not correlate with route learning performance. Hence, we may speculate that it is not the success rate that drives the QoL rating but more the route learning effort (together with at least some experience of learning success). Another factor that could drive QoL judgments could be an enhancement in physical fitness. Vagetti et al. [49] reported in a systematic review a clear association between physical activity and quality-of-life ratings in older people. Moreover, also being more frequently outside and having access to natural spaces, such as parks, may have contributed to the observed improvements in self-reported QoL [50].

4.3. Physical Fitness

In the foregoing, we have already mentioned the possibility of physical fitness increases after the route training. Interestingly, we observed that over the three training moments, the patients clearly improved on the six-minute walking test, a standardized physical rehabilitation test. At the end of the training, the patients were close to the reference norm set by healthy older people [45]. This promising result underscores the importance of regular physical activity in patients with KS.

We should give a warning here. Part of the improvement could follow from the fact that the physical fitness level of the participants was already very low at the start (T0). Knulst-Verlaan et al. [26] reported a clearly low physical ability level in patients with KS residing in long-term care. Hence, the observed fitness improvements could rather reflect the stimulating effects of the standard clinical care patients receive rather than the specific route walking influence. While this certainly is a possibility, we want to mention that the participants had been hospitalized in most cases for a relatively long time already. As a part of care as usual, patients with KS typically are stimulated to improve their physical fitness through exercise in a gym, and at least reach a basic fitness level. The observed fitness improvement after T0 must therefore be directly linked to the novel route walking regime that had started.

4.4. Neuropsychological Tests

Physical fitness effects could also lead to neurocognitive alterations. Several studies have reported cognitive improvements after physical training exercises in diverse patient groups [27–29]. Reiter et al. [51] found an increase in cortical thickness in MCI patients in a number of cortical sites after a 12-week moderate intensity walking intervention. As one of the sparse physical exercise studies on KS, Genc et al. [52] reported an increase in mobility, daily living functioning, and certain cognitive domains after an 8-week physiotherapy program for a case of Wernicke–Korsakoff syndrome (5 days a week, 2 times every day).

Given that our route walking training was limited in intensity and duration, we do not think it is likely that it has had a direct neural impact. At a cognitive level, we did not observe effects in the working memory, long-term memory and executive functioning tasks. Interestingly, route training appeared to elevate attention performance. These results are particularly promising when replicated in larger patient groups, because these functions are commonly severely impaired in patients with KS, causing problems with daily activities and decreasing the feeling of autonomy [15,16]. Guiney and Machado [53] mention in a review paper that regular aerobic exercise can improve attention, task switching, and inhibition in older adults, in line with our findings. Moreover, Ali et al. [54] and Deodato et al. [55] observed that a combination of heightened physical exercise and cognitive dual tasking may yield particular increases in neuropsychological functioning. Applied to our route training, it thus would be of interest to examine in future studies how the more

active route learning conditions (i.e., errorless and trial-and-error learning) affect general neuropsychological functioning.

4.5. Limitations

We have to acknowledge a number of limitations of the present study. A first limitation to be mentioned concerns the relatively small sample sizes. This could have limited the power to find differences between the route learning methods. It turned out to be relatively hard to recruit sufficient participants because of COVID-19-related restrictions at the time of the study. Moreover, the training schedule was relatively long for certain individual patients residing in long-term KS care, and they lost the motivation to continue. This is quite typical for patients with KS, as suggested by earlier work showing high levels of apathy in this population [56]. When computing the required sample size for obtaining a medium effect size given the group by training session design, we would have needed at least 42 participants [44]. Hence while the learning effect is clearly established, subtle differences between learning methods could have been masked by the small group sizes.

Another reason for not finding any learning method effects could be that differences between learning methods are limited to the initial stages of the training sequence. We can see that in the trial-and-error group, the error rate dropped by approximately 50% when going from the first training to the midterm training session. For the errorless and the passive learning group, the first measurement was made halfway though the training program. This was done to refrain the participants from making errors. In a completely different setup, it could be interesting to compare groups already at the second or third training moment. However, any subsequent learning would then be flawed by the errors made on that occasion. One may question whether the groups were comparable in their route learning ability at baseline. Given the comparable scores on the MoCA—a cognitive screener—it is not very likely that the groups initially would have differed in route learning ability. One way to determine this more precisely is to offer participants a second route that was learned on a single occasion in the passive learning condition and was tested next. This could, however, have caused inter-route interference, especially since both routes would have to start from the same point, the exit of the clinic where the patients resided.

A further limitation to be mentioned relates to some of the cognitive tests included in the study. As there is no parallel version of the Stroop Test and the FAB, we used the same test versions in the pre- and post-training measurements. There is the possibility that the improvement in attention functioning we observed may have been influenced by practice effects. Davidson et al. [57] showed practice effects on the Stroop task in younger and older participants. However, they used a rather large number of multiple consecutive task blocks with many trials, separated by either no delay (experiment 1) or about a week (experiment 2). In the present study, we had a much shorter task, and the two measurements were separated by at least 6 weeks. We therefore think that practice might have had a minimal influence on the observed training-related attention improvements, if any at all.

While no objective learning method differences were observed, we still want to point towards a more qualitative observation. The experimenters casually noticed that the errorless learning participants appeared to have a stronger appreciation of doing the route task than the participants in the other two groups. Actively searching and finding the correct solution (route continuation) and also not being frustrated by mistakes arguably is a much more rewarding experience. The errorless learning condition in this study made the participants actively scan the environment and focus on landmarks. Landmarks form important building blocks for cognitive maps of the environment—perspective-free, allocentric spatial maps [46,47,58]. The present route learning test did not offer the opportunity to test whether a more cognitive map-related, allocentric representation was

created, and if so whether this was strongest in the errorless learning condition. It now mostly assesses sequential egocentric route performance (see [46,47]). In future studies, it might be interesting to include a detour-taking task as well in order to test allocentric spatial performance in patients (e.g., how to go from landmark 5 to landmark 17; see Figure 1) [59].

5. Conclusions

In conclusion, the results of the current study demonstrate that Korsakoff syndrome patients, despite the severity and chronicity of the amnesia, can learn a new route when given enough practice occasions. Errorless learning did not yield superior results to passively following the experimenter or trial-and-error learning. Still, it might be a promising technique to use in clinical rehabilitation. It is efficient (no frustrating errors are made), and it positively activates the patients. Future research should examine both whether errorless learning advantages are present early in the learning process or instead lead to more enduring memory traces and appear in particular at long recall delays (cf. [20]). Route learning gives hospitalized patients new pathways to autonomy and mobility. As such, it can enhance experienced quality of life, physical fitness, and selective cognitive abilities (attention and executive functioning). In the present study, the experimenter controlled the tablet on which the route landmarks were shown. A future step could be to install GPS tracking on the tablet, allowing participants to walk fully independently guided by the tablet (or smartphone) that automatically shows the next landmark when the participant comes close. Advanced route training programs may contribute to numerous facets of daily life functioning and general health in patients with KS and possibly also in other patient groups. We recommend the implementation of route training into care as usual for patients with KS.

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