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# Preoperative Cognitive Intervention Reduces Cognitive Dysfunction in Elderly Patients after Gastrointestinal Surgery: A Randomized Controlled Trial

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Data Interpretation D
Manuscript Preparation E
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**Background:** Preoperative conditions may play a significant role in postoperative cognitive dysfunction (POCD) development in elderly patients. We aimed to investigate whether preoperative cognitive training could lower the incidence of POCD one week after surgery.

**Material/Methods:** A total of 141 ASA I-III elderly patients who underwent gastrointestinal surgery were enrolled into the study. Patients were randomized into either the Intervention group (69 analyzed) or the Control group (72 analyzed). Patients in the intervention group were instructed and trained in a cognition mnemonic skill for a total of three 1-hour sessions with the method of *loci* (MoL). Controls did not receive any cognitive training during hospitalization. All patients were tested using neuropsychological battery tests (NPTs) on admission and one week after surgery.

**Result:** The incidence of POCD in the intervention group (15.9%) was significantly lower than in the controls (36.1%) ($P<0.05$). Patients' performance in Brief Visuospatial Memory Test-Revised and Symbol-Digit Modalities Test were improved by the cognitive training. Increasing age, longer length of anesthesia and surgery, and lack of cognitive training were associated with a significantly higher risk of POCD ($P<0.05$).

**Conclusions:** Cognitive training with MoL can reduce the decline of early postoperative cognitive function in elderly patients undergoing major gastrointestinal surgery.

**MeSH Keywords:** **Anesthesia • Delirium, Dementia, Amnestic, Cognitive Disorders • Surgical Procedures, Elective**

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## Background

Postoperative Cognitive Dysfunction (POCD) is a decline in cognitive ability after surgery, and can manifest on a range of neuropsychological features in the early postoperative period [1]. The causes of POCD are poorly understood and the severity of cognitive decline is often detected only by the neuropsychological battery tests used before and after the surgery [2]. Anesthesia and surgical event may cause cognitive decline through several perioperative factors, especially in elderly patients. However, the molecular mechanisms underlying cognitive disorders are still unknown [3]. On the other hand, the impaired preoperative cognitive "brain reserve" of patients may also manifest as a potential postoperative cognitive impairment and might be accelerated by anesthesia and surgery [4], as well as the delayed dementia occurring after POCD [5]. Thus, early learning coping strategies that may avoid excess cognitive disability over time as a result of pre- and/or perioperative factors are very important [6].

Numerous studies including cognition intervention programs in older adults have shown that some improvement in cognitive function when the cognition training is provided with intensive training in strategies that promote thinking and remembering [7], suggesting that in older adults there is a considerable reserve potential in cognition that can be enhanced through cognition training strategies using simple mnemonic techniques, and such training is highly effective in improving the cognitive performance of non-demented adults [8,9]. However, the benefits of cognitive training strategy before surgery are less well explored, particularly in older patients.

We hypothesized that an early and short cognitive training in the preoperative period would impact the occurrence of cognitive changes after surgery. Therefore, the aim of this study was to evaluate whether preoperative cognitive training could lower the incidence of early cognitive dysfunction in elderly patients one week after surgery.

## Material and Methods

### Study participants

This study was approved by the Institutional Ethics Committee of 3rd Xiangya Hospital of Central South University, Hunan, P.R.China (approval number 2013-S124, January 1st 2013). After a written informed consent was given at one to four weeks prior to surgery, we obtained records on 141 patients who were scheduled to undergo elective gastrointestinal tumor resection via laparotomy expected to last 2 h or longer. Eligibles included elderly patients who were older than 60 years and American Society of Anesthesiologists (ASA) physical status I to III. Exclusion criteria included those with history of dementia or any disease of the central nervous system or those unwilling to comply with the protocol or procedures. Additional exclusion criteria included Mini-Mental State Examination (MMSE) ≤23 before surgery [10], or inability to read, and the presence of serious hearing or vision loss, or who had poor comprehension of the Chinese language. To determine the practice effect for repeated neuropsychological tests, we enrolled a group of age-matched control participants who shared the same inclusion and exclusion criteria. These participants were recruited from the patients' primary family members. Control participants did not undergo surgery or anesthesia during the study period

### Neuropsychological assessment

To assess patient cognitive function, neuropsychological battery tests (NPTs) were performed on admission (before the cognitive training) and one week after surgery. The NPTs was selected on the basis of demonstrated efficiency in similar subject populations [11,12]. The NTP include: (1) Benton Judgment of Line Orientation, a test used to assess the ability of judgment and visuospatial analysis; (2) Digit Span Test (forward and backward), a test of the Wechsler memory scale measures of attention and concentration, with higher scores indicating better function; (3) Brief Visuospatial Memory Test-Revised (BVMT-R), a test to measure the learning and immediate visuospatial memory; (4) Symbol-Digit Modalities Test, a measure of psychomotor speed, with a high score indicating better function; (5 and 6) BVMT-R Delayed Recall Test and BVMT-R Discrimination Index, used to estimate delayed recall abilities; (7) Trail Making Test (part A and B), a measure of hand-eye coordination, attention, and concentration, with a low score indicating better function; and (8) Verbal Fluency Test, used to asses executive function and fluency.

In order to minimize the practice effects, we chose tests that have alternative versions (version A and version B) [12,13]. We required that the NPTs were sensitive, not influenced by culture, and suitable for use by all participants in this study. The cognitive assessment took approximately 40 minutes and was administrated in a quiet environment by the researchers (L.Y. and C.M.H). The test was performed in Chinese (Mandarin).

### Cognitive training

After the first NPTs session, patients in the intervention group were introduced to a cognitive training program with the method of *loci* (MoL) [13]. The MoL involves teaching patients to visualize a series of familiar locations, visualize an imagined word representing each to-be-remembered item, and mentally place each item into a corresponding location [14,15]. Patients





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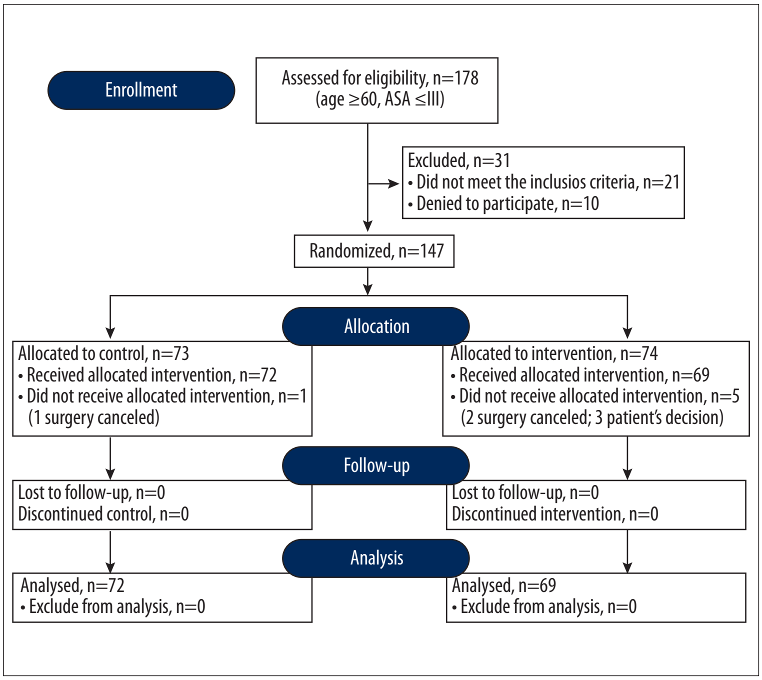


**Figure 1.** CONSORT 2010 flow diagram of patient enrollment, allocation, follow-up, and analysis.

were trained in individualized sessions at hospital in a quiet environment for a total of three 1-hour sessions, scheduled one day apart with the MoL, by a different trained investigator (A.J.S. And T.G.X.) who was blind to the study. Before starting of the first session, patients started to practice the technique of MoL with a list of five paired words (for example. Fish, ant, airplane, apple,…etc) and were asked to visualize a familiar geographical environment such as the room arrangement of their house when entered from the front door and turned in a counterclockwise direction (e.g., dining room, bedroom, bathroom, kitchen, etc.). Patients were trained so that they could remember the 5 *loci* in correct order. The memory training was performed with five paired words in every session as follows: patients were instructed to create an image for each paired words to be remembered and place images in the selected *loci*. For instance, the words 'tortoise and washbasin' could be linked to the *loci* 'dinning-room' by imagining that the tortoise is swimming in the washbasin which in the dining room. During training, participants practiced the mnemonics while learning paired associates and single words. In the recall phase, patients were asked to recall the five paired words in order when mentally retracing the *Loci* pathway. The words were common vocabularies chosen from the Modern Chinese Dictionary. The words were different in every session but the five distinct *loci* were the same. The Patients received less than 3 sessions training would be excluded.

The study was designed as a randomized controlled single blinded study. Before the preoperative neuropsychological assessment, Patients were randomly allocated to either intervention group or control group according to a random number table by an investigator not clinically involved in our study. Patients were not told what intervention was being evaluated, whether it was the neuropsychological assessment or the cognitive training. The investigator had no contact with patients after randomization. The trained researchers who performed the screening assessment and the training were blinded to patients grouping.

All surgery was performed with general anesthesia, and there were no restrictions on the type of anesthesia or postoperative analgesia. All patients were visited daily during their hospital stay, and the medical records were reviewed for complications.

## Definition and outcome measures

To obtain the "change" score of each cognitive test, we subtracted the raw score of the baseline preoperative test from the raw score of the postoperative cognitive tests. A postoperative deficit in any test was defined as the change scores were negative and the absolute value of each of these change scores was larger than one standard deviation (SD) of the baseline score of the same cognitive test from all subjects. Any patient having deficit in 2 or more neuropsychological tests was deemed to have POCD. We used this one SD criterion as described in previous studies [12,13,16].

The primary outcome was the incidence of POCD during hospitalization. For the sample size calculation, we calculated that 68 patients per group was needed to detect a reduction in the incidence of POCD from around 40% to 15% with 80% power at the 5% significance level.





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**Table 1.** Baseline characteristics of the patients in the intervention and control.

| | Intervention (n=69) | Control (n=72) |
|---|---|---|
| Age (year) | 71±6 | 70±6 |
| Sex | | |
| Male | 36 (52%) | 38 (53%) |
| Female | 33 (48%) | 34 (47%) |
| High (cm) | 161.3±8.1 | 162.1±7.6 |
| Weight (kg) | 62.3±6.4 | 63.2±8.1 |
| Education (years) | 5.7±2.0 | 6.0±2.4 |
| Pain assessments after admission | | |
| Numerical rating scale | 2.4±3.0 | 2.5±3.1 |
| ASA physical status | | |
| I | 18 (26%) | 21 (29%) |
| II | 36 (52%) | 31 (43%) |
| III | 15 (22%) | 20 (28%) |
| Cognitive performance | | |
| MMSE (score) | 28.9±1.5 | 28.1±1.5 |
| Benton judgment of line orientation test (score) | 15.2±1.5 | 15.3±1.9 |
| Digit Span Test (score) | 19.1±2.2 | 19.3±1.7 |
| BVMT-R (score) | 10.3±2.1 | 10.2±1.4 |
| Symbol-Digit Modalities Test (score) | 24.2±3.6 | 24.1±3.8 |
| BVMT-R Delayed Recall Test (score) | 3.4±1.4 | 3.6±1.2 |
| BVMT-R recognition discriminating index (score) | 10.3±1.3 | 10.8±1.2 |
| Trail Making Test (score) | 193.2±33.1 | 194.5±35.5 |
| Verbal Fluency Test (score) | 45.3±6.2 | 44.7±6.3 |

ASA – American Society of Anesthesiologist; BVMT-R – Brief Visuospatial Memory Test-Revised; MMSE – Mini Mental Examination. Data presented as n (%) or mean (standard deviation) unless indicated.

### Statistical analysis

SPSS 13.0 statistical software for analysis was used. Data were analyzed using SPSS 13.0 software, and are presented as number (n)or percentage (%), or mean ±sd as appropriate. We used chi-square test or Fisher exact test for bivariate of data comparison. We modeled the binary outcome of POCD in a logistic regression to determine which demographic and perioperative factors were associated with cognitive decline one week after surgery. All statistical tests were bilateral probability. $P<0.05$ for the difference was accepted as statistically significant.

**Table 2.** Characteristics of the surgical procedure and postoperative complications.

| | Intervention (n=69) | Control (n=72) |
|---|---|---|
| Length of anesthesia (min) | 207±61 | 216±47 |
| Length of surgery (min) | 178±49 | 189±47 |
| Estimated blood loss (ml) | 295±116.5 | 336±112.8 |
| Duration of hospital stay (days) | 12.21±1.9 | 13.26±1.2 |
| Postoperative complication (n) | | |
| Neurological | 1 (1%) | 2 (3%) |
| Respiratory | 3 (4%) | 2 (3%) |
| Cardiovascular | 2 (3%) | 1 (1%) |
| Infection | 6 (9%) | 8 (11%) |
| ICU stay for >24 h | 2 (3%) | 3 (4%) |

Data presented as n (%) or mean (standard deviation) unless otherwise indicated.

## Result

In the present study, a total of 178 patients were assessed for eligibility. Of them, 21 did not meet the inclusion criteria, 10 refused to participate and 6 did not received allocated intervention. Therefore, a total of 141 patients were enrolled in the study, with 69 patients in the intervention group and 72 patients in the control group (Figure 1). The clinical and demographic characteristics of the patients included in the study are presented in Table 1. There was no significant differences in demographic characteristics such as age, gender, body weight, education or ASA classification between the two groups ($P>0.05$). Preoperative pain score and baseline MMSE score were similar among both groups. No difference was found between intervention and control groups with regard to the type of surgery, postoperative complication, length of anesthesia and surgery, estimated blood loss or length of hospital stay (Table 2). The number of subjects who had deficit in each cognitive test at one week relative to pre-operation was presented in Table 3. Subjects' performance in BVMT-R and Symbol-Digit Modalities Test were improved in the intervention group which supported by more number of subjects having deficit in the two tests in the control group than that in the intervention group ($P<0.05$). Patients were define as POCD when exhibited





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**Table 3.** Postoperative cognitive decline incidence and the number of subjects who declined by one SD or more on each cognitive test at one week relative to pre-operation. Value are number (proportion).

| | Control (n=72) | Intervention (n=69) | $\chi^2$ | * P value |
|---|---|---|---|---|
| Brief Visuospatial Memory Test-Revised | 13 (18%) | 4 (6%) | 4.993 | 0.025 |
| Symbol-Digit Modalities Test | 5 (7%) | 6 (9%) | 0.150 | 0.698 |
| BVMT-R Recognition Discrimination Index | 7 (10%) | 3 (4%) | 1.545 | 0.214 |
| Trail Making Test | 5 (7%) | 6 (9%) | 0.150 | 0.698 |
| Benton Judgment of Line Orientation Test | 5 (7%) | 1 (1%) | 2.611 | 0.106 |
| Digit Span Test | 6 (8%) | 5 (7%) | 0.058 | 0.810 |
| Symbol-Digit Modalities Test | 7 (10%) | 1 (1%) | 4.506 | 0.034 |
| Verbal Fluency Test | 12 (17%) | 9 (13%) | 0.365 | 0.546 |
| Number of patients who developed POCD (defined by decline in two or more cognitive tests) | 26 (36.1%) | 11 (15.9%) | 7.405 | 0.007 |

BVMT-R – Brief Visuospatial Memory Test-Revised; POCD – Postoperative Cognitive Dysfunction. * P value applies to comparison across groups.

impairment in 2 or more of 8 cognitive tests. Collectively, 11 of 69 patients (15.9%) in the intervention group and 26 of 72 patients (36.1%) in the control group developed POCD one week after surgery (P<0.05) (Table 3). We compared the possible predictors of cognitive decline at one week after surgery between those who show POCD and those who have no POCD, such as age, education level, etc. T test analysis found that increasing age, longer length of anesthesia and surgery, lacking of cognitive training were associated with a significantly higher risk of POCD (P<0.05) (Table 4). In contrast, gender, education, blood loss, ASA physical status and baseline MMSE score were not significantly associated with POCD. Through step-wise multiple logistic regression models, age, length of surgery and cognitive training with MoL were identified as the independent predictors of POCD (Table 5).

## Discussion

In the present study our finding indicated that an early short-term cognitive training with mnemonic technique such as the MoL in the preoperative period significantly reduced the incidence of POCD in elderly patients one week after surgery. In our study, the beneficial effect of cognitive training produces modest gains on the cognitive tests were also demonstrated in Borella and Becker's research which focus on healthy elders [17,18]. The total hours of the cognitive training varied widely between studies, a systematic review by Reijnders et al. [19] found that cognitive training can be effective in improving various aspects of cognitive functioning and the intervention effect was not significantly related to the total hours of cognitive training, but may be related to the efficiency of the intervention we used. The mnemonic skill (MoL) used before the surgery is based on familiar *loci* so that it is an easy-to-use strategy for the elders who have rich life experience to master this memory training. Visualizing each item within a location provides cues that can be used at retrieval to distinguish the sought after item from others stored in memory. Most patients could understand and practice the MoL well after 3 sessions training and they reported that this technique affect their process of memory even after the training, and this maybe explain why the short term memory training were effective in reducing the decline of cognitive function in elders. Meanwhile, age was independent risk factors for POCD development. Moller et al. in one of the largest POCD studies, evaluated cognitive dysfunction in a multicenter study among elderly and his focus was on patients-related risk factors such as age, and other perioperative causative factors such as hypoxia and arterial hypotension [20]. Our study accords well with the finding of the international study of postoperative cognitive dysfunction (ISPOCD) that advanced age is a risk factor.

At present, the possible mechanism behind cognitive training strategy may reduce the decline of cognitive function in elders, built on the premise of cognitive reserve. Cognitive reserve is a potential mechanism for coping with brain damage, additional synapsis or increased number of redundant neuronal networks from the reserve capacity can be a potential mechanism for coping with brain damage in elderly [21,22]. Hampstead et al. found that memory training can improve the level of subjective cognitive function in patients with MCI, and with increase in the degree of activation of the hippocampus region of the

**Table 4.** Predictors of cognitive decline at one week after surgery. Value are number (proportion).

| | POCD (n =37) | | No POCD (n =104) | | $\chi^2$ | * P value |
|---|---|---|---|---|---|---|
| Age (years) | | | | | 17.305 | 0.000 |
| ≤65 | 5 | (14%) | 55 | (53%) | | |
| 65–70 | 15 | (40%) | 23 | (22%) | | |
| >70 | 17 | (46%) | 26 | (25%) | | |
| Gender | | | | | 3.443 | 0.064 |
| Female | 24 | (65%) | 49 | (47%) | | |
| Male | 13 | (35%) | 55 | (53%) | | |
| Education(years) | | | | | 3.215 | 0.360 |
| ≤3 | 4 | (11%) | 11 | (11%) | | |
| 3–6 | 4 | (11%) | 5 | (5%) | | |
| 6–9 | 28 | (76%) | 78 | (75%) | | |
| >9 | 1 | (2%) | 10 | (9%) | | |
| Length of surgery (h) | | | | | 13.847 | 0.001 |
| 2–3 | 11 | (30%) | 61 | (59%) | | |
| 3–4 | 18 | (49%) | 38 | (37%) | | |
| >4 | 8 | (21%) | 5 | (4%) | | |
| Length of anesthesia (h) | | | | | 8.711 | 0.013 |
| 2–3 | 4 | (11%) | 37 | (36%) | | |
| 3–4 | 21 | (57%) | 46 | (44%) | | |
| >4 | 12 | (32%) | 20 | (20%) | | |
| Blood loss | | | | | 0.337 | 0.953 |
| ≤500 | 31 | (83%) | 91 | (87%) | | |
| 500–800 | 4 | (11%) | 9 | (9%) | | |
| 800–1200 | 1 | (3%) | 2 | (2%) | | |
| >1200 | 1 | (3%) | 2 | (2%) | | |
| ASA physical status | | | | | 1.321 | 0.250 |
| I | 5 | (13%) | 34 | (33%) | 5.233 | 0.073 |
| II | 22 | (60%) | 45 | (43%) | | |
| III | 10 | (27%) | 25 | (24%) | | |
| Baseline MMSE score | | | | | 1.657 | 0.198 |
| 23–25 | 29 | (78%) | 90 | (87%) | | |
| 26–30 | 8 | (12%) | 14 | (13%) | | |
| Grouping | | | | | 7.405 | 0.007 |
| Intervention group | 11 | (30%) | 58 | (56%) | | |
| Control group | 26 | (70%) | 46 | (44%) | | |

ASA – American Society of Anesthesiologist; MMSE – Mini-Mental State Examination; POCD – Postoperative Cognitive Dysfunction.
* P value applies to comparison across groups.





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**Table 5.** Multiple logistic regression analysis for the predictors of POCD. The variables firstly included into the analysis model are age, length of anesthesia and surgery, grouping (intervention or control).

| | Regression coefficient | Wald | P value | Odds ratio (95% CI) |
|---|---|---|---|---|
| Age | 1.172 | 15.944 | 0.000 | 3.227 (1.816, 5.735) |
| Length of surgery | 1.281 | 12.657 | 0.000 | 3.600 (1.776, 7.297) |
| Cognitive training with MoL | –1.215 | 6.607 | 0.010 | 0.297 (0.117, 0.749) |

MoL – method of *loci*. Chi-square=37.166, P=0.000; excluded variable: Length of Anesthesia –2 Log likelihood=124.531, Cox&Snell R Square=0.233, Nagelkerke R Square=0.340 Backward: LR. * P value applies to comparison across groups.

brain related to further support the plasticity of cognitive function [23]. Furthermore, major results emerge from cognitive training studies using techniques such as the MoL. According to Verhaeghen et al. instruction and practice in a mnemonic technique such as MoL lead to considerable performance improvements in healthy older adults [24]. The focus on simple bedside prevention technique with cognitive training such as the MoL in hospital setting may protect to a certain extent the patient's cognitive reserve capacity, and enable them to more effectively respond to the perioperative various factors damage caused by the anesthesia and surgery, this suggest that elderly surgical patient cognitive function is may be associated with a reduction but not with a complete loss of cognitive plasticity after surgery or during hospitalization [25,26].

It is therefore unclear whether such mnemonic technique with cognitive training may help elder surgical patients to protect certain cognitive plasticity or the changed cognitive function was due to an obtained in the amount of neuron plasticity even if some of their cognitive function revert back to normal and there cognitive deteriorations attenuated on the result of the NPTs during the first week after surgery. In our study, POCD was defined when any subject having deficit in two or more on the NPTs. Interestingly, patients experienced different deficit on the NPTs between the intervention group and control group, and there were less number of patients having cognitive decline in BVMT-R and Symbol-Digit Modalities Test in the intervention group which suggested that subjects' performance in BVMT-R and Symbol-Digit Modalities Test were improved by the cognitive training. This improvement in the cognitive tests may be because of the cognitive training could benefit patients more in the intervention group, or may be because of "learning effect" caused by memory training on the results. Of course, we must acknowledge that the present cognitive training strategy did not develop cognitive function in all domains (e.g., executive function, memory, attention), rather than maintain and/or protect certain individuals in the intervention group from any reduction in cognition that may occur during or after surgery. Therefore, further investigation should test different mnemonic techniques to enhance cognitive function and reduce the severity of POCD in elder surgical patients.

There are some limitations in our study. First, the heterogeneity mechanism of POCD symptoms has not been clearly elucidated, therefore, the efficacy of the cognition training could not be evaluated easily. Second, the POCD definition, the NPTs, the time interval between each sessions, and the statistical methods used to analyze the data still a major issue of debate among researchers [27]. Finally, to perform the study on a large sample size and investigate the incidence of POCD for three months and even one year after surgery or from hospital discharge would give the chance that the precision of the effect shown could have been even better even if the effect of a 15.9% reduction of POCD is of borderline statistical significance. Future studies may include more subjects, more number of cognitive training sessions and longer follow-up times.

## Conclusions

In summary, the use of cognitive training program with the MoL lowered the incidence of POCD in elderly patients one week after surgery, compared with that of the control group. Our study analysis provides some evidence that early preoperative training with cognitive mnemonic skills are promising and can prevent or maintain good cognition functioning in elderly patients during hospitalization.

**Competing of interest**

None.

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