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Long-term Post-Operative Cognitive Decline in the Elderly: the Effects of Anesthesia Type, Apolipoprotein E Genotype, and Clinical Antecedents

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Running title: Post-operative cognitive decline in the elderly

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Abstract

Cognitive dysfunction in the elderly commonly observed following anesthesia has been attributed to age-related neuronal changes exacerbated by pharmacotoxic effects. However, the extent to which these changes may persist following recovery from surgery is still largely unknown. This study investigates the long-term effects of anesthesia on cognitive functioning after orthopedic surgery in 270 elderly patients over the age of 65 who completed a computerized cognitive battery before and 8 days, 4 and 13 months after surgery. Their performance was compared to that of 310 elderly controls who completed the same neuro-psychiatric evaluation at baseline and one-year interval. Multivariate analyses adjusted for socio-demographic variables, depressive symptomatology, vascular pathology as well as baseline cognitive performance. We found early and transient post-operative decline in reaction time and constructional praxis. With regard to long-term changes we observed improvement compared to controls in most verbal tasks (probably due to learning effects). On the other hand, a clear dissociation effect was observed for several areas of visuospatial functioning which persisted up to the 13-month follow-up. This specific pattern of visuospatial deficit was found to be independent of apolipoprotein E genotype and closely resembles what has recently been termed vascular mild cognitive impairment, in turn associated with subtle sub-cortical vascular changes. The observation of only minor differences between persons operated by general and regional anesthesia makes it difficult to attribute these changes directly to the anesthetic agents themselves, suggesting that cognitive dysfunction may be attributable at least in part to peri-operative conditions, notably stress and glucocorticoid exposure.

INTRODUCTION

Although cognitive decline in elderly persons following anesthesia has been reported in the literature for over a century, there is still lack of consensus as to whether anesthetic agents may directly cause permanent cognitive loss. The general concern has been that while the potential neurotoxicity of anesthetics may be well tolerated by younger persons, age-related losses in cerebral reserve, increased permeability of the blood-brain barrier and slower drug elimination rates may lead to adverse effects and perhaps also precipitate neurodegenerative disorders. Some neuropathophysiological studies have suggested that post-operative cognitive disorder (POCD) may even share common mechanisms with Alzheimer's disease through plasma β amyloid deposition and Tau phosphorylation [1-3]. The principal methodological problem for research in this area lies in controlling for the many other causes of cognitive dysfunction which may confound results, notably clinical antecedents, co-morbidity and genetic vulnerability (see for reviews [4-6]). Most early studies were carried out on patients undergoing cardiac surgery revealing extensive cognitive disorder in a wide range of functions, most of which, however, were attributable to pre-existing cardiac insufficiency, peri-operative hemodynamic instability and very high rates of post-operative depression.

While subsequent studies conducted on non-cardiac surgery have generally agreed POCD to be quite common in the short-term (up to several weeks after surgery) with no differences between regional (RA) and general anesthesia (GA) [7-9], there have been few non-cardiac studies of long term consequences (over a year) [4-6]. While there is limited evidence of POCD 6 months after surgery, the validity of the results remains questionable due not only to failure to take into account the confounding factors described above but also a too narrow a range of cognitive tests (often restricted to tests used to diagnose dementia) and underpowered statistical analyses [4]. In addition, most studies have excluded patients with pre-existing cognitive, psychiatric, or central nervous system disorders, as well as patients taking tranquilizers or antidepressants making them not only non-representative of elderly

populations undergoing anesthesia, but also excluding the possibility of examining interaction effects [10, 11]. Cognitive difficulties are, however, also common in elderly persons who do not undergo anesthesia, so that the failure of previous studies to provide a non-operated control groups may have led to an overestimation of anesthetic effects especially when long-term effects are examined. To date only one long-term study of POCD after major non-cardiac surgery has made a comparison with healthy controls (172 orthopedic patients compared to 190 controls) reporting no significant POCD after a 10 month follow-up [12]. However cognitive testing did not adequately cover all information-processing domains and comorbidity was not taken into account.

In addition to increased vulnerability due to pre-existing clinical factors, certain persons may be genetically more susceptible to anesthetic effects. In this regard the apolipoprotein E (ApoE) $\epsilon 4$ allele has been the focus of attention as it is not only associated with increased risk for Alzheimer's disease, but also worse outcome after cerebral injury and accelerated cognitive decline in normal elderly [13-18]. An association between the $\epsilon 4$ allele and POCD after cardiac surgery has also been suggested in small -mostly inadequately adjusted- studies [19-21] although not consistently [22-26]. Only two studies have to date examined ApoE effects in non-cardiac surgery, both finding no significant association [27, 28].

The present study examines the long-term (13 months) effects of anesthesia on cognitive tests covering a full range of information-processing skills rather than tests designed to screen for dementia. The study takes into account covariate effects of socio-demographic characteristics, pre-operative cognitive functioning, physical health, depressive symptomatology, genetic vulnerability (ApoE) and anesthesia type (regional or general). Subjects are compared with elderly persons with stable cognitive functioning over the past year at baseline, and no exposure to anesthetic agents over the one-year study period.

METHODS

Selection of patients and control subjects

Two hundred and seventy patients over the age of 65 coming for elective orthopedic surgery (hip or knee replacement for 94.1% of the subjects) were recruited into the study between October 1998 and January 2002. Persons with dementia, auditory or visual impairment that would preclude cognitive testing or non-fluent French speakers were excluded from the study. Ethics approval was given by the national ethics committee and written informed consent was obtained from all participants. For ethical reasons, randomization to RA or GA was not possible and furthermore the study aimed to observe current clinical practice. The anesthetists in the study declared the principal reason for allocation to RA or GA were the physical and mental status of the patient and these factors are included as co-variables in the analyses relating to anesthesia type. The 310 subjects constituting the comparison group are taken from the Euseria longitudinal study of cognitive ageing. These were persons over 60 years of age recruited through 63 randomly selected general practitioners in the Montpellier region [29]. Subjects selected for the control group were free of dementia and without pre-existing cognitive deterioration at baseline (DECO Score > 30, see below) and did not undergo anesthesia during follow-up. Control subjects had been given the same neuropsychological examination as the anesthetized patients at baseline and one year later.

Cognitive evaluation

Each subject was examined pre-operatively, and at eight days [median (IQR): 8 (7-8) days], four months [112 (98-145) days], and 13 months [391 (372-410) days] after surgery using a comprehensive computerized cognitive battery. This examination, ECO (Examen Cognitif par Ordinateur) assesses primary memory, verbal and visuospatial secondary memory, implicit memory, language skills (naming, verbal fluency), visuospatial performance

(ideational, ideo-motor and constructive apraxia), functional and semantic categorization of visual data, visual reasoning and form perception, and focused and divided attention (visual and auditory modalities) [29]. Reaction time and response latencies were recorded using a tactile screen. The following summary cognitive domains were examined in the present study:

Reasoning: assessed by a multiple choice task requiring completion of a logical visual series with increasingly complex decision rules

Attention: measured by response time on a dual task (simultaneous visual selection and counting of auditory stimuli)

Primary memory: assessed by immediate recall of a list of first names (verbal memory) and recall of a trail traced on the computer screen (visuospatial memory)

Secondary verbal and visual memory: measured by (i) delayed recall of proper names with and without semantic and phonetic cueing and (ii) delayed recall of faces associated with the proper names and (iii) recall of two narratives – one with a logical sequence and the other a description requiring visual recall

Implicit memory: time taken to recognize the previously learnt proper names and distractors progressively built up by random pixels on the computer screen

Visuospatial ability: measured by the number of elements correct in the copying of complex meaningful and meaningless figures

Language: assessed by object naming and verbal fluency.

In addition to cognitive assessment at the time of admission, pre-existing cognitive deterioration is established by an informant questionnaire completed by care-givers (DECO - Détérioration Cognitive Observée) which measures changes in cognitive performance over the past year. Previous validation studies in both clinical and population settings have shown this instrument to be highly sensitive to early modifications in cognitive functioning due to multiple causes [30]. DECO scores have a maximum of 38 (no change over the past year)

down to 0 (significant change over the 19 areas of cognitive performance examined). A score lower than 30 has been established by Receiver Operating Characteristics analysis to indicate a high probability of dementia within a general population sample [30].

General questionnaire

A general questionnaire obtained information on socio-demographic status, current pathologies and treatment, previous surgical interventions, pre-operative physical status using the American Society of Anesthesiologists' (ASA) classification, surgical procedures, type of anesthesia, duration of hospitalization and management after discharge. The Center for Epidemiologic Studies-Depression Scale (CES-D) [31] was used to detect levels of current depressive symptomatology with a cut-off score equal or above 16 indicating clinical levels of depression. Ability to perform activities of daily living was assessed by the Adaptation and Behaviour scale (ECA - Echelle de Comportement et d'Adaptation) [32]. This questionnaire is completed by relatives and has been constructed with reference to the disability classifications given by the W.H.O. in the International Classification of Impairments, Disabilities and Handicaps [33]. Venous blood samples were taken for ApoE genotyping as described previously [34].

Statistical analysis

Logistic regression was used to compare cognitive decline between inclusion and each follow-up with one-year changes in cognitive functioning in the control group (reference, OR=1). ORs were adjusted for age, gender, education level, depressive symptomatology, cerebrovascular and cardiac pathology, and baseline cognitive score (*i.e.* covariates that were associated with cognitive decline at $p < 0.10$). Cognitive decline at each follow-up was defined as a decrease of at least one point between baseline cognitive score and the score at either following visit.

The effects of anesthesia type (GA vs. RA) on cognitive change over one year were compared using random-effect linear models for cognitive variables which were approximately normal (reaction time, geometric form association, verbal fluency, and implicit memory). For cognitive variables with non-normal distribution, we performed mixed logistic models where cognitive decline (dichotomized variable) was defined as being in the lowest quartile of the difference between baseline score and either follow-up visit. Each (linear or logistic) model included age, gender, education level, ASA score, ApoE4 (carrying at least one $\epsilon 4$ allele), time (number of days between inclusion and follow-up), anesthesia type, and the interaction between time and anesthesia. The term anesthesia represents the cross-sectional association between anesthesia and the selected cognitive test at baseline. The term for time indicates the linear evolution per month on the cognitive test. The term for interaction between time and anesthesia represents the additional monthly modification on the selected cognitive tests for anesthesia. SAS (v9.1) was used for the statistical analyses with a significance level of $p < 0.05$ (SAS Institute, Inc., North Carolina).

RESULTS

Population characteristics

Of the 270 patients who completed the pre-operative interview, 171 (63.3%) had a complete follow-up, at 8 days, 4 and 13 months, 65 (24.1%) had two examinations and 34 (12.6%) only one examination during the follow-up period. The 55 (20.4%) subjects who had no examination at the last 13-month follow-up did not differ significantly from those who were examined at 13 months with regard to age, education level, gender, depressive symptomatology, pre-operative cognitive decline and baseline cognitive variables, type of anesthesia or frequency of undesirable severe post-operative sequelae consequences (data not shown).

The characteristics of the samples of anesthetized patients and non-anesthetized controls

are given in **Table 1**. Controls were significantly older, had a higher education level, were more frequently women and had less cerebrovascular and cardiac pathologies than anesthetized patients. They also tended to be less depressed.

Of the 270 anesthetized patients 184 (68.1%) had GA and 31.9% RA of whom 59.3% were sedated. Among the patients who had GA, 95.7% received a mixed combination of halogenated and intravenous anesthetics (such as propofol and thiopental) and none received only halogenated small-sized molecules. Patients with GA were younger (median age 70 years vs. 74 years in the RA group, $p < 0.001$) and had lower ASA scores, *i.e.* less frequent pre-operative co-morbidity (in general related to vascular pathologies) than patients receiving RA (15.8% were in ASA group 3 corresponding to patients with severe systemic disease limiting their activities vs. 38.4% in the RA group, $p = 0.0001$) (data not shown). They did not differ significantly in education level, sex, depressive symptomatology, and mean duration of post-operative hospitalization (10 days).

Post-operative cognitive change across time

In multivariate logistic models, anesthesia exposure was associated with specific cognitive changes (**Table 2**). Eight days after anesthesia, a decline was observed in reaction time (OR = 1.74, $p = 0.01$), constructional praxis (OR = 3.6, $p < 0.0001$) and geometric form association (OR = 1.96, $p = 0.003$). Decline on geometric form association persisted 4 months (OR = 2.56, $p < 0.001$) and 13 months after anesthesia (2.68, $p < 0.001$). Delayed decline (at 13 months) was also observed for immediate visual memory (OR = 1.90, $p = 0.004$). No significant changes were observed in attention, implicit memory, delayed visual memory, verbal fluency, and logical series. On the other hand significant improvement was observed in object naming, immediate and delayed verbal recall, and name-face pair and narrative recall.

Effect of anesthesia type

Decline after 8 days was observed in patients undergoing GA in reaction time (OR =1.97, p=0.006) and verbal fluency (OR=1.54, p=0.04) and in immediate visual memory for RA patients (OR=2.13, p=0.01) (data not shown). Decline in constructional praxis was observed both with RA (OR=2.19, p=0.03) and GA (OR=4.61, p<0.0001), but returning to normal levels at 4 or 13 months. Decline in immediate visual memory was observed for GA at 13 months (OR=2.15, p=0.002). Decline in geometric form association persisted even at 13-month follow-up in RA (OR=2.96, p=0.002) or GA patients (OR=2.60, p=0.0002).

Mixed models were used to compare the global cognitive evolution of persons receiving GA compared to RA over the observation period (**Table 3**). Persons receiving GA appeared to undergo a slightly more rapid recovery in constructional praxis (OR=0.88, p=0.01) during the 13 month follow-up compared to those with RA. No significant differences were observed on other cognitive tasks. The same results were obtained when the ApoE variable was not included as a confounding factor.

DISCUSSION

Post-operative cognitive change across time

This study, using a wider range of neuropsychological tests than in previous reports, suggests that anesthesia during orthopedic surgery has adverse effects on reaction time, constructional praxis, geometric form association and immediate visual memory. These effects appeared to be independent of ApoE genotype as observed by previous studies of both cardiac [24-26] and non-cardiac [27, 28] surgery.

Early and transient post-operative decline was observed for reaction time and constructional praxis as previously reported [35] suggesting reversibility of the deleterious effect of the anesthesia and/or complete elimination of residual anesthetics. On the other hand, a highly significant deterioration in geometric form association and visual memory were observed to persist even after 13-month follow-up suggesting more permanent effects on brain

functioning. In contrast improvement was observed on some verbal tasks (naming, immediate and delayed verbal recall, narrative and name-face pair recall). Improvement on verbal tasks compared to the control group is most likely due to practice effects as controls only completed the battery at baseline and one year whereas the patients exposed to anesthesia completed it four times. Indeed, the control group used had already been assessed in the year before this study so it was not possible to have equal number of administrations. This learning effect is likely on the other hand to have led to an underestimation of the decline observed on visuospatial tasks. Our study shows a probable unilateral effect which is consistent with observations that even in normal ageing visuospatial functions may be particularly vulnerable, and are amongst the earliest signs of mild cognitive impairment [36, 37]. A distinction has recently been made between vascular and non-vascular mild cognitive impairment; the former showing significant deterioration in visuospatial functions whereas the latter concerns primarily verbal memory [38] indicating a possible double dissociation. Cases of vascular mild cognitive impairment are more likely to evolve towards either vascular or mixed vascular and Alzheimer's disease dementia. Furthermore a distinctive pattern of predominantly visuospatial dysfunction has been shown to be related to microalterations in white matter lesions and other subcortical vascular changes [39]. This would suggest that anesthesia may have initiated or accelerated subtle vascular lesions leading to more permanent effects. The question remains as to whether the changes we have observed in visuospatial functioning can be directly attributed to the anesthetic agents themselves. Indeed, corticosteroid secretion, whether endogenous (stress reaction which may be consecutive to illness, pain and surgery) or exogenous (as frequently used in orthopedic geriatric patients) has previously been associated with cognitive decline [40-45].

Effect of anesthesia type

No significant differences were found on most neuropsychological tests according to the

type of anesthesia used. An increased risk of cognitive decline was observed after 8 days only in reaction time and verbal fluency with GA and in immediate visual memory for RA. Constructional praxis was found to decline in both GA and RA, with GA patients appearing to have a more rapid recovery during the 13-month follow-up compared to those with RA. The few randomized studies which have previously been conducted failed to observe significant differences in cognitive impairment as a function of anesthesia type [7-9]. Recent *in vivo* and *in vitro* NMR studies have shown selective neurotoxic effects, including increased capacity to oligomerize amyloid β -peptide, after GA by inhalation with halogenated anesthetics of small molecular weight compared to intravenous anesthetics such as propofol or thiopental [1, 46-48]. In our sample, 95.7% of the patients who had GA received a combination of both halogenated and intravenous anesthetics and we could not address this specific question. While a pattern of visuospatial decline consistent with vascular changes suggests anesthesia may be responsible for subtle sub-cortical damage, failure to find a difference according to anesthesia type suggests that it may not be the anesthetic compounds *per se* which precipitate POCD, but rather the peri-operative effects of surgery, anxiety, stress, pain, prolonged starvation, all of which may be cumulative [49].

Limitations and strengths

Although the dropout rate between eight days and 13 months (21.1%) in this study was a cause of concern, analysis of the various demographic variables suggested that non-returners were not significantly different in terms of socio-demographic or clinical variables and there was no interaction between return/no return and anesthetic choice.

Unlike most previous studies, the absence of exclusion criteria concerning the initial health status of the patients permitted the evaluation of cognitive change under externally valid conditions, reflecting fairly well the geriatric orthopedic surgery population, and also allowing us to examine the individual effects of these variables. Lastly, since the same test

battery was used on all four test occasions, repeated examination could have led to an underestimation of the proportion of subjects with cognitive decline, considering that subjects who did not decline could be those for whom a learning effect did not occur.

In this study, the subjects were not randomly assigned to anesthesia type and the proportion of subjects at risk (older and more frequently with severe co-morbidity) was higher in the RA than in the GA group, which may reflect the existing concerns of anesthetists and patients as to the possible effects of GA. This may be a significant indication bias both in our study and previous observations. Even in randomized studies the rate of subjects excluded due to contraindications to one given type of anesthesia is high (for instance 37% in [7]). On the other hand age, health status and cognitive functioning at the time of surgery, which anesthetists declared to be the principal criteria for anesthesia type, were taken into account in the multivariate analyses.

Despite these limitations, this study has several strengths, namely a larger sample size (270 patients) than in most previous long-term controlled studies and longer duration of follow-up (up to 13 months). The study used a neuropsychological battery which aimed at detecting changes in the full range of information-processing functions and not just confined to tests used in dementia screening. We also had access to a cognitively healthy control group and were able to adjust for a large range of confounding factors (age, sex, education level, depressive symptomatology, cerebrovascular and cardiac pathology, genetic vulnerability to cognitive decline, and baseline cognitive performance). However, we could not control for other preoperative factors (such as pain or stress) which may have led to an under-estimation of post-operative cognitive decline.

Conclusion

In this study, transient cognitive decline was observed in the early post-operative period in reaction time and constructional praxis, with decline on certain visuospatial functions

persisting to over one year follow-up. Improvement on the other hand in verbal domains probably reflects learning effect. This dissociation between verbal and visuospatial skills is suggestive of underlying sub-cortical vascular damage but as few clinically significant differences were observed according to anesthesia type it is difficult to attribute this detriment to anesthesia *per se* as cumulative peri-operative factors may also have played a role. Neuroimaging studies for the detection of subtle cerebrovascular changes before and after surgery are required to confirm the link with visuospatial deficits.

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Table 1.**Comparison of subjects exposed to general and regional anesthesia with controls**

	Subjects with anesthesia (n= 270)	Subjects without anesthesia (n=310)	<i>p</i> *
Age, median (IQR))	71 (66-76)	74 (69-81)	< 0.001
Sex (female %)	60.4	70.6	0.009
Education level (%)			< 0.001
5 years	25.9	4.2	
9 years	45.6	45.2	
12 years	17.8	32.9	
> 12 years	10.7	17.7	
CESD \geq 16 (%)	17.4	11.9	0.06
Cerebrovascular and cardiac pathology	6.7	2.3	0.009

* Chi2 or Mann Whitney

Table 2.**Changes in specific cognitive functions across time in anesthesia-exposed subjects compared to controls**

Follow-up	D8		D126		D399	
	OR [95%CI]	p	OR [95%CI]	p	OR [95%CI]	p
REACTION TIME	1.74 [1.13-2.69]	0.01	1.01 [0.64-1.59]	0.96	1.19 [0.76-1.88]	0.44
ATTENTION dual task	1.21 [0.80-1.82]	0.36	0.83 [0.55-1.26]	0.39	1.22 [0.80-1.87]	0.36
VISUOSPATIAL ABILITY						
Constructional praxis	3.60 [2.15-6.05]	<0.0001	0.60 [0.30-1.19]	0.14	1.05 [0.57-1.94]	0.87
Logical visual series	0.70 [0.42-1.18]	0.18	0.72 [0.42-1.22]	0.22	0.96 [0.57-1.61]	0.88
Geometric form association	1.96 [1.26-3.05]	0.003	2.56 [1.62-4.05]	<0.0001	2.68 [1.69-4.24]	<0.0001
LANGUAGE						
Object naming	0.36 [0.21-0.61]	0.0002	0.25 [0.14-0.47]	<0.0001	0.30 [0.16-0.54]	<0.0001
Verbal fluency	1.30 [0.90-1.89]	0.16	0.94 [0.64-1.38]	0.75	0.79 [0.53-1.16]	0.23
IMMEDIATE RECALL						
Immediate verbal recall	0.20 [0.12-0.33]	<0.0001	0.26 [0.16-0.43]	<0.0001	0.19 [0.11-0.33]	<0.0001
Visuospatial span	1.46 [0.95-2.22]	0.08	1.15 [0.74-1.79]	0.53	1.90 [1.23-2.94]	0.004
DELAYED RECALL						
Implicit memory	0.69 [0.45-1.06]	0.09	1.07 [0.69-1.66]	0.75	0.95 [0.61-1.46]	0.81
Narrative recall	0.44 [0.30-0.65]	<0.0001	0.50 [0.34-0.75]	0.0007	0.41 [0.27-0.61]	<0.0001
Delayed verbal recall	0.14 [0.08-0.26]	<0.0001	0.23 [0.13-0.40]	<0.0001	0.21 [0.12-0.38]	<0.0001
Delayed visual recall	1.13 [0.72-1.78]	0.60	0.80 [0.49-1.30]	0.36	0.91 [0.56-1.48]	0.71
Name-face pair recall	0.33 [0.20-0.56]	<0.0001	0.57 [0.35-0.93]	0.02	0.59 [0.36-0.97]	0.04

*Adjusted for age, education level, sex, depressive symptomatology, cerebrovascular and cardiac pathology and baseline cognitive performance. The reference (OR=1) corresponds to the Eugeria control group (n=310).

Table 3.

Evolution in specific cognitive functions over 1 year in subjects exposed to general anesthesia (GA, n=184) and regional anesthesia (RA, n=86).

Cognitive function	GA effect		GA*Time^a effect	
	beta (SE)	p	beta (SE)	p
Linear Mixed Model				
Reaction time ^b	-0.014(0.019)	0.46	0.0006 (0.002)	0.80
Geometric form association	-0.18 (1.55)	0.91	-0.17(0.16)	0.28
Verbal fluency	-0.92 (1.21)	0.45	0.040 (0.069)	0.56
Implicit memory	-0.56 (0.27)	0.04	0.008(0.038)	0.83
Narrative recall	-1.15 (0.96)	0.23	0.014(0.058)	0.80
Logistic Mixed Model	OR [95%CI]	p	OR [95%CI]	p
Attention dual task	0.97 [0.57-1.65]	0.90	0.99 [0.92-1.06]	0.74
Constructional praxis	2.06 [1.03-4.12]	0.04	0.88 [0.80-0.97]	0.01
Logical visual series	0.79 [0.42-1.51]	0.48	0.96 [0.89-1.05]	0.39
Object naming	0.78 [0.41-1.49]	0.45	1.01 [0.93-1.10]	0.75
Immediate verbal recall	1.58 [0.85-2.94]	0.15	0.92 [0.84-1.00]	0.06
Visuospatial span	1.10 [0.66-1.82]	0.72	1.04 [0.98-1.11]	0.20
Delayed verbal recall	1.52 [0.67-3.46]	0.32	1.00 [0.90-1.11]	0.99
Delayed visual recall	1.04 [0.60-1.82]	0.88	0.99 [0.92-1.06]	0.67
Name-face pair recall	0.87 [0.45-1.70]	0.69	0.97 [0.90-1.05]	0.50

Each (linear or logistic) model included age, gender, education level, time, ASA score, ApoE4, anesthesia type, and, the interaction between time and anesthesia.

^a time = number of months between inclusion and follow-up.

^b log-transformed values.