Comparison of the type and severity of early attentional network decline after total intravenous or epidural anesthesia in middle-aged women after gynecological surgery

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Compared with regional anesthesia, general anesthesia may increase the risk of postoperative cognitive decline. This study aimed to investigate the type and severity of attentional network decline and the recovery of attentional networks in middle-aged women after gynecological surgery. A total of 140 consenting women undergoing elective gynecological surgery were enrolled in the study. Patients were assigned randomly to receive either total intravenous anesthesia or epidural anesthesia. To determine the efficacy of the attentional networks, patients were examined for alerting, orienting, and executive networks on the preoperative day and on the first and fifth postoperative days using the attentional network test. Significant differences were observed in the effect scores of the three attentional networks at all time points. These effect scores differed significantly between groups and between 1 and 5 days postoperation (DPO). Participants showed significantly lower effect scores for the alerting and orienting network tasks and had more difficulties in resolving conflict at 1 DPO compared with the baseline. On comparing effect scores between baseline and 5 DPO, no significant differences on the alerting and orienting network tasks were observed in the epidural anesthesia group, a significant difference on the orienting network task was observed in the general anesthesia group, and significant differences on the executive control network were observed in both the groups. Compared with epidural anesthesia, total intravenous anesthesia is more likely to impair and delay the recovery of attentional networks in middle-aged women undergoing elective hysterectomy. The executive control function showed marked damage and there were difficulties in recovery from either type of anesthesia. ***Int Clin Psychopharmacol*** **00:000–000 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Postoperative cognitive dysfunction (POCD) is a common yet complicated phenomenon that occurs after anesthesia and surgery. POCD affects patients in all age groups, including 36.6% in youth (18–39 years), 30.4% in middle-aged patients (40–59 years), and 41.4% in the elderly (≥60 years) (Monk *et al.*, 2008). The underlying causes of POCD, including the effects of the duration/type of surgery and the use of certain anesthetics, remain unknown (Zywiel *et al.*, 2014). Previous reports have suggested that compared with regional anesthesia, general anesthesia may increase the risk of the development of POCD (Davis *et al.*, 2014). Anesthetics have been reported to elicit cognitive dysfunction. For example, the addition of sedation to epidural anesthesia led to verbal memory impairment (Ancelin *et al.*, 2001). Sieber *et al.* (2010) found that deep sedation during spinal surgery led to increased delirium compared with lighter sedation. However, other investigators have shown that POCD is quite common after surgery involving either regional or general anesthesia, even up to several postoperative weeks (Rasmussen *et al.*, 2003). Moreover, various anesthetic routes and types did not show any significant differences in the development of POCD (Ancelin *et al.*, 2014). Therefore, the role of anesthesia in the development of POCD remains controversial (Mason *et al.*, 2010).

POCD affects a wide variety of cognitive domains, including recent memory, attention, and executive function (Rasmussen, 2006; Krenk *et al.*, 2010). Attention is an umbrella term for various psychological phenomena (Garmezy, 1977). Posner divided the human attentional system into three independent networks: alerting, orienting, and executive control. These networks have been distinguished at the biochemical and cognitive levels, and they have been confirmed as distinct neuroanatomical correlates (Posner and Petersen, 1990; Liu *et al.*, 2013).

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The attentional network test (ANT), which is based on the flanker and exogenous cueing paradigms, simultaneously measures the activities of all three networks and evaluates their interrelationships (Fan *et al.*, 2002). The ANT has been used widely to examine attentional functions in both healthy individuals and patients with various diseases, such as schizophrenia, Alzheimer disease, and others (Posner *et al.*, 2002; Wang *et al.*, 2005; Gu *et al.*, 2008). Despite being used to study attentional functions in a wide range of populations, the ANT has not been used to investigate the relationship between POCD and anesthetic type in the three attentional networks after surgery. Moreover, little is known about the types of cognitive changes experienced in the middle-aged population after anesthesia and surgery. Examination of the type of cognitive changes that occur after surgery may further the understanding of which brain systems are most vulnerable during the perioperative period and may influence postsurgical rehabilitation approaches.

Propofol is an intravenous sedative–hypnotic agent that induces and maintains surgical anesthesia (Bilotta *et al.*, 2011). However, strong evidence from previous animal experiments suggests that standard doses of routine anesthetics may lead to long-lasting learning and memory decline over weeks or months (Culley *et al.*, 2004; Wan *et al.*, 2007). The current data suggest that anesthetics may contribute toward adverse cognitive complications after surgery (Chan *et al.*, 2013). Bispectral index-guided anesthesia decreases the incidence of POCD by reducing the anesthetic dose (Chan *et al.*, 2013); however, human studies remain inconclusive (Cottrell and Hartung, 2012; Chan *et al.*, 2013).

Gynecological surgery is common in middle-aged women, who show less of a systemic reaction than expected in patients undergoing major surgery. General or epidural anesthesia is frequently used in gynecological surgery; however, the physiological effects of these anesthetic types on cerebral blood flow, oxygen delivery, and cerebral metabolism are markedly different. General anesthesia also exerts direct pharmacological effects on the brain.

Although POCD has been investigated thoroughly in neonates and in the elderly, little is known about the type and the recovery trajectories of cognitive changes after surgery in middle-aged patients, and the investigation of cognitive change may provide further information on POCD.

We conducted a randomized-controlled trial to test the hypothesis that a more severe risk of cognitive impairment at 1 and 5 days postoperatively (1 and 5 DPO, respectively) would be induced with general compared with epidural anesthesia after gynecological surgery in middle-aged women. We compared the types of cognitive changes and the differences in the attentional network impairment after surgery between women receiving general versus epidural anesthesia. Recovery trajectories after impairment of the attentional network were also investigated.

Materials and methods

Participants and ethical approval

Among the 140 women who were screened, 110 female patients 40–59 years of age with an American Society of Anesthesiologists (ASA) physical status of I or II completed the study. All participants were scheduled to undergo elective gynecological surgery (hysterectomy) under general or epidural anesthesia from May 2013 to July 2015 at the First Affiliated Hospital of Anhui Medical University, China. Exclusion criteria were an ASA physical status of III or IV, history of smoking or alcohol abuse, inadequate comprehension of the Chinese language, history of psychiatric or neurological disorders, Mini-Mental State Examination score of 23 or less, contraindication to epidural anesthesia, inadequate postoperative analgesia, and unwillingness to comply with the protocol or procedures at any time.

Ethical approval (Ethical Committee No. 20130406) was provided by the Ethical Committee of Anhui Medical University, Hefei, Anhui, China, in July, 2013. Each patient provided written informed consent before participating in the study. Each procedure was carried out in accordance with the declaration of Helsinki.

Randomization of participants and anesthesia

A computer-generated allocation program was used to assign 70 patients randomly to receive total intravenous anesthesia (general anesthesia group) and 70 patients to receive epidural anesthesia (epidural anesthesia group). Randomization results were concealed in opaque envelopes until after informed consent was obtained. Patients and postoperative observers were blinded to group allocation.

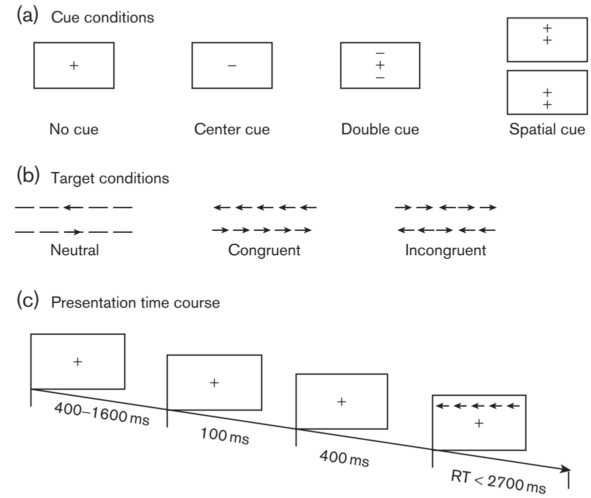
No premedication was used. Intravenous access was obtained and 4 l/min oxygen administration through a face mask was commenced upon arrival in the operating room. Routine monitoring included ECG and the noninvasive measurement of blood pressure, oxygen saturation, and heart rate.

After intravenous preloading, all patients in the general anesthesia group received 4 l/min O_2 through a face mask for 5 min, followed by the administration of propofol (1.5–2.5 mg/kg), sufentanil (0.3–0.5 μg/kg), and vecuronium bromide (0.1 mg/kg) during anesthesia induction. Laryngeal masks were inserted after 3 min. Propofol (target controlled infusion: 1.5–4 μg/ml), remifentanil (0.1–0.4 μg/kg/min), and intermittent vecuronium bromide were used to maintain the appropriate depth of anesthesia.

All patients in the epidural anesthesia group were placed in the left lateral decubitus position and epidural anesthesia was administered to the T_{12}–L_1 and $L_{3–4}$ vertebral interspace using a 16 G Tuohy needle by the loss of resistance to saline technique. An epidural catheter was placed 4 cm into the epidural space and the patient was turned supine. After administering a 4 ml test dose of 2% lidocaine into the $L_{3–4}$ epidural space, 10 ml of 0.75% ropivacaine was administered with an epidural catheter to achieve a block between T_6 and T_4. Next, 4 ml of 0.75% ropivacaine was administered every 80 min by an epidural catheter to maintain anesthesia.

Predefined complications were managed according to our typical clinical practice. Specifically, for hypotension (systolic blood pressure < 90 mmHg or 20% less than the baseline), the fluid infusion rate was accelerated and 6 mg boluses of ephedrine were used. For bradycardia (heart rate < 60 beats/min), an intravenous bolus of 0.25 mg atropine was administered. At the end of surgery, each patient received sufentanil (0.2–0.3 μg/kg) and 100 mg flurbiprofen in a total volume of 100 ml of saline solution, administered by patient-controlled intravenous analgesia at a background infusion rate of 2 ml/h for effective postoperative analgesia, a pump program set at 0.5 ml boluses, and a lockout time of 15 min. A visual analog scale (VAS; 0 = no pain, 10 = worse pain imaginable) was used to assess the degree of postoperative pain during patient-controlled intravenous analgesia treatment. If the VAS score was rated greater than 3, which means inadequate analgesia, the patient was excluded from the study.

Fig. 1



Experimental paradigm of the attentional network test. (a) Four cue conditions and (b) six stimuli used in the present experiment. (c) Example of the procedure.

Research procedure

Attentional network test

The attention network test was created using E-Prime (version 1.1; Psychology Software Tools, Pittsburgh, Pennsylvania, USA). Stimuli were presented on a 17 inch color monitor controlled by a personal computer. Participants focused on the stimuli shown on a computer screen and responses were collected by two response buttons (the '←' key and the '→' key). The visual stimuli presented included a row of five visually presented horizontal black lines, with arrowheads pointing left or right. The target was a left-pointing or a right-pointing arrowhead, presented at the center of the field, and flanked by stimuli that created three possible conditions on the screen against a gray background. Three conditions included the target stimulus flanked on either side by two arrows in the same direction (congruent condition) or in the opposite direction (incongruent condition) or by nothing (neutral condition; Fig. 1).

The arrow appears below or above the fixation point (a central cross shown on a computer screen: '+'); it may or may be not preceded by a warning cue (represented by an asterisk: '*') and may or may be not accompanied by flankers (two arrows on either side). Participants were instructed to focus on a centrally located stationary cross throughout the task and to respond by clicking on the directional buttons (the '←' key or the '→' key) as quickly and accurately as possible when a stimulus emerged on the screen. The task involved identifying the direction of the center arrow by pressing one button (the '←' key) for the left direction with the index finger of his/her left hand or a second button (the '→' key) for the right direction with the index finger of his/her right hand. The first fixation duration varied randomly (400–1600 ms). The second fixation, with or without a warning cue: '*', lasted for 100 ms. The target and flankers appeared simultaneously, 400 ms after offset of the cue until the participant responded with a button press (the '←' key for the left direction or the '→' key for the right direction). The target stimulus remained on the screen until the participant responded or until a maximum of 2700 ms had elapsed (Fig. 1). The duration of the post-target fixation period was based on the duration of the first fixation and the response time.

Cues consisted of an asterisk appearing for 100 ms that was presented 400 ms before the presentation of the target. There were four cue-related conditions: (i) no cue: the participant was shown a cross at the same location as the first stationary cross for 100 ms; (ii) center cue: an asterisk was presented at the central point; (iii) double cues: asterisks were presented at two target locations simultaneously above and below the central point; and (iv) spatial cue: an asterisk was presented at a target location either above or below the central point to provide the participant with the target location (Fig. 1).

According to the ANT design principles, the experiment included a 24-trial practice block and three experimental trial blocks. Trials were presented in a random order for each participant. The participant received feedback on whether his or her responses were accurate, no other feedback was included in the test process. Each experimental block consisted of 96 trials [48 different conditions: four cue types × two target locations (above or below) × two target directions (right or left) × three congruencies, with two repetitions]. The entire ANT was completed in 30 min.

Calculation of attentional network efficiencies

The ANT uses differences in response time (RT; including reaction time and movement time) (Moisello *et al.*, 2009; Fang *et al.*, 2014) derived from the different experimental conditions to measure the alerting, orienting, and executive control networks (Fan *et al.*, 2002). The effect score of the alerting network was calculated by subtracting the mean RTs of the conditions with double cues from the mean RTs of the conditions with no cues, alerting effect = RT no cue − RT double cue. Higher alerting effect scores, better alerting function, indicated enhanced readiness to respond to an impending stimulus. The effect score of the orienting network was calculated by subtracting the mean RTs of the conditions with spatial cues from the mean RTs of the conditions with center cues, orienting effect = RT center cue − RT spatial cue. Higher orienting effect scores, better orienting function, reflected faster covert orienting of attention to a spatially cued location. The effect score of the executive control network was calculated by subtracting the mean RTs of congruent target conditions from the mean RTs of incongruent target conditions, execution effect = RT incongruent − RT congruent. A higher execution effect score indicated more severe execution dysfunction because a longer time was needed to execute correctly upon the incongruent cue, and there were more difficulties in resolving conflict.

Statistical analysis

The statistical significance of differences among the baseline, 1 and 5 DPO time points was evaluated by repeated-measures one-way analysis of variance with post-hoc testing. Between-patient comparisons were made by a general linear model analysis with multivariate and repeated measures. Data were tested using Mauchly's test of sphericity. Categorical data were tested using the χ^2-test. All analyses were carried out using SPSS software (version 13.0; SPSS Inc., Chicago, Illinois, USA). A *P*-value of less than 0.05 (two sided) was considered statistically significant.

Results

Patient characteristics

Of the 140 patients who were screened for the study, six patients declined participation, in 10 patients changes were to their anesthetic plan, two patients were excluded because of severe cardiac disease (ASA physical status III), and 12 patients rated their pain as more than three on the VAS for pain after analgesia. Finally, 110 patients (55 patients each in the general anesthesia group and the epidural anesthesia group) participated in and completed the study. The general anesthesia group and the epidural anesthesia group were similar in terms of their baseline characteristics, including age, weight, education level, duration of surgery, Hospital Anxiety and Depression Score, Mini-Mental State Examination, and underlying diseases (anemia, hypertension, and diabetes; Table 1).

Analysis of accuracy

In this study, the accuracy is the % of the overall correct responses of the attentional networks (including alerting, orienting, and executive networks). There were no significant differences between the two groups in terms of the accuracy and attentional network efficiencies or in terms of the accuracy at baseline, 1 and 5 DPO (Table 2).

Analysis of the effect scores of the three attentional networks

Significant differences in the effect scores of the three attentional networks were present at all three time points and between the two groups (Table 2 and Fig. 2). Participants showed significantly lower effect scores on the alerting network tasks at 1 DPO compared with baseline and in the general anesthesia group compared with the epidural anesthesia group. However, no significant differences in the effect scores of the alerting network tasks were observed between baseline and 5 DPO or between the general anesthesia group and the epidural anesthesia group at either time point. Participants showed significantly lower effect scores on

Table 1 Preoperative and intraoperative data for the two anesthetic groups

Characteristics	General anesthesia group (*n* = 55)	Epidural anesthesia group (*n* = 55)	*P*-value
Age (years)	46.9 ± 5.8	48.7 ± 5.3	0.2
Weight (kg)	62.1 ± 9.9	60.9 ± 8.1	0.6
Diabetes [*n* (%)]	2 (3.6)	2 (3.6)	1.000
Hypertension [*n* (%)]	6 (10.9)	7 (12.7)	0.8
Anemia [*n* (%)]	19 (34.5)	25 (45.5)	0.2
Education level [*n* (%)]			0.5
Illiteracy	8 (14.5)	7 (12.6)	
Primary school	3 (5.5)	9 (16.4)	
Junior school	22 (40)	20 (36.4)	
High school	12 (21.8)	10 (18.2)	
University and above	10 (18.2)	9 (16.4)	
Duration of surgery (min)	128.2 ± 24.2	132.4 ± 28.1	0.4
HADS			
Depression (range)	4 (2–6)	4 (2–6)	0.1
Anxiety (range)	6 (3–9)	7 (3–10)	0.2
MMSE	28.2 ± 1.7	28.3 ± 1.8	0.9

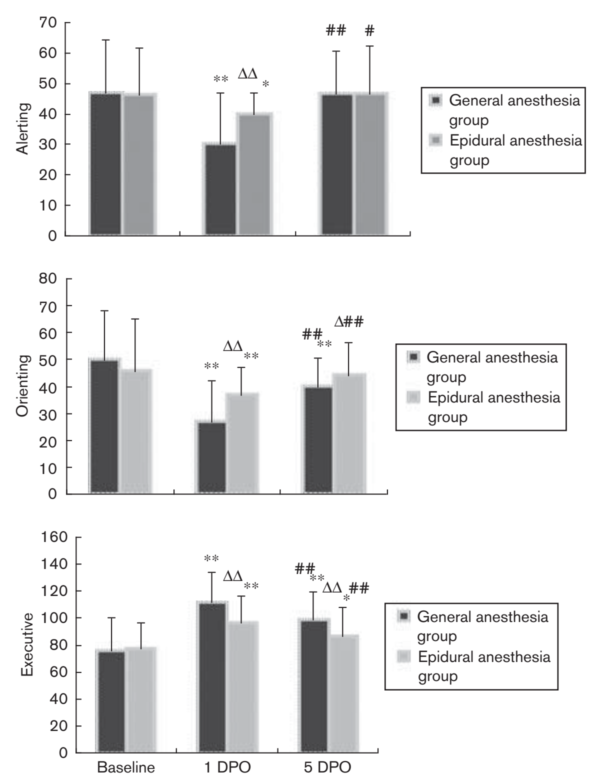
Data are presented as mean (SD), median (range), or number (%).
HADS, Hospital Anxiety and Depression Score [range 0 (lowest) to 21]; MMSE, Mini-Mental State Examination.

Table 2 Differences in attentional network efficiency and accuracy at baseline, 1 and 5 DPO between the general anesthesia group and the epidural anesthesia group

Group	Item	Baseline	1 DPO	5 DPO
General anesthesia group ($n=55$)	Alerting RT (ms)	46.8 ± 17.5	30.3 ± 16.6**	46.4 ± 14.2$^{\#\#}$
	Orienting RT (ms)	49.9 ± 18.2	26.9 ± 15.3**	39.8 ± 10.9$^{**\#\#}$
	Executive control RT (ms)	76.1 ± 24.1	111.5 ± 22.6**	99.1 ± 20.5$^{**\#\#}$
	Accuracy (%)	93.6 ± 4.2	92 ± 8.2	92.4 ± 7.3
Epidural anesthesia group ($n=55$)	Alerting RT (ms)	46.2 ± 15.3	39.9 ± 6.9$^{\triangle\triangle*}$	46.4 ± 15.8$^{\#}$
	Orienting RT (ms)	45.7 ± 19.3	36.6 ± 10.5$^{\triangle\triangle**}$	44.2 ± 11.9$^{\triangle\#\#}$
	Executive control RT (ms)	77.7 ± 18.8	96.3 ± 20.2$^{\triangle\triangle**}$	86.3 ± 21.3$^{\triangle\triangle*\#\#}$
	Accuracy (%)	94.7 ± 4.7	92 ± 7.2	92 ± 7.1

Data are presented as mean (SD).
DPO, days postoperation; RT, response time.
$^{*}P < 0.05$.
$^{**}P < 0.01$ versus baseline values.
$^{\#}P < 0.05$.
$^{\#\#}P < 0.01$ versus 1 DPO.
$^{\triangle}P < 0.05$.
$^{\triangle\triangle}P < 0.01$ versus the general anesthesia group.

Fig. 2



Selective modulation of the three attention networks at 1 and 5 DPO after total intravenous or epidural anesthesia in middle-aged women after gynecological surgery. $^{*}P < 0.05$, $^{**}P < 0.01$ versus baseline, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ versus 1 DPO, and $^{\triangle}P < 0.05$, $^{\triangle\triangle}P < 0.01$ versus the general anesthesia group.

the orienting network tasks at 1 and 5 DPO compared with baseline as well as between the general anesthesia group and the epidural anesthesia group at 1 and 5 DPO. However, the epidural anesthesia group did not show any significant differences in the effect scores on the orienting network tasks at 5 DPO compared with baseline.

A significant effect was observed for the executive control network tasks at all time points, and a comparison between the general anesthesia group and the epidural anesthesia group indicated a significant difference. Participants had more difficulties in resolving conflict at 1 and 5 DPO compared with baseline as well as at 1 DPO compared with 5 DPO. At 1 and 5 DPO, participants in the general anesthesia group had more difficulties in resolving conflict compared with participants in the epidural anesthesia group (Table 2 and Fig. 2).

Discussion

General anesthesia may increase the risk of developing POCD compared with regional anesthesia (Mason *et al.*, 2010). However, this conclusion is controversial (Davis *et al.*, 2014). To understand the impact of anesthesia on the three distinct attentional networks, we used the ANT to measure the cognitive performance of middle-aged women before and on the first and fifth days after elective hysterectomy under total intravenous or epidural anesthesia. We found significant differences in the three attentional networks at baseline, 1 and 5 DPO. Compared with patients who underwent epidural anesthesia, participants who underwent total intravenous anesthesia showed significantly lower effect scores on the orienting and alerting network tasks, more difficulties in resolving conflict, and slower recovery in all three network tasks.

The ANT was chosen for this study on the basis of its sensitivity and applicability for determining small changes in attentional deficits (Sobin *et al.*, 2004). To ensure test validity, the test was performed by a well-trained researcher.

General and epidural types of anesthesia are frequently used in gynecological surgery. However, which anesthetic type results in the fewest cognitive effects has been controversial. A previous study showed that the anesthetic type used did not significantly influence the results of neuropsychological tests (Ancelin *et al.*, 2010). The effects of general anesthesia are temporary because the anesthesia is typically cleared from the body quickly (Chan *et al.*, 2013). In contrast, findings from animal studies strongly suggest that standard doses of routine anesthetics may produce long-lasting learning and memory impairments, which may persist for weeks or months after anesthesia (Wan *et al.*, 2007; Bianchi *et al.*, 2008). General anesthesia contributes toward cognitive impairments by affecting tau hyperphosphorylation (Run *et al.*, 2009), caspase-3 activation (Zhang *et al.*, 2008), and β-amyloid deposition, increasing the activity of γ-aminobutyric acid type A receptors in the brain (Monk *et al.*, 2008; Abramov *et al.*, 2009), or by altering central cholinergic transmission through nicotinic and muscarinic receptors (Hussain *et al.*, 2014). Recent research also suggests that the function of γ-aminobutyric acid type A receptor ($GABA_AR$) cannot return to baseline even a brief exposure to a general anesthetic after the anesthetic drug is eliminated (Zurek *et al.*, 2014). Our findings also point toward this phenomenon. Each of these processes is directly associated with the development of Alzheimer's disease.

Cognitive functions are localized or linked to specific brain regions (e.g. medial temporal lobe for memory). Disruption of any of these brain systems during the perioperative period can induce cognitive changes. The alerting network is localized to the thalamus, frontal, and parietal areas of the right hemisphere, involves cortical projections of the norepinephrine system (Coull *et al.*, 2001), and is responsible for activating and maintaining a vigilant state. The orienting network activates sections of the superior and inferior parietal lobe, superior colliculus, temporal parietal junction, and frontal eye field, all of which involve the acetylcholine system (Thiel *et al.*, 2005). Deficits in executive network function involve the frontal areas, including the anterior cingulate cortex and the lateral prefrontal cortical regions. These deficits are caused by damage, such as tumors and lesions, and are modulated by dopamine (Simon *et al.*, 1980; Posner, 2008). Executive control of attention is often studied with tasks that involve conflict between competing information. Lesions to dopaminergic neurons located in the prefrontal cortex result in impairment of the executive control network (Brozoski *et al.*, 1979; Simon *et al.*, 1980).

Brain activities during anesthesia have been studied by neuroimaging, with the degree of baseline activity being reflected by regional cerebral blood flow (CBF) and regional cerebral metabolic rate. However, the physiological effects of general and regional anesthesia on CBF, cerebral metabolism, and oxygen delivery are markedly different, and general anesthesia has direct pharmacological effects on the brain. Previous studies using propofol found CBF reductions in the frontal cortex (Veselis *et al.*, 2004), posterior cingulate, and retrosplenial cortex (Fiset *et al.*, 1999). Positron emission tomographic studies showed that in the propofol-anesthetized state, the cerebral metabolic rate ranged from highest to lowest among brain regions in the order of frontal > temporal > occipital > parietal (Alkire *et al.*, 1995). Propofol has been reported to affect cognitive changes by increasing tau phosphorylation (Whittington *et al.*, 2011) and attenuating muscarinic acetylcholine receptor-mediated signal transduction, both of which influence the orienting network (Murasaki *et al.*, 2003). A zoological study showed that propofol inhibits the release of norepinephrine, which reduces the attentional network efficiency and is related to attentional network neural mechanisms (Fan *et al.*, 2003). Research by Hvarfber *et al.* (1995) suggested that propofol reuptakes dopamine and inhibits neurotransmitters in the central synapses.

Further explaining these previous findings, the present study showed that total intravenous anesthesia is more likely than epidural anesthesia to impair and delay the recovery of attentional networks. Although we only observed early cognitive dysfunction, we found that the executive control function showed marked damage and there were difficulties in recovery after surgery and anesthesia. Differences in executive control function between the two groups need to be further studied.

Currently, the etiology of POCD remains unclear, but likely includes factors related to the patient, surgery, and anesthesia. Numerous animal studies examining the effects of surgery on cognitive function have shown that the inflammatory response and resultant cognitive deficits may largely be the result of surgery, rather than because of any specific effects of general anesthesia. However, the extent to which these findings extend to humans remains unknown. The relationships between network deficits and changes in the corresponding brain areas also require clarification.

One potential limitation of the current study was the absence of biomarkers in the blood serum and cerebrospinal fluid, which are closely related to cognitive changes. In addition, the long-term effects of total intravenous anesthesia and epidural anesthesia on cognition were not examined.

In conclusion, different methods of anesthesia can induce different postoperative cognitive changes. Total intravenous anesthesia is more likely than epidural anesthesia to impair and delay the recovery of attentional networks in middle-aged women undergoing elective gynecological surgery. The executive control function showed marked damage and there were difficulties in recovery from either anesthesia.

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Conflicts of interest

There are no conflicts of interest.

References

Abramov E, Dolev I, Fogel H, Ciccotosto GD, Ruff E, Slutsky I (2009). Amyloid-beta as a positive endogenous regulator of release probability at hippocampal synapses. *Nat Neurosci* **12**:1567–1576.

Alkire MT, Haier RJ, Barker SJ, Shah NK, Wu JC, Kao YJ (1995). Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. *Anesthesiology* **82**:393–403. (discussion 27A).

Ancelin ML, de Roquefeuil G, Ledésert B, Bonnel F, Cheminal JC, Ritchie K (2001). Exposure to anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. *Br J Psychiatry* **178**:360–366.

Ancelin ML, de Roquefeuil G, Scali J, Bonnel F, Adam JF, Cheminal JC, *et al.* (2010). Long-term post-operative cognitive decline in the elderly: the effects of anesthesia type, apolipoprotein e genotype, and clinical antecedents. *J Alzheimers Dis* **22** (Suppl 3):105–113.

Ancelin ML, de Roquefeuil G, Ledesert B, Bonnel F, Cheminal JC, Ritchie K (2014). General anesthetic and the risk of dementia in elderly patients: current insights. *Clin Interv Aging* **9**:1619–1628.

Bianchi SL, Tran T, Liu C, Lin S, Li Y, Keller JM, *et al.* (2008). Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics. *Neurobiol Aging* **29**:1002–1010.

Bilotta F, Doronzio A, Stazi E, Titi L, Zeppa IO, Cianchi A, *et al.* (2011). Early postoperative cognitive dysfunction and postoperative delirium after anaesthesia with various hypnotics: study protocol for a randomised controlled trial – the PINOCCHIO trial. *Trials* **12**:170.

Brozoski TJ, Brown RM, Rosvold HE, Goldman PS (1979). Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science* **205**:929–932.

Chan MT, Cheng BC, Lee TM, Gin T, CODA Trial Group (2013). BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* **25**:33–42.

Cottrell JE, Hartung J (2012). Developmental disability in the young and postoperative cognitive dysfunction in the elderly after anesthesia and surgery: do data justify changing clinical practice? *Mt Sinai J Med* **79**:75–94.

Coull JT, Nobre AC, Frith CD (2001). The noradrenergic alpha2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. *Cereb Cortex* **11**:73–84.

Culley DJ, Baxter MG, Yukhananov R, Crosby G (2004). Long-term impairment of acquisition of a spatial memory task following isofluranenitrous oxide anesthesia in rats. *Anesthesiology* **100**:309–314.

Davis N, Lee M, Lin AY, Lynch L, Monteleone M, Falzon L, *et al.* (2014). Postoperative cognitive function following general versus regional anesthesia: a systematic review. *J Neurosurg Anesthesiol* **26**:369–376.

Fan J, McCandliss BD, Sommer T, Raz A, Posner MI (2002). Testing the efficiency and independence of attentional networks. *J Cogn Neurosci* **14**:340–347.

Fan J, Fossella J, Sommer T, Wu Y, Posner MI (2003). Mapping the genetic variation of executive attention onto brain activity. *Proc Natl Acad Sci USA* **100**:7406–7411.

Fang D, Jiang J, Sun X, Wang W, Dong N, Fu X, *et al.* (2014). Attention dysfunction of postoperative patients with glioma. *World J Surg Oncol* **12**:317.

Fiset P, Paus T, Daloze T, Plourde G, Meuret P, Bonhomme V, *et al.* (1999). Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. *J Neurosci* **19**:5506–5513.

Garmezy N (1977). The psychology and psychopathology of attention. *Schizophr Bull* **3**:360–369.

Gu X, Liu X, Guise KG, Fossella J, Wang K, Fan J (2008). Alexithymic trait and voluntary control in healthy adults. *PLoS One* **3**:e3702.

Hussain M, Berger M, Eckenhoff RG, Seitz DP (2014). General anesthetic and the risk of dementia in elderly patients: current insights. *Clin Interv Aging* **9**:1619–1628.

Hvarfber A, Hammas B, Yhorn SE, Wattwil M (1995). The influence of propofol on vomiting induced by apomorphine. *Anesth Analg* **80**:967–969.

Krenk L, Rasmussen LS, Kehlet H (2010). New insights into the pathophysiology of postoperative cognitive dysfunction. *Acta Anaesthesiol Scand* **54**: 951–956.

Liu G, Ma HJ, Hu PP, Tian YH, Hu S, Fan J, *et al.* (2013). Effects of painful stimulation and acupuncture on attention networks in healthy subjects. *Behav Brain Funct* **7**:23.

Mason SE, Noel-Storr A, Ritchie CW (2010). The impact of general and regional anesthesia on the incidence of postoperative cognitive dysfunction and postoperative delirium: a systematic review with metaanalysis. *J Alzheimers Dis* **22** (Suppl 3):67–79.

Moisello C, Crupi D, Tunik E, Quartarone A, Bove M, Tononi G, *et al.* (2009). The serial reaction time task revisited: a study on motor sequence learning with an arm-reaching task. *Exp Brain Res* **194**:143–155.

Murasaki O, Kaibara M, Nagase Y, Mitarai S, Doi Y, Sumikawa K, *et al.* (2003). Site of action of the general anesthetic propofol in muscarinic M1 receptor-mediated signal transduction. *J Pharmacol Exp Ther* **307**:995–1000.

Posner MI (2008). Measuring alertness. *Ann N Y Acad Sci* **1129**:193–199.

Posner MI, Petersen SE (1990). The attention system of the human brain. *Annu Rev Neurosci* **13**:25–42.

Posner MI, Rothbart MK, Vizueta N, Levy KN, Evans DE, Thomas KM, *et al.* (2002). Attentional mechanisms of borderline personality disorder. *Proc Natl Acad Sci USA* **99**:16366–16370.

Rasmussen LS. Postoperative cognitive dysfunction: incidence and prevention. *Best Pract Res Clin Anaesthesiol* 2006; **20**:315–330.

Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, *et al.* (2003). Does anaesthesia cause postoperative cognitive dysfunction? A randomized study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand* **47**:260–266.

Run X, Liang Z, Zhang L, Iqbal K, Grundke-Iqbal I, Gong CX (2009). Anesthesia induces phosphorylation of tau. *J Alzheimers Dis* **16**:619–626.

Sieber FE, Zakriya KJ, Gottschalk A, Blute MR, Lee HB, Rosenberg PB, *et al.* (2010). Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc* **85**:18–26.

Simon H, Scatton B, Moal ML (1980). Dopaminergic A10 neurones are involved in cognitive functions. *Nature* **286**:150–151.

Sobin C, Kiley-Brabeck K, Daniels S, Blundell M, Anyane-Yeboa K, Karayiorgou M (2004). Networks of attention in children with the 22q11 deletion syndrome. *Dev Neuropsychol* **26**:611–626.

Thiel CM, Zilles K, Fink GR (2005). Nicotine modulates reorienting of visuospatial attention and neural activity in human parietal cortex. *Neuropsychopharmacology* **30**:810–820.

Veselis RA, Feshchenko VA, Reinsel RA, Dnistrian AM, Beattie B, Akhurst TJ (2004). Thiopental and propofol affect different regions of the brain at similar pharmacologic effects. *Anesth Analg* **99**:399–408.

Wan Y, Xu J, Ma D, Zeng Y, Cibelli M, Maze M (2007). Postoperative impairment of cognitive function in rats: a possible role for cytokine-mediated inflammation in the hippocampus. *Anesthesiology* **106**:436–443.

Wang K, Fan J, Dong Y, Wang CQ, Lee TM, Posner MI (2005). Selective impairment of attentional networks of orienting and executive control in schizophrenia. *Schizophr Res* **78**:235–241.

Whittington RA, Virag L, Marcouiller F, Papon MA, El Khoury NB, Julien C, *et al.* (2011). Propofol directly increases tau phosphorylation. *PLoS One* **6**: e16648.

Zhang G, Dong Y, Zhang B, Ichinose F, Wu X, Culley DJ, *et al.* (2008). Isoflurane-induced caspase-3 activation is dependent on cytosolic calcium and can be attenuated by memantine. *J Neurosci* **28**:4551–4560.

Zurek AA, Yu J, Wang PS, Haffey SC, Bridgwater EM, Penna A, *et al.* (2014). Sustained increase in α5GABAA receptor function impairs memory after anesthesia. *J Clin Invest* **124**:5437–5441.

Zywiel MG, Prabhu A, Perruccio AV, Gandhi R (2014). The influence of anesthesia and pain management on cognitive dysfunction after joint arthroplasty: a systematic review. *Clin Orthop Relat Res* **472**:1453–1466.