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New Trends in the Empirical Study of Consciousness: Measures and Mechanisms

The arousal level of consciousness required for working memory performance: An anaesthesia study

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Abstract

Regarding the stage of arousal level required for working memory to function properly, limited studies have been conducted on changes in working memory performance when the arousal level of consciousness decreases. This study aimed to experimentally clarify the stages of consciousness necessary for optimal working memory function. In this experiment, the sedation levels were changed step-by-step using anaesthesia, and the performance accuracy during the execution of working memory was assessed using a dual-task paradigm. Participants were required to categorize and remember words in a specific target category. Categorization performance was measured across four different sedative phases: before anaesthesia (baseline), and deep, moderate and light stages of sedation. Short-delay recognition tasks were performed under these four sedative stages, followed by long-delay recognition tasks after participants recovered from sedation. The results of the short-delay recognition task showed that the performance was lowest at the deep stage. The performance of the moderate stage was lower than the baseline. In the long-delay recognition task, the performance under moderate sedation was lower than that under baseline and light sedation. In addition, the performance under light sedation was lower than that under baseline. These results suggest that task performance becomes difficult under half sedation and that transferring information to long-term memory is difficult even under one-quarter sedation.

KEYWORDS

anaesthesia, arousal level, attention control, long term memory, working memory

Abbreviations: ACC, anterior cingulate cortex; DAN, dorsal attention network; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; LTM, long term memory; MRI, Magnetic Resonance Imaging; PFC, prefrontal cortex; PPC, posterior parietal cortex; RSN, resting state network; STM, short term memory; WM, working memory.

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1 | INTRODUCTION

Working memory (WM) maintains the information necessary for goal-directed tasks and enhances cognitive task performance by processing and retaining relevant information aligned with task objectives (Baddeley, 1986; Engle, 2002). WM capacity reflects the central executive's capabilities, according to Baddeley (1986), and acts as an attentional controller that allocates and coordinates resources for cognitive tasks. Previous research has shown that attention control is essential for effective task performance (Engle, 2002; Osaka & Osaka, 2007), and the functioning of the central executive system is believed to be intertwined with consciousness (Baddeley, 2007, 2012).

In our previous investigations (Osaka et al., 2003, 2004), we identified three important regions as the neural substrate of WM function: the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC) and the posterior parietal cortex (PPC). The DLPFC governs top-down attentional control, while the ACC is involved in managing cognitive conflicts. Additionally, the PPC plays a role in shifting attention towards the task objectives.

Recent evidence based on resting-state functional connectivity (Menon, 2011) has highlighted the default mode network (DMN) as a typical resting-state brain network, with the dorsal attention network (DAN) being involved in cognitive activities related to WM performance, particularly executive functions. Consequently, WM performance, notably executive function, relies on the DAN, which establishes connections between the frontal and parietal regions. Furthermore, studies have revealed a negative correlation between components of the DMN and the DAN (Fox et al., 2005; Fransson, 2005; Raichle et al., 2001).

In prior studies, brain network analysis revealed that alterations in arousal level (consciousness) induced by anaesthesia modified the DMN connectivity of the resting network. Moreover, the correlation between the DMN and DAN varies depending on the level of consciousness. For instance, during propofol-induced mild sedation, the inverse correlation between the two networks decreases (Amico et al., 2014; Boveroux et al., 2010; Guldenmund et al., 2016). These networks, centred in the frontal and parietal regions, play a crucial role in WM, as mentioned previously. Consequently, decreased levels of consciousness hinder WM performance through alterations in frontal and parietal lobe functions.

While the impact of anaesthetics on higher-order cognitive activities has been extensively explored, their effects on WM remain unclear due to the limited number of systematic studies investigating the influence of consciousness level on WM task performance. Some studies examining changes in memory during dental procedures involving anaesthesia have been conducted (Andrade, 1995, 2005; Andrade et al., 1994). According to the findings of these studies, as anaesthesia dosage is administered during a continuous word task, patients encounter difficulty in detecting the same word.

However, to our knowledge, there is limited research on changes in WM performance due to alterations in consciousness level. In a study involving the administration of ketamine and midazolam, sedated participants were required to perform an N-back task with visual stimuli (Forsyth et al., 2021). During the study, the participants performed an N-back task with two levels of difficulty: 0 back and 2 back. In both cases, a decline in behavioural performance was observed as the difficulty increased.

However, no studies have quantified changes in the behavioural performance of WM in response to varying the depth of sedation induced by anaesthesia. Therefore, in the current investigation, we systematically adjusted participant' sedation levels through successive stages of anaesthesia administration and compared their behavioural performance at each stage while maintaining a consistent sedation level. We hypothesized that such an examination would elucidate the specific consciousness stage requisite for WM task execution.

Recent investigations into consciousness have suggested that the level and content of consciousness may not be invariably the same (Bayne et al., 2016). It has also been noted that both the level and content of consciousness are affected by anaesthesia (Fontan et al., 2021). Therefore, in the present study, because the sedation stage is changed by anaesthesia, we refer to the resulting change in the sedation stage as the arousal level.

We assessed the accuracy of task execution in a WM task based on the administered amount of anaesthesia. To facilitate the experiment even in a supine position on an operating bed under anaesthesia-induced sedation, we implemented a dual-task paradigm. This dual task involved listening to words and categorizing each word in a target category as the primary task, while memorizing only words belonging to the matched target category as the secondary task. In this task, participants were required to recognize the words in a target category while ignoring non-category words.

2 | MATERIALS AND METHODS

2.1 | Participants

The study sample comprised 20 healthy men (mean age: 23.1 ± 3.5 years; American Society of Anesthesiologists classification of physical health: 1 or 2). All study participants were volunteers who did not belong to our lab, had undergone a physical examination, and were considered to be safe for the administration of anaesthesia. Two weeks after the experiment, a health checkup was performed again. Only young men who were able to carry out the tests and participate in both the pre- and post-examinations for about one month were considered for the experiments. Therefore, we only included men with minimal changes in physical condition as participants.

2.2 | Sedative phases

We measured a reference level that produced arousal loss based on eyelash reflexes (4/4 sedation level). Next, we decreased the level by one-fourth of a step for each phase (i.e., 3/4 for deep, 1/2 for moderate and 1/4 for light anaesthesia; see Figure 1).

The sedative phases were individually manipulated using target-controlled infusion (TCI). Using a TCI pump or a pharmacokinetic simulation system, we first determined sedation levels by measuring the reference level that produced a loss of arousal based on eyelash reflexes and name-calling.

Thus, we controlled arousal levels of consciousness in one-fourth of a step as follows:

- Before sedation, baseline
- Three-fourths level, deep sedation
- Two-fourths level, moderate sedation
- One-fourth level, light sedation

Two anaesthetics were selected to confirm whether they had a sedative effect. The participants were randomly selected by an individual other than the investigators to receive either of the two anaesthetics. Subsequently, the participants received either propofol ($n = 10$) or midazolam ($n = 10$). Both are widely used gamma-aminobutyric acid-potentiated anaesthetic agents for general use in anaesthesia or sedation procedures (Kang et al., 2017).

During the measurements, the participants were placed in bed and underwent standard anaesthesia monitoring, including noninvasive blood pressure, oxygen saturation

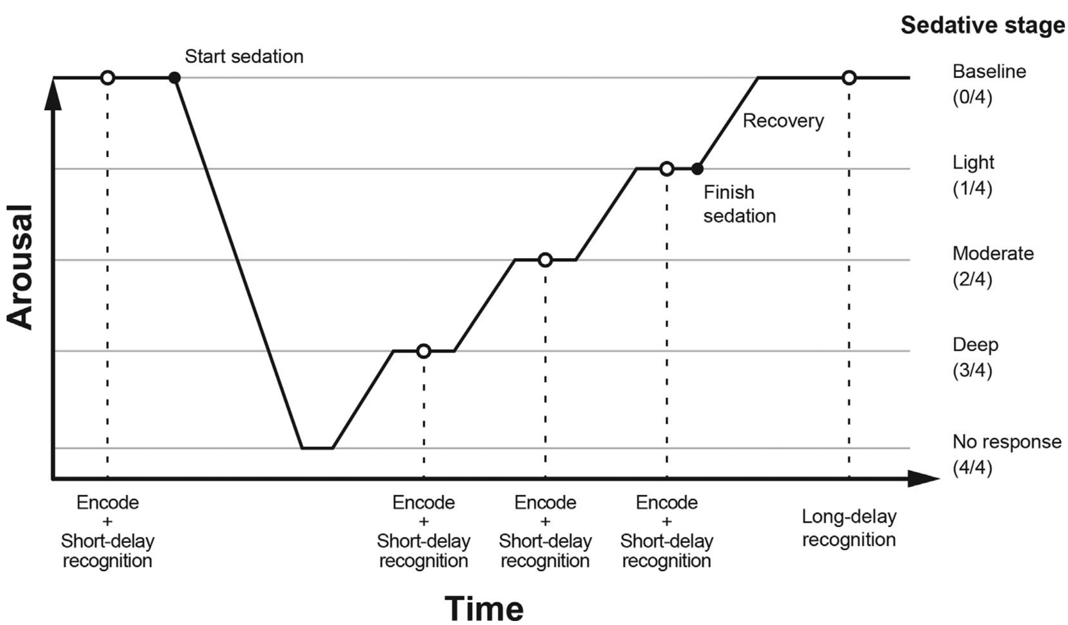

FIGURE 1 Changes in sedation stage due to anaesthesia administration.

and electrocardiography assessments. Consciousness level was assessed according to the Observer's Assessment of Alertness/Sedation score and bispectral index (BIS) (BIS-XP monitor; Medtronic, Minneapolis, MN, USA), which is an electroencephalogram-derived measure (score range: 0–100) used to monitor awareness status under anaesthesia (Kang et al., 2017).

2.3 | Experimental procedures

2.3.1 | Encoding phase: categorizing of words and memorization of target words

By manipulating the level of sedation, we examined the effects of the level of anaesthesia on WM task performance. As a dual task that can be performed even under sedation due to anaesthesia, we set a dual task of categorical judgement and the memorization of words belonging to a specific category. Before the experiment began, the target (i.e., the word to memorize) category was taught in advance (e.g., furniture, animals, fruits). The participants listened to the words and decided whether to press the right or left button depending on the current target category (Figure 2).

During the encoding phase, a category judgement task was performed. The participants were presented with words aurally and instructed to press the right button when hearing a word belonging to a particular category and the left when hearing words belonging to other categories; for example, pressing the right button for the furniture category for "chair" and the left button for the fruit category for "apple".

The participants were also instructed to memorize words belonging to a specific category while ignoring non-category words. For example, when the participants heard a furniture word that should be memorized, such as chair or desk, they pressed the right button and memorized that word, whereas when they heard a word that was not a furniture word, such as apple or strawberry, they pressed the left button to avoid remembering the word. The task consisted of the following eight categories: furniture, fruits, vehicles, vegetables, sports, birds, clothing and fish. In each category, 30 words belonging to that category were selected. Two categories were selected in each sedation stage, and one of the two categories was selected as a target. Therefore, in each sedation stage, the participants had to categorize 30 target and 30 nontarget words. Stimulus words were presented aurally once every 3 seconds. The task took approximately 3 minutes to complete. Category judgements were measured in four different sedative phases: baseline and in the deep, moderate and light sedation stages. The categories of target and nontarget differed depending on the level of sedation and participants.

2.4 | Recognition task

2.4.1 | Short-delay recognition: recognition 1

The recognition task was performed approximately 7 minutes after the categorization task (see Figure 2). A spatial test previously reported by Minamoto et al. (2018) was conducted between the categorization and recognition tasks. During the recognition task, the participants

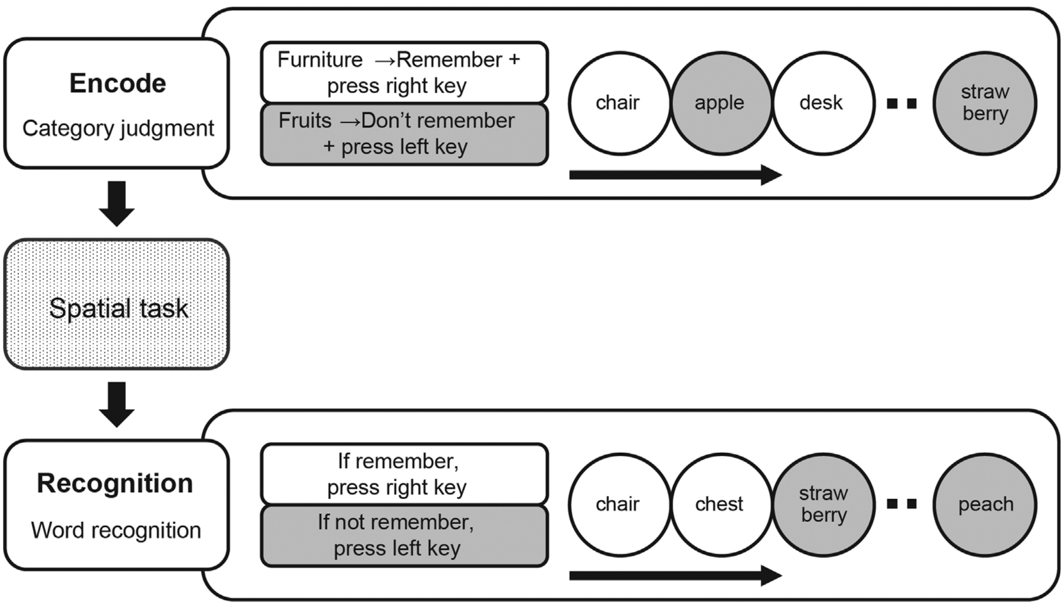

FIGURE 2 Dual task of category judgement and memory.

continuously listened to each word and pressed the right or left reaction button to indicate whether it was a target or nontarget word, respectively. The recognition task consisted of 15 target words, 15 nontarget words and 6 newly added disturbance stimuli (i.e., fillers). This recognition task was performed during the baseline, deep, moderate and light sedation phases and took approximately 3 minutes.

2.4.2 | Long-delay recognition: recognition 2

Recognition of remembered words was tested again after recovery. This long-delay recognition task was performed after the participants had returned from the operation room to the examination room after recovering from sedation. The long-delay recognition task was the same as the short-delay recognition task, except that the words presented were 15 target and 15 nontarget words that had not been presented in the short-delay task, along with 6 filler words belonging to each category that had not been presented. Therefore, the participants did not hear the same word twice.

3 | RESULTS

3.1 | Analysis 1

Participants who had missing values from any sedation stage were excluded from the analysis. As a result, the final study sample for analysis comprised 12 participants (five who received propofol and seven who received midazolam).

Figure 3 shows the performance accuracies for the encoding and recognition tasks. The white and grey boxes represent the results of the propofol and midazolam groups, respectively. Figure 3a shows the category judgement accuracies, and Figure 3b shows the recognition accuracies under the four sedation stages. Figure 3b also shows the accuracies under both short- and long-delay recognition. The accuracies were calculated using the average number of hits and correct rejections during each sedation stage.

3.2 | Categorization task results

Analysis of variance (ANOVA) with two factors (anaesthetic and sedation stage) was performed on task accuracy. A main effect of the sedation phase was observed (F [3, 30] = 4.75, $P < .01$). However, no significant main effect of the anaesthetic (propofol or midazolam) or interaction between the anaesthetic and sedation stage was found. Multiple comparisons revealed no significant differences among the sedation stages.

3.3 | Recognition of short- and long-delay tasks

ANOVA with three factors, namely, anaesthesia (propofol or midazolam), sedation stage (baseline, deep, moderate or light stage) and recognition task (short-

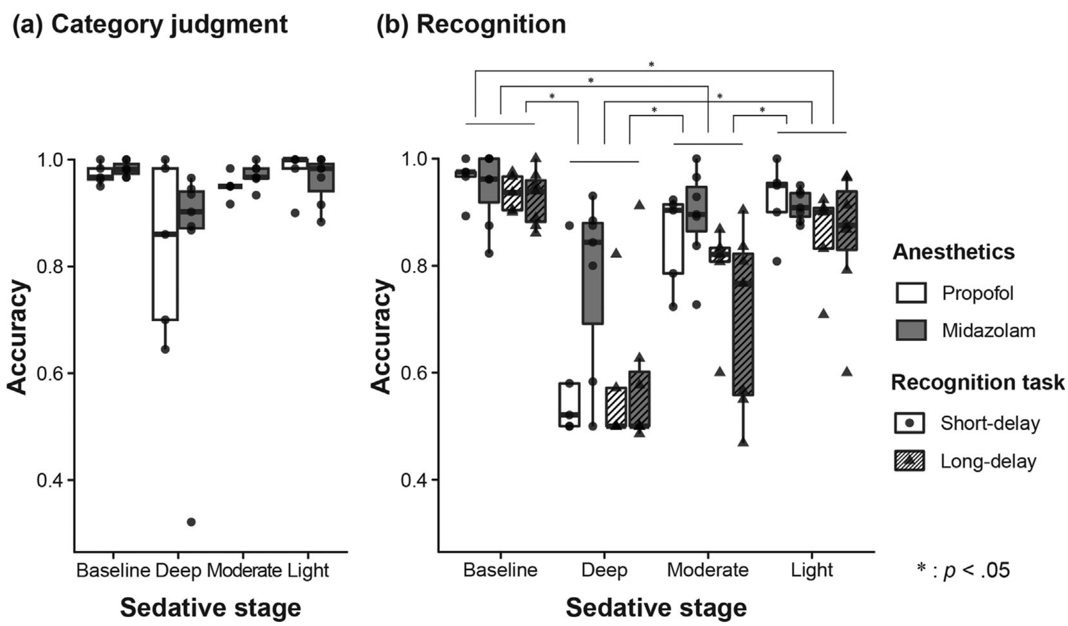

FIGURE 3 The accuracies for (a) category judgements (encoding) and (b) short- and long-delay recognition at baseline and in all sedation stages.

vs. long-delay), was performed. The main effects of the recognition task (F[1, 10] = 22.11, $P < .001$) and sedation stage (F[3, 30] = 30.39, $P < .0001$) were confirmed. No significant main effect of anaesthetic (propofol or midazolam) was observed; however, a significant tendency was seen for an interaction between the anaesthetic and recognition task (F [1, 10] = 4.45, $P < .06$).

Multiple comparisons showed that performance was lowest in the deep stage (deep vs. baseline, $t = 8.71$, $P < .0001$; deep vs. moderate, $t = 4.22$, $P < .01$; deep vs. light, $t = 5.79$, $P < .001$). In addition, performance in the moderate stage was lower than that in the baseline and light stages (moderate vs. baseline, $t = 4.51$, $P < .01$; moderate vs. light, $t = 2.88$, $P < .05$). Performance in the light stage was lower than that at baseline (light vs. baseline, $t = 2.23$, $P < .05$).

As a significant tendency was observed for an interaction between the anaesthesia and recognition tasks, we conducted multiple comparisons between the anaesthesia and recognition tasks to further investigate the difference in efficacy between the two types of anaesthesia. The results showed no main effect of the recognition task for propofol (F[1, 4] = 6.87, $P < .059$). However, a significant main effect for the recognition task was found for midazolam (F[1, 6] = 20.08, $P < .004$).

3.4 | Analysis 2

In the deep sedation stage, many of the participants had a correct answer rate under 50%. Therefore, to explore in more detail the function of WM in response to sedation stages, we conducted a re-analysis after excluding the results from the deep sedation stage. Consequently, the sample comprised nine participants (both propofol and midazolam).

Figure 4 shows the performance accuracies for the encoding and recognition tasks among the 18 participants. Accuracy was also calculated using the average of the hit and correct rejection rates during the three sedation stages (i.e., baseline, moderate and light). Figure 4a shows the encoding accuracies, and Figure 4b shows the recognition accuracies (short- and long-delay).

3.5 | Categorization task in analysis 2

ANOVA with two factors, anaesthesia and sedation stage, was performed. The results revealed no main effect of either factor; however, the interaction between the anaesthesia and sedation phases was significant (F[2, 32] = 3.63, $P < .05$). Multiple comparisons showed that the performance of propofol was lower than midazolam in the moderate stage ($P < .005$).

3.6 | Recognition task in analysis 2

ANOVA with three factors, anaesthesia, sedation phase and recognition task was performed. The main effect of the recognition task (short- vs. long-delay) was confirmed (F[1, 16] = 36.63, $P < .0001$). The main effect of the

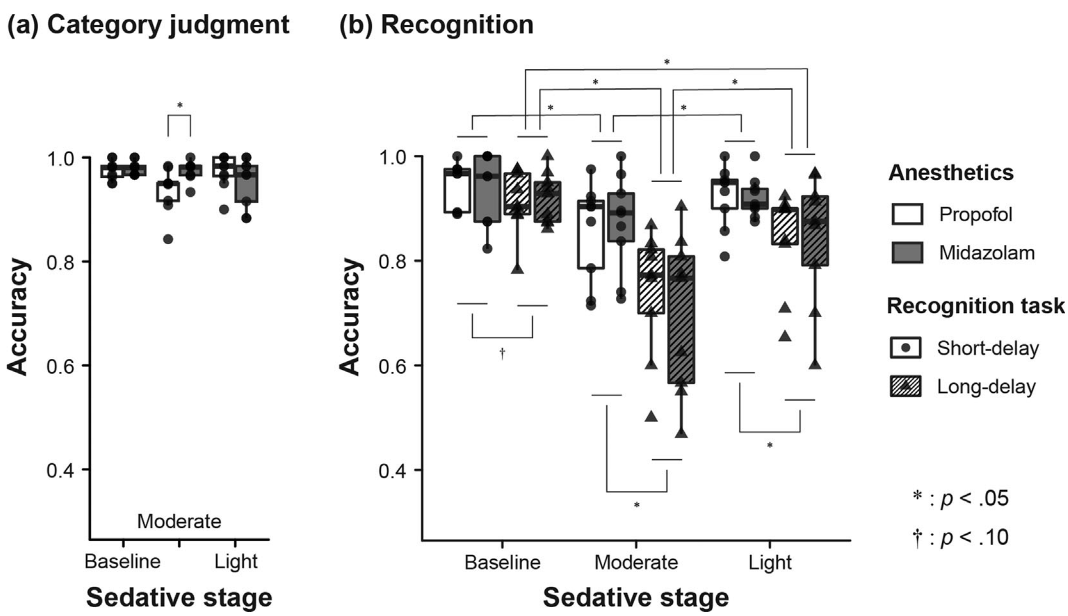

FIGURE 4 The accuracies for (a) category judgements (encoding) and (b) short- and long-delay recognition at baseline and in the moderate and light sedation stages.

sedation stage (baseline, moderate and light) was also significant ($F[2, 32] = 21.05$; $P < .0001$). Moreover, the interaction between the recognition task and sedation stage was significant ($F[2, 32] = 4.99$, $P < .05$).

Multiple comparisons revealed that under moderate and light conditions, the effect of the recognition task (short- vs. long-delay) was significant (moderate: $F[1, 16] = 15.92$, $P < .01$; light: $F[1, 16] = 15.65$, $P < .01$). However, under the baseline condition, the effect of the task tended to be significant ($F[1, 16] = 4.38$, $P < .053$).

In addition, in the short-delay recognition, the performance was lower in the moderate than in the baseline and light stages (moderate vs. baseline, $t = 3.04$, $P < .05$; moderate vs. light, $t = 2.55$, $P < .05$). However, a significant difference was not observed between light sedation and the baseline condition ($t = 1.49$, $P > .05$).

By contrast, in the long-delay recognition, the performance was lower in the moderate than in the baseline and light stages (moderate vs. baseline, $t = 5.60$, $P < .001$; moderate vs. light, $t = 3.30$, $P < .01$), and also a significant difference was observed between light sedation and the baseline condition ($t = 2.69$, $P < .05$).

4 | DISCUSSION

The present results demonstrated that sedation, ranging from deep to light, impeded the performance of WM tasks. This is possible because the changes in the level of arousal associated with sedation via anaesthesia impede the executive function of WM, which is necessary for performing dual tasks. This is consistent with the view that consciousness is involved in attentional regulation, which is important for WM (Baddeley, 2012).

However, when encoding categorical judgements, we observed no significant changes between the sedation stages. This suggests that participants were able to perform categorical judgements with a success rate exceeding 80%, even under deep sedation, although participants who had missing values from any sedation stage were excluded from the analysis in order to make the results more accurate.

In the category judgement task of this experiment, participants were tasked with classifying words (e.g., desk, apple) into specific categories (e.g., furniture, fruit). Successful completion of this task required accessing long-term memory to identify the appropriate category for each word, followed by verification to confirm its alignment with the target category. Remarkably, our findings demonstrate that such long-term memory references remain viable even during deep anaesthesia sedation, although with reduced performance.

For the category judgement task, we selected words that are easily visualized, such as animals and fruits. This selection aimed to minimize listening errors by utilizing words that were readily recognizable under anaesthesia. Furthermore, our prior research has reported that recalling concrete objects is facilitated through the use of the visuo-spatial sketchpad (Osaka et al., 2012). These factors likely contributed to the notably high rate of correct answers in our participants' category judgements.

In previous research on working memory (WM), categorical judgement has been utilized. In a study investigating the relationship between WM and attentional control, participants were instructed to respond to words belonging to specific categories. The findings revealed that participants experienced difficulty inhibiting attention to the words. Interestingly, this difficulty was particularly notable among participants classified under the low WM capacity group (De Beni et al., 1998). Similarly, categorization tasks have been employed in complex span tests, commonly used for assessing individual differences in WM capacity. The Categorization Working Memory Span Test (CWMST), which incorporates such tasks, effectively assesses WM capacity (Spironelli & Borella, 2021; Spironelli et al., 2020).

In the present study, we considered that it would be difficult to perform a general complex span test under anaesthesia sedation with limited measurement time. Therefore, we opted for a specific category judgement dual task.

Regarding the relationship between WM and LTM, it has been noted that the process of retrieving and retaining stimuli from LTM is important for working memory performance (Baddeley, 2012). Input stimuli are temporarily stored in WM after referencing the contents of LTM. Subsequently, only relevant information is retained and transferred to LTM. Baddeley emphasizes this WM-LTM relationship by introducing an episodic buffer into the working memory model to accommodate this function (Baddeley, 2000).

Similarly, in the present study, category determination involves searching from LTM, focusing on words of the target category and transferring them to WM. Moreover, recognition processing after both short and long delays also necessitates retrieval of information held in WM to determine whether the word falls within a specific category designated as a target or not.

The results of the short-delay recognition tasks indicated that the recognition performance was lowest in the deepest stage. Although it was possible to make category judgements, participants seemed to find it difficult to perform dual tasks, such as making category judgements and memorizing specific target words. This finding indicates that dual tasks such as temporary retention, maintaining the information and transferring it to LTM are hindered during the deep sedation stage.

At the moderate-sedation stage, lower performance in short-delay recognition was noted when compared with baseline and light sedation. Lower performance was also confirmed in the light sedation stage compared with baseline. Although light sedation is attenuated by one-fourth of normal levels, it still interferes with performance in short-delay recognition tasks, which suggests that WM performance is affected even at this light level of sedation.

A difference in the recognition results between short- and long-delay recognition phases was observed in Analysis 2 under the light sedation condition. According to the results, under the short-delay condition, moderate sedation resulted in lower performance than the baseline and light sedation conditions, but no difference was observed between light sedation and baseline. By contrast, under the long-delay condition, the performance was lower under light sedation than at baseline. Therefore, recognition after a long delay leads to a decline in recognition performance under light sedation. This finding indicates that the longer the delay time, the weaker the retention of WM, and the more difficult it is to transfer information to LTM even under light sedation.

In a study investigating anaesthesia-induced brain changes (Guldenmund et al., 2016), when mild sedation and loss of responsiveness were induced in healthy participants administered propofol, the detectability of resting state network (RSN) reduced the loss of responsiveness (Guldenmund et al., 2016). In addition, based on the results of MRI measurements, the connectivity of the whole brain was greatly reduced, especially in the frontal cortex. They therefore suggested that the frontal cortex plays a crucial role in propofol-induced loss of responsiveness.

The importance of the frontal cortex was also suggested in our previous study (Osaka et al., 2021), which investigated individual differences in WM capacity based on brain RSN. Additionally, our investigation revealed that capacity differences in working memory, assessed through a reading span test, which is one of the complex span tests, are linked to differences in the strength of RSN connectivity in the brain. These results imply that the connectivity between the frontal and parietal regions holds a crucial significance in determining WM performance. Despite the absence of fMRI measurements in the current experiment, the observed decrease in dual-task performance under anaesthesia, in comparison to the baseline condition, suggests a potential decline in connections between the frontal and parietal regions.

In addition, Forsyth et al. (2021) measured fluctuations in brain waves under sedation with ketamine and midazolam and identified diminished performance in the N-back task. Moreover, the decrease was more in 2 backs than in 0 backs, indicating that the more difficult the task, the more prominent the decline during sedation.

In their research utilizing the N-back task, participants were required to memorize sequential arrow directions while continuously updating this information. Specifically, in the 2-back condition, participants had to memorize two stimuli and update them consecutively. The experimental findings indicated that, under sedation, the connectivity of the DMN, centred on the frontal lobe, was lower in the 2-back condition compared to the 0-back condition.

During performing WM tasks, attention control such as focus of attention and inhibitory control are required (Baddeley, 2012; Cowan, 1999; Osaka et al., 2007; Osaka & Osaka, 2007; Oberauer, 2002). The N-back task specifically involves attentional focus and inhibition, leading to the conclusion that the anaesthesia used in the study may have diminished connectivity in networks responsible for attentional control, thereby impairing task performance.

In our current experiment, categories to be memorized and those to be ignored were presented in a mixed format, necessitating strong attentional focusing and inhibition. Consequently, it appears that the decrease in frontal lobe function induced by anaesthesia contributed to a reduction in both attentional focusing and inhibitory control during the task.

A recent study compared the effects of sedation using propofol by presenting conscious and nonconscious stimuli (Fontan et al., 2021). Brain activity measured using fMRI showed that the effects of sedation of conscious processing were mainly observed in higher-order areas, whereas the effects of nonconscious processing were mainly observed in sensory areas. These results suggest that sedation induced by anaesthesia has an impact on both conscious and unconscious stimulation, even though the observable activations in fMRI images are confined to different brain areas.

Using visual stimuli presented under subthreshold presentation times, recent researches on unconscious visual stimuli also suggest that unconscious stimuli influence WM performance (Soto et al., 2011; Soto & Silvanto, 2014 Persuh et al., 2018). Moreover, Gambarota et al. (2022) confirmed the presence of an unconscious WM effect by using Bayesian meta-analysis and pointed out that the type of visual stimulus and the amount of information can also affect unconscious WM.

In the present study, category judgements showed a correct response rate of over 80% at all stages of sedation, suggesting that participants were aware of all stimuli and were able to refer to them from LTM. However, at deep sedation levels, performance on the recognition task after a short delay was reduced significantly. It was also confirmed that the performance accuracy was still worse than the baseline when the sedation level was 1/2 and 3/4. These declines may be because attentional control of WM, such as focusing and inhibitory control, becomes difficult under sedation.

The difficulty in attentional control may be linked to the limited capacity of WM, as reported in studies indicating a smaller capacity limit (approximately 4 plus or minus 1) compared to simple memory (Cowan, 2001). In this experiment, the categorization task was relatively easy, so it appears that less WM capacity was spent on it and more capacity was used on memory retention. Consequently, the sedative effect of anaesthesia likely manifested prominently in memory retention.

Capacity limitations of WM may extend to visual WM tasks involving subthreshold visual stimuli. Previous studies using change detection tasks have indicated comparable capacity limitations between visual and verbal stimuli (Luck & Vogel, 1997). Thus, exceeding the capacity by inputting a substantial amount of information in visual WM tasks may hinder performance, prompting the attention control system to elevate or lower the threshold for input information.

However, the relationship between the content of consciousness, encompassing both visual and verbal stimuli and the attention control system of WM requires further exploration in future investigations.

Finally, regarding anaesthesia differences, in analysis 2, there was a significant interaction between the drug and sedation stage in the encoding task, with midazolam performing better than propofol in the moderate stage. On the other hand, no difference was observed between the two anaesthesia in the word recognition task, resulting in a discrepancy between category judgement and transfer to long-term memory. It seems necessary to consider this issue in further research.

5 | CONCLUSION

The current findings elucidate that WM performance is significantly affected and decreased under anaesthesia-induced sedation. Moreover, the task performance level of dual tasks showed the greatest decline under deep sedation, gradually improving as the sedation levels transitioned to moderate and light stages. These results suggest that consciousness is deeply involved in the executive system of WM, which focuses and inhibits attention. Furthermore, memory contents could not be accurately recalled after long compared to short delays, and the level of sedation influenced performance on cognitive tasks even after recovery from sedation. In particular, these findings show that even the lightest level of sedation causes difficulties in transferring information to LTM.

The findings of this experiment showed that the level of consciousness is deeply involved in encoding and memory retention. Furthermore, the WM executive system, which is responsible for attention control, was found to play a crucial role in these processes.

AUTHOR CONTRIBUTIONS

Mariko Osaka: Conceptualization; funding acquisition; investigation; methodology; project administration; validation; visualization; writing—original manuscript; writing review and editing. **Takehiro Minamoto:** Conceptualization; data curation; investigation; methodology. **Takashi Ikeda:** Conceptualization; methodology; investigation; software; preparation; writing review and editing. **Aya Nakae:** Conceptualization; investigation; methodology. **Satoshi Hagihira:** Conceptualization; methodology; investigation. **Hiroshi Ito:** Methodology; investigation. **Yuji Fujino:** Conceptualization; project administration; supervision. **Takashi Mashimo:** Conceptualization; methodology; project administration; supervision.

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CONFLICT OF INTEREST STATEMENT

We all have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

For data of this experiment, please contact the correspondence author.

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