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Research Report

Post-encoding modulation of spatial memory consolidation by propofol

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ABSTRACT

Memory consolidation is a continuous transformative process between encoding and retrieval of mental representations. Recent research has shown that neural activity immediately after encoding is particularly associated with later successful retrieval. It is currently unclear whether post-encoding neural activity makes a distinct and causal contribution to memory consolidation. Here, we investigated the role of the post-encoding period for consolidation of spatial memory in neurologically normal human subjects. We used the $GABA_A$-ergic anesthetic propofol to transiently manipulate neural activity during the initial stage of spatial memory consolidation without affecting encoding or retrieval. A total of 52 participants undergoing minor surgery learned to navigate to a target in a five-armed maze derived from animal experiments. Participants completed learning either immediately prior to injection of propofol (early group) or more than 60 min before injection (late group). Four hours after anesthesia, participants were tested for memory-guided navigation. Our results show a selective impairment of navigation in the early group and near-normal performance in the late group. Analysis of navigational error patterns further suggested that propofol impaired distinct aspects of spatial representations, in particular sequences of path segments and spatial relationships between landmarks. We conclude that neural activity during the post-encoding period makes a causal and specific contribution to consolidation of representations underlying self-centered and world-centered memory-guided navigation. Distinct aspects of these representations are susceptible to $GABA_A$-ergic modulation within a post-encoding time-window of less than

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60 min, presumably reflecting associative processes that contribute to the formation of integrated spatial representations that guide future behavior.

1. Introduction

Memory consolidation is an umbrella term for processes that transform novel mental representations into lasting memories (Dudai et al., 2015; Müller & Pilzecker, 1900; Squire et al., 2015). The standard model holds that early memory consolidation is a hippocampus-dependent process on the level of synapses and neural circuits. In contrast, late memory consolidation is a large-scale rearrangement process characterized by a decreasing role of the hippocampus and increasing neocortical involvement (Alvarez & Squire, 1994; McClelland et al., 1995). After encoding, synaptic consolidation is thought to occur within minutes to hours while systems consolidation may continue for days, months or even years (Kelleher et al., 2004; Smith & Squire, 2009; Takashima et al., 2009). Recent research, however, shows that significant hippocampal-neocortical rearrangement can already occur shortly after encoding, i.e., on a timescale that is traditionally associated with processes of synaptic consolidation (Kitamura et al., 2017; Lesburguères et al., 2011; Tambini & D'Esposito, 2020). Results both from human and animal studies further suggest that processes during the first minutes to hours after encoding might be relevant for successful consolidation of associative memories (Lesburguères et al., 2011; Tambini & D'Esposito, 2020). It is nevertheless not clear, whether post-encoding neural activity plays a specific role for consolidation of conscious memories or mainly reflects persistence of encoding-related activity (Tambini & Davachi, 2019).

There are currently few experimental tools to manipulate neural activity of hippocampus-dependent networks during the early steps of human memory consolidation without affecting encoding or retrieval. A possible causal relationship between post-encoding neural activity and distinct aspects of memory consolidation has rarely been investigated in humans (Tambini & Davachi, 2019). In one recent study, transcranial magnetic stimulation over lateral occipital cortex (LOC) shortly after learning of face–object associations was found to impair memory of associations, while items were spared. Functional MRI showed reduced functional connectivity between hippocampus and LOC, thus suggesting that hippocampo-neocortical interactions during the post-encoding period might determine consolidation of associative memories (Tambini & D'Esposito, 2020). One new pharmacological approach to interfere more directly with hippocampal activity is the systemic administration of the short-acting anesthetic propofol (2,6-diisopropylphenol) during consolidation. This drug is commonly used in routine medical procedures and acts as an agonist on the gamma-aminobutyric-acid (GABA)-A receptor and as a partial antagonist on N-methyl-D-aspartate (NMDA) receptors (Sahinovic et al., 2018; Walsh, 2018). Propofol affects long-term-potentiation and synaptic consolidation in hippocampal slices and spatial memory consolidation in rats (Nagashima et al., 2005; Wei et al., 2002; Zhang et al., 2013). In humans, functional MRI (fMRI) results show that sub-hypnotic doses of propofol significantly modulate hippocampal activation by visual memory items (Pryor et al., 2015). Furthermore, by using a verbal memory task in humans undergoing short propofol anesthesia, we could recently demonstrate a pattern of memory impairments that is suggestive of interference with hippocampus-dependent memory consolidation (Moon et al., 2020). The study included two groups that received general anesthesia with propofol at two different time points after learning a word list (13 min and 105 min after learning, respectively). While the subjects with early propofol anesthesia showed significant deficits in word list recall, this effect was not found in the second group with late propofol anesthesia.

In the present study, we combined the propofol-approach established in previous work (Moon et al., 2020; Vallejo et al., 2019) with a spatial memory task to investigate the causal relationship between post-encoding neural activity and early memory consolidation further. Neurologically normal patients undergoing short propofol anesthesia learned to navigate to a target location in a virtual five-armed maze. The maze was a modified version of a setup developed for rodent research that allows to separately investigate memory-guided navigation based on a subject's body coordinates and movement sequences (egocentric representations) and by using spatial relationships in the environment (allocentric representations) (Iglói et al., 2009; Rondi-Reig et al., 2006). Successful completion of the task requires memory of single items such as landmarks and path segments as well as memory of associations between landmarks, landmarks and subject and sequential associations of path segments. fMRI in humans performing a virtual analog of the task has shown that egocentric and allocentric navigational modes yield activation of the left and right hippocampus respectively (Iglói et al., 2010).

In our experiment, patients received a general anesthesia with propofol either some minutes or more than 1 h after learning to navigate the maze. Following recovery from anesthesia, we tested subjects for memory-guided navigation in egocentric and allocentric conditions. We reasoned that a causal role of post-encoding neural activity for consolidation of spatial memory should lead to measurable navigational deficits at testing. We further speculated that a specific role of post-encoding neural activity for spatial memory should lead to modulation of distinct navigational parameters rather than to an overall deterioration of performance.

2. Materials and methods

2.1. Participants

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

We included 78 subjects (52 patients, 26 controls; 37 female and 41 male) in our study (Table 1). Patients underwent total intravenous anesthesia with propofol for minor surgery of nasal septal deviation, sinusitis, or tonsillitis (Table 1). All patients were recruited from the ear-nose-throat-(ENT)-department of the Charité-Universitätsmedizin Berlin during a visit to the outpatient clinic at least one day before surgery. Participants were between 18 and 49 years old, spoke German fluently, had normal or corrected-to-normal vision, normal hearing, reported to be in good health and denied any history of a neuropsychiatric disorder or substance abuse. All participants completed a German version of the Santa Barbara Sense of Direction scale (SBSODs), i.e., a questionnaire that assesses spatial abilities, preferences and experiences (Hegarty et al., 2002). Legal copyright restrictions prevent public archiving of the SBSOD, which can be obtained from the copyright holders in the cited reference.

Twenty-six patients learned a spatial memory task about 18 min before anesthesia (Mdn 18, inter-quartile range (IQR) 13–22.8; "propofol-early"; Fig. 1B, Table 1) and 26 patients learned the task about 145 min before anesthesia (Mdn 145, IQR 99.5–172; "propofol-late"; Fig. 1B, Table 1). Each patient received intravenous general anesthesia, starting with a propofol bolus for anesthesia induction (Mdn 200 mg, IQR 165–200), followed by continuous propofol administration with 6 mg/kg/h for about 65 min for maintenance (Table 1). For analgesia, subjects received a continuous infusion of remifentanil with .2 μg/kg/min (Table 1). We further recruited 26 age-, sex-, and education-matched healthy control participants (Fig. 1, Table 1). The three subject groups did not differ significantly in terms of age, gender ratio, years of education and SBSODs scores (Table 1).

All participants gave written informed consent. All experimental procedures were conducted according to the declaration of Helsinki and were approved by the local ethics committee of the Charité-Universitätsmedizin Berlin. No part of the study procedures or analyses was pre-registered prior to the research. Sample size was estimated prior to analysis based on data from a previous study on propofol effects on verbal memory (Moon et al., 2020). Inclusion/exclusion criteria were established prior to data analysis. Of 94 subjects screened for study inclusion, 16 were excluded from study participation (control: n = 4, propofol-early: n = 6, propofol-late: n = 6). Ten participants did not meet the learning criteria (control: n = 4, propofol-early: n = 2, propofol-late: n = 4) and six suffered from postoperative complaints (propofol-early: n = 4, propofol-late: n = 2). All manipulations and measures of the study are reported.

2.2. Behavioral testing

2.2.1. Virtual navigation setup

The setup consisted of a virtual star-shaped maze with environmental cues (Fig. 1). The maze was an adapted version of a maze used in previous human and animal studies on navigation (Iglói et al., 2009, 2010; Rondi-Reig et al., 2006). The starmaze consisted of five symmetrically arranged peripheral alleys connected by five central alleys and was surrounded by five distant environmental cues, embedded in a virtual landscape (2× forest, 2× mountains with village, 1× group of transmission towers; Fig. 1). A treasure was hidden at the end of one of the peripheral alleys (Fig. 1A). The task was presented on a Lenovo Thinkpad X1 Carbon laptop computer (14.0-inch screen). Participants used a joystick controller to move and turn within the environment. We created the stimuli in Blender (version 2.79b, Blender Foundation) and Unity3D (version 2018.2.14f, Unity Technologies). The trial structure and recording of movement trajectories was

Table 1 – Demographic and clinical data of the investigated groups. Data presented as median and interquartile range (25–75%).[1]χ^2-test, [2]K.–Wallis – χ^2-test.

	Control (n = 26)	Propofol-early (n = 26)	Propofol-late (n = 26)	*p*-value
Female/male	15/11	13/13	9/17	.237[1]
Age	27.5 (22–36.5)	28 (24–32)	29 (22–32)	.666[2]
Years of education	16 (15–18)	15.5 (13–18)	15 (13.75–15.5)	.245[2]
SBSODs	5 (4.1–5.45)	4.3 (3.6–5.2)	4.7 (4.3–5.1)	.294[2]
Medical Procedure	n.a.	Tonsillectomy (n = 8) Rhinoplasty/functional endoscopic sinus surgery (n = 18)	Tonsillectomy (n = 5) Rhinoplasty/functional endoscopic sinus surgery (n = 21)	
Propofol bolus dose (mg)	n.a.	200 (165–200)	200 (165–200)	.938
Propofol maintenance dose (mg/kg/h)	n.a.	6.1 (6–6.7)	6 (6–6.5)	.841
Duration propofol administration (min)	n.a.	63.5 (54.3–81.3)	73.5 (55.3–98.3)	.264
Remifentanil maintenance dose (μg/kg/h)	n.a.	.2 (.2–.21)	.2 (.2–.25)	.327
Delay end of learning and propofol (min)	n.a.	18 (13–22.8)	145 (99.5–172)	<.001
Delay end of propofol and recall (min)	n.a.	246.5 (217.8–264.3)	232 (214.3–253.5)	.314
Delay end of learning and recall (min)	301 (282.3–341)a	320.5 (297.3–356.8)b	441 (413.3–510.8)c	<.001 b*a = .180 b*c < .001 a*c < .001

b*a, b*c, a*c: Post-hoc tests between groups.

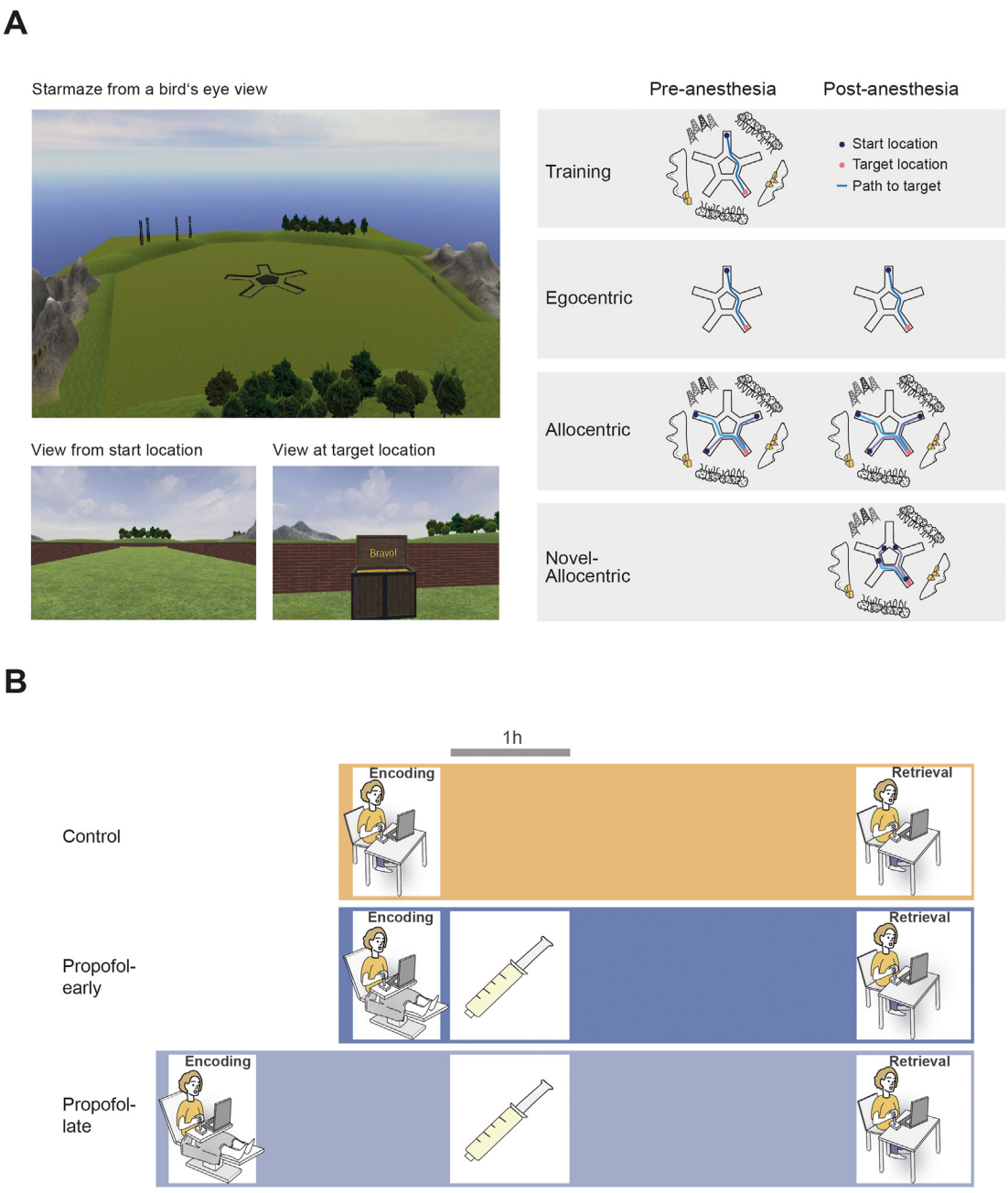

Fig. 1 – Experimental design. A. Virtual navigation setup. Left, five-armed maze surrounded by environmental cues, bird's eye view; example views at starting-location and target location in training trials, subject's view. Right, schematic of the four trial types of the study. Blue lines denote ideal paths connecting starting and target locations. B. Experimental timeline. First row, control group. Second row, early propofol group. Third row, late propofol group. All groups learned to navigate to a target in a virtual maze. The control group received no propofol and was tested about 5 h after learning, the early propofol group received propofol 18 min after learning and was tested about 5 h after learning, the late propofol group received propofol 2.5 h after learning and was tested about 7.5 h after learning.

implemented using the Unity Experiment Framework (Brookes et al., 2020).

2.2.2. *General instructions*

Before the experiment, we informed the participants that they would perform a navigation task before and after anesthesia but did not mention any details of the trials in the post-anesthesia testing session. We instructed the participants to search for a treasure hidden somewhere in the virtual maze. The treasure was always at the same position and appeared as soon as the subject reached its location (training trial). We also informed participants that in some trials they would have to indicate the memorized position of the treasure by pressing a red button as soon as they had reached its location (probe trial). In these trials, the treasure would not appear, even if the location was correctly remembered. We asked the

participants to navigate directly to the treasure and informed them that neither the maze nor the environment would change during the experiment. Trials were terminated 4 s after the treasure appeared (training trials) or after the button was pressed (probe trials). If neither event occurred within ninety seconds, the trial was terminated. Prior to the starmaze task, all participants familiarized themselves with the joystick and task requirements by completing three practise trials in a simple virtual three-armed maze.

2.2.3. *Pre-anesthesia session*

The pre-anesthesia session lasted about 15 min and aimed to ensure encoding of both egocentric and allocentric spatial representations (Fig. 1A). During the first four training-trials, participants navigated freely until they found the treasure. For navigation to the remembered location of the treasure, they could either reproduce their own successful path from a previous trial (egocentric strategy) and/or orient themselves based on the spatial relationships between environmental cues and the location of the treasure (allocentric strategy) (Iglói et al., 2009, 2010). After four training trials, participants had to indicate where the treasure was hidden in one probe trial. In case the participants failed to locate the target correctly, they were allowed one more training and one more probe trial. We then removed all environmental cues for the egocentric condition and participants had to navigate from the original starting point to the treasure. This manipulation was chosen to enforce egocentric navigation based on remembered sequences of path segments (Iglói et al., 2009, 2010). After three training trials, participants had to indicate where the treasure was hidden in one probe trial. Afterwards, the environmental cues reappeared for the allocentric condition, and we informed the participants that now their starting point would vary between trials. This manipulation was chosen to enforce allocentric navigation based on the spatial relationships between landmarks (Iglói et al., 2009, 2010). After six training trials, participants had to indicate the location where the treasure was hidden in three consecutive probe trials. We assumed proper learning of the task if participants solved the probe trial requiring egocentric navigation and at least two out of three probe trials requiring allocentric navigation. We intentionally started with egocentric trials to avoid distortion of egocentric representations by newly navigated paths in the allocentric condition. Conversely, we assumed only little interference of egocentric representations with the allocentric condition, because no landmarks were available in the egocentric condition.

2.2.4. *Post-anesthesia session*

The post-anesthesia session lasted about 15 min and aimed to test memory of spatial representations from the pre-anesthesia session. Before the session, we informed the participants that they would not receive feedback throughout the session and that they should always indicate the location of the treasure (i.e., probe trials only). Testing consisted of three experimental trial types. To test memory of spatial representations for egocentric navigation, we removed all environmental cues for the first three trials (egocentric trials). In the following trials, all environmental cues were visible. To test for retention of spatial representations for allocentric navigation, participants started from varying starting locations for seven consecutive trials. The first three locations had also been used during the pre-anesthesia session (allocentric trials), the last four were novel starting locations (novel allocentric trials). These latter trials were designed to test for flexible landmark-based navigation. Here we deliberately included starting positions that were clearly different from all other starting positions, so participants started either in the inner alleys or in the target alley, which had not been used as starting positions in previous trials.

2.3. *Data acquisition and statistical analysis*

During virtual navigation, we recorded positions within the maze as x- and y-coordinates in a Cartesian coordinate system combined with a timestamp at an average sampling rate of 110 Hz. For analysis, we then determined four parameters that capture distinct aspects of spatial navigation.

1. We determined whether participants successfully navigated to the target by calculating the final distance to the target location (Eq.: $\Sigma(\sqrt{[(x(\text{treasure}) - x(\text{end}))^2 + (y(\text{treasure}) - y(\text{end}))^2]})$). A trial was rated as successful, when the final distance to the target location was less than a third of the length of an external alley of the maze. We then calculated the percentage of successful trials in each subject for each condition ("success rate").
2. We extracted the trial duration from the timestamps (Eq.: $t(\text{end}) - t(1)$) to calculate the average navigation time in successful trials in each subject for each condition ("time").
3. We calculated the path length (Eq.: $\Sigma(\sqrt{[(x(i+1) - x(i))^2 + (y(i+1) - y(i))^2]})$) to determine the total distance covered to reach the target location in successful trials in each subject for each condition ("path error").
4. We calculated the distance to the target location averaged across all time stamps of a trial (Eq.: $\Sigma(\sqrt{[(x(\text{treasure}) - x(i))^2 + (y(\text{treasure}) - y(i))^2]})/\text{length}(\text{coordinates})$) in each subject for each condition to determine whether participants delayed their navigation toward the target ("distance error"). This measure does not necessarily correlate with path length but rather relates to the degree of uncertainty in navigational behavior, even in trials with normal path length (Garthe & Kempermann, 2013; Maei et al., 2009).

To account for different starting positions, the path-length and the average distance to target were normalized by calculating the absolute percent error (path error/distance error = (ideal value − actual value)/ideal value) × 100. Since we were primarily interested in performance changes between pre-anesthesia and post-anesthesia sessions, we subtracted the first measured value from the second measured value to receive a delta score (Eq.: Δ = post-anesthesia value − pre-anesthesia value) for all main variables (Dimitrov & Rumrill, 2003). All analyses of navigational behavior were performed in Matlab (Matlab 2020b, Mathworks, USA).

All statistical analyses were performed in R (v. 4.1.0). Shapiro–Wilk-testing showed that the assumption of normality had to be rejected for our main dependent variables. We thus chose non-parametric tests for statistical analyses. To detect

between-group differences of metric variables, we used the non-parametric Kruskal–Wallis-test followed by post-hoc testing with a two-sided Wilcoxon rank sum test or Mann–Whitney U-test. For all statistical tests, the significance level was set to .05. We applied a Bonferroni correction to adjust for multiple comparisons. We multiplied the raw p-values by the number of groups and reported adjusted p-values for group comparisons. Because the number of observations exceeded 50 and some measurements were identical, the p-value was based on asymptotic significance. For effect sizes, η^2 was determined for the Kruskal–Wallis test and r for the Mann–Whitney U test.

Stimuli are publicly available at https://osf.io/ykcd8/. Analysis scripts and functions are available on github: https://github.com/DeetjeIggena/five-arm-maze-analysis/. All data are available at https://osf.io/ykcd8/.

3. Results

3.1. Egocentric navigation

In pre-anesthesia egocentric trials, all participants successfully learned the sequence of path segments and left and right turns to reach the target location (Fig. 2). Navigation behavior in the pre-anesthesia session did not differ between groups (time: K.–Wallis – $\chi^2(2) = .802$, $p = .670$, $\eta^2 = 0$; path error: K.–Wallis – $\chi^2(2) = 1.05$, $p = .592$, $\eta^2 = 0$; distance error: K.–Wallis – $\chi^2(2) = 1.458$, $p = .482$, $\eta^2 = 0$. Suppl. Table 1).

At post-anesthesia testing, the propofol-early group showed a 29.5% decrease in successful egocentric trials (100% success rate pre-anesthesia, 70.5% success rate post-anesthesia). These subjects terminated navigation in a wrong alley of the maze more frequently, whereas the success rate of the control group did not change (100% success rate pre-anesthesia, 100% success rate post-anesthesia), and the success rate of the propofol-late group decreased by 4% only (100% success rate pre-anesthesia, 96% success rate post-anesthesia; K.–Wallis – $\chi^2(2) = 18.624$, $p < .001$, $\eta^2 = .222$; control *vs* propofol-early, Z = 3.465, p.adj = .002, r = .480, control *vs* propofol-late, Z = 1.0, p.adj = .952, r = .139, propofol-early *vs* propofol-late, Z = −2.955, p.adj = .009, r = .408. Fig. 2B). In the remaining successful trials, the other parameters of egocentric navigation did not change significantly. Propofol had no significant effect on pre-/post-anesthesia changes in navigation time (K.–Wallis – $\chi^2(2) = .115$, $p = .944$, $\eta^2 = 0$. Fig. 2B), path error (K.–Wallis – $\chi^2(2) = .603$, $p = .740$, $\eta^2 = 0$. Fig. 2B), and distance error between groups (K.–Wallis – $\chi^2(2) = 5.908$, $p = .052$, $\eta^2 = .058$. Fig. 2B). Thus, while the control and the propofol-late groups correctly reproduced the paths learned in the pre-anesthesia session, the propofol-early group more frequently generated erroneous paths without changes in navigational efficiency or signs of uncertainty, therefore suggesting a deficit mainly in memory of sequences of path segments.

3.2. Allocentric navigation – repeated starting positions

In pre-anesthesia allocentric trials, all participants successfully learned to reach the target location by using environmental landmarks (Fig. 2). Navigation behavior in the pre-anesthesia session did not differ between groups (time: K.–Wallis – $\chi^2(2) = 1.953$, $p = .377$, $\eta^2 = 0$; path-error: K.–Wallis – $\chi^2(2) = 2.303$, $p = .316$, $\eta^2 = .005$; distance-error: K.–Wallis – $\chi^2(2) = .566$, $p = .754$, $\eta^2 = 0$. Suppl. Table 1).

At post-anesthesia testing, when participants started from positions that had also been used in the pre-anesthesia session, we found a moderate effect on changes in success rates between groups. These changes however fell far below the ones seen in egocentric trials. While the control group showed a decrease in success of up to 6.4%, both propofol groups showed a slight increase of up to 5.1% in the propofol-early and 3.8% in the propofol-late group (Control: 98.7% success rate pre-anesthesia, 92.3% success rate post-anesthesia; propofol-early: 92% success rate pre-anesthesia, 97.4% success rate post-anesthesia; propofol-late: 96% success rate pre-anesthesia, 100% success rate post-anesthesia. K.–Wallis – $\chi^2(2) = 7.190$, $p = .027$, $\eta^2 = .069$; control *vs* propofol-early, Z = −2.306 p.adj = .063, r = .320, control *vs* propofol-late, Z = −2.409 p.adj = .048, r = .334, propofol-early *vs* propofol-late, Z = .390, p.adj = 1.0, r = .054. Fig. 2B). Propofol induced significant changes in other navigational parameters in the propofol-early group. We found a significant pre-/post-anesthesia increase in navigation time of 3.9 sec compared to .3 sec in controls (K.–Wallis – $\chi^2(2) = 6.429$, $p = .040$, $\eta^2 = .060$; control *vs* propofol-early, Z = −2.525, p.adj = .035, r = .354, control *vs* propofol-late, Z = −1.470, p.adj = .429, r = .206, propofol-early *vs* propofol-late, Z = 1.043, p.adj = .891, r = .145. Fig. 2B). Subjects in the propofol-early group spent more time at maze locations remote from the target, as also reflected by a 5.6% pre-/post-anesthesia increase in distance error (K.–Wallis – $\chi^2(2) = 7.594$, $p = .022$, $\eta^2 = .076$; control *vs* propofol-early, Z = −2.732, p.adj = .019, r = .383, control *vs* propofol-late, Z = -.886, p.adj = 1.0, r = .124, propofol-early *vs* propofol-late, Z = −1.757, p.adj = .237, r = .244. Fig. 2B). However, the change in the temporal properties of navigational behavior in the propofol-early group was not accompanied by significant modifications of path geometry, as indicated by similar pre-/post-anesthesia changes in path-error between groups (K.–Wallis – $\chi^2(2) = 1.045$, $p = .593$, $\eta^2 = 0$. Fig. 2B). These results therefore suggest that propofol did not significantly alter recognition of landmarks or memory of the paths that had been traveled in the pre-anesthesia session but rather induced a significant increase in navigational uncertainty.

3.3. Allocentric navigation – novel starting positions

In the post-anesthesia session, subjects started from four additional locations in the allocentric condition that were not used in the pre-anesthesia session. Successful navigation thus critically depended on the ability to flexibly update subject position in relation to environmental landmarks rather than on mere repetition of navigational paths that had been traveled in the pre-anesthesia session (Fig. 1). Consistent with our previous observation in allocentric trials with repeated starting positions, we only observed few unsuccessful trials in each group with a success rate of almost 100% in each group (K.–Wallis – $\chi^2(2) = 2.045$, $p = .360$, $\eta^2 = .001$.Fig. 2B).

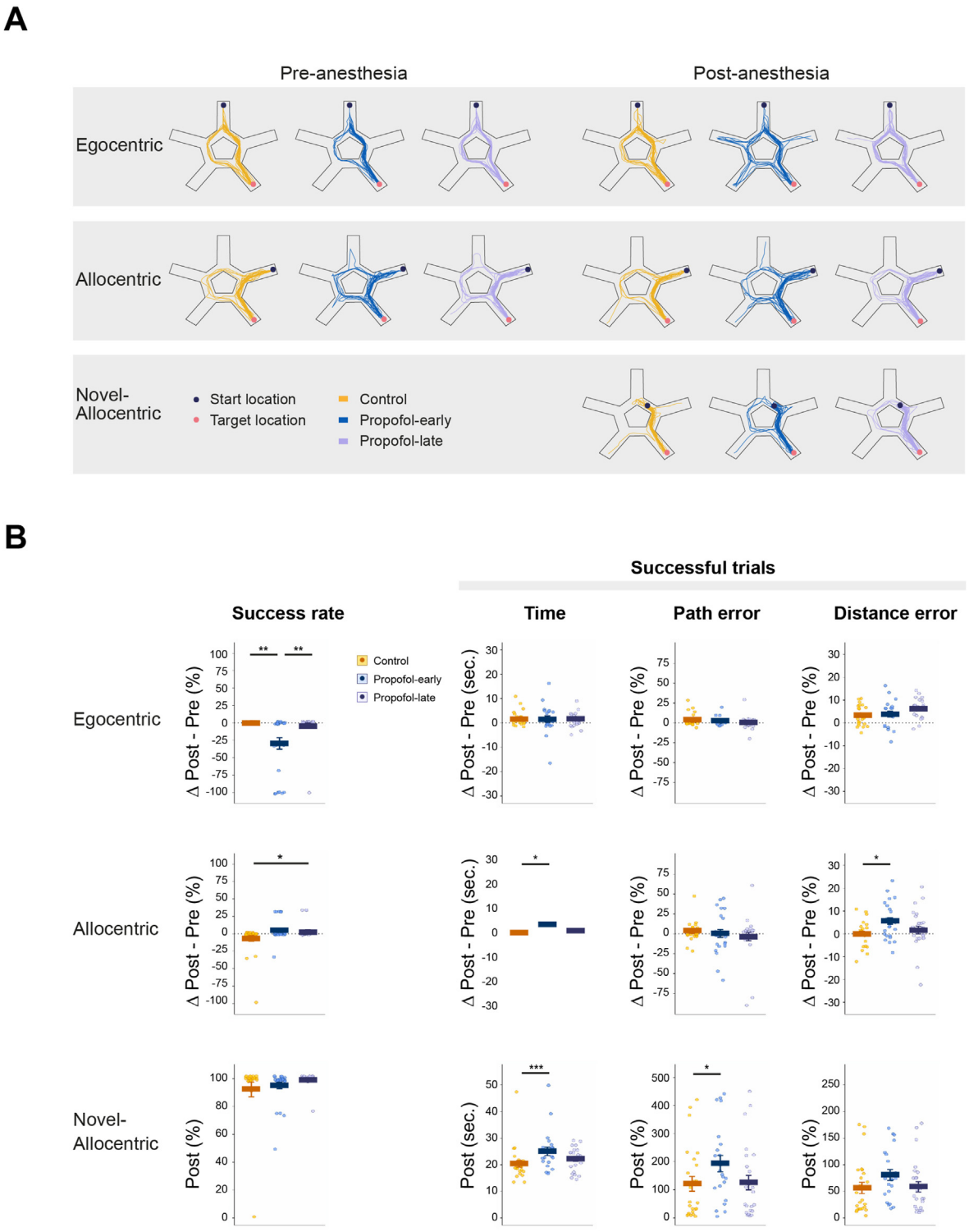

Fig. 2 – Navigation performance. A. Exemplary navigation paths from the three investigated subject groups. Left, pre-anesthesia paths; right, post-anesthesia paths. First row, egocentric condition, second row allocentric condition, third row novel-allocentric condition. Note increased number of paths into wrong alleys in the propofol-early group in the egocentric condition. Note increased number of detours in the propofol-early group in the novel-allocentric condition. B. Group performance. First row, egocentric condition, second row allocentric condition, third row novel-allocentric condition. Note that in the egocentric condition, administration of propofol caused a significant and selective pre-/post-anesthesia decrease in the number of successful trials. Note that in the allocentric condition, propofol caused a pre-/post-anesthesia increase in navigation time and distance-error in the propofol-early group. Note that in the novel-allocentric condition (post-anesthesia testing only), administration of propofol caused an increase in navigation times and path error in the propofol-early group compared to the other groups. Yellow, control group; blue, propofol-early group, violet propofol-late group. Data presented as means and single datapoints for each participant. *$p < .05$; **$p < .01$; ***$p < .001$.

However, subjects in the propofol-early group showed significantly longer navigation time to reach the target than the control group (K.–Wallis – $\chi^2(2) = 12.356$, $p = .002$, $\eta^2 = .142$; control *vs* propofol-early, Z = −3.456, *p*.adj = .002, r = .489, control *vs* propofol-late, Z = −2.020, *p*.adj = .130, r = .286, propofol-early *vs* propofol-late, Z = 1.592, *p*.adj = .334, r = .221. Fig. 2B). We therefore analyzed the number of entries into external maze alleys and calculated the time spent within in these alleys. This analysis showed that participants in the propofol-early group visited incorrect external alleys of the maze significantly more often than controls (K.–Wallis – $\chi^2(2) = 8.297$, $p = .016$, $\eta^2 = .086$; control *vs* propofol-early, Z = −2.777, *p*.adj = .016, r = .393, control *vs* propofol-late, Z = −2.241, *p*.adj = .075, r = .317, propofol-early *vs* propofol-late, Z = .613, *p*.adj = 1.0, r = .085). The propofol-early group also spent significantly more time within incorrect alleys than the control group (K.–Wallis – $\chi^2(2) = 8.832$, $p = .012$, $\eta^2 = .094$; control *vs* propofol-early, Z = −2.866, *p*.adj = .012, r = .405, control *vs* propofol-late, Z = −2.017, *p* = .131, r = .285, propofol-early *vs* propofol-late, Z = 1.237, *p* = .648, r = .172). The increase in navigation time in the propofol-early group was associated with an increase in path-length as reflected in an average path-error of 197.5%, compared to 121.3% in the control group and 122.2% in the propofol-late group (K.–Wallis – $\chi^2(2) = 9.525$, $p = .009$, $\eta^2 = .051$; control *vs* propofol-early, Z = −2.058, *p*.adj = .012, r = .291, control *vs* propofol-late, Z = −.039, *p* = 1.0, r = .005, propofol-early *vs* late-propofo-latel, Z = −2.068, *p* = .056, r = .2876. Fig. 2B). There was no evidence that participants in the propofol-early group spent more time at a greater distance from the target, as the distance-error did not differ significantly between groups (K.–Wallis – $\chi^2(2) = 5.200$, $p = .074$, $\eta^2 = .044$. Fig. 2B). Thus, when participants were forced to base navigation solely on a flexible integration of their navigational position with the spatial relationship of landmarks in the post-anesthesia session, the propofol-early group took detours and spent more time in incorrect alleys with concomitant increases in navigation time and path error. These results therefore suggest a weakened representation of the spatial relationship between landmarks in the propofol-early group.

4. Discussion

We investigated effects of the $GABA_A$-ergic anesthetic propofol on consolidation of spatial memory in humans. We used a virtual variant of a star-shaped maze that allows to disentangle ego- and allocentric navigational strategies and that has previously been shown to be sensitive to hippocampal dysfunction (Iglói et al., 2009; Rondi-Reig et al., 2006). Our results show that administration of propofol after learning to navigate the maze significantly impairs spatial representations required for later memory-guided navigation. These effects were confined to a post-encoding time window of less than 1 h and affected memory-guided navigation based on egocentric as well as allocentric representations. Error patterns in these conditions however suggest that propofol impaired distinct post-encoding processes supporting consolidation of distinct aspects of egocentric and allocentric spatial representations. Memory-guided navigation performance in the egocentric condition was consistent with impaired representation of sequences of path segments whereas navigation performance in allocentric conditions mainly suggested a weakened representation of the spatial relationship of landmarks.

Theoretically, the memory impairments might mainly be due to differences in rehearsal between groups. The propofol-early group might simply have had less opportunity to rehearse mentally what they had learned prior to anesthesia. We nevertheless deem interruption of rehearsal an unlikely main explanation for our findings for several reasons: 1. If interruption of rehearsal would be the main cause for memory impairments at retrieval, we would expect a less selective deficit. However, the pattern that we observed was a combination of preserved and altered navigational parameters in the propofol-early group. 2. Memory deficits were prominent in the novel allocentric condition in the propofol-early group, i.e., in a condition that required navigation by using spatial relationships that were not experienced from the same perspective and in the same sequential order as during learning. 3. Previous studies suggest that rehearsal of visuospatial information critically depends on environmental support (e.g., Lilienthal et al., 2018). In our study there were no environmental references from the learning period that might have supported rehearsal after learning. Moreover, rehearsal by eye movement-based overt orienting during the memory delay is unlikely, as control subjects freely moved in the veridical environment as soon as the learning phase in the virtual maze ended. 4. Research on navigating humans showed that post-encoding rest periods promote consolidation of spatial memory irrespective of intentional rehearsal after learning (Craig et al., 2016). Similarly, explicit cue-triggered retrieval of object-location associations after learning was found not to be responsible for driving the benefit of awake rest periods on subsequent memory in an object-location memory task (Tambini et al., 2017). We are therefore confident that the observed deficits are mainly related to interference with early steps of memory consolidation rather than with rehearsal.

In our subjects, propofol was administered systemically. With a context-sensitive half-time of less than 10 min (Hughes et al., 1992; Sahinovic et al., 2018) its effects are quite selective in time but not necessarily confined to a distinct region of the brain. It has been shown previously that propofol modulates neuronal networks by activating intra- and extra-synaptic $GABA_A$ receptors. The influx of anions attenuates synaptic transmission (Collins, 1988; Orser, 1994; Otsuka et al., 1992), regulates long term potentiation (LTP) (Wang et al., 2006) and disturbs the rhythmic activity of neurons (Perouansky & Pearce, 2011). $GABA_A$ receptor subtypes differ with respect to propofol sensitivity (Wang et al., 2018) and central nervous system (CNS) distribution (Fritschy et al., 1997; Pirker et al., 2000; Sperk et al., 2020). $GABA_A$ receptors containing the α5-subunit ($\alpha5GABA_A$) are probably crucial for memory effects of propofol (Engin et al., 2020; Perouansky & Pearce, 2011). $\alpha5GABA_A$ receptors are highly expressed in the CA1-region of the hippocampus, where this specific subtype contributes to 25% of all $GABA_A$ receptors (Fritschy et al., 1997; Pirker et al.,

2000; Sperk et al., 2020). Pharmacological stimulation of hippocampal α5GABA$_A$ receptors has been shown to reduce hippocampal excitability, to disturb hippocampal sharp wave and ripple oscillations and to prevent excessive activation of excitatory synapses by downregulating LTP (Davenport et al., 2021; Papatheodoropoulos & Koniaris, 2011; Viereckel et al., 2013).

Consistent with the anatomical distribution of α5GABA$_A$-receptors, electrophysiological experiments showed that propofol modulates key mechanisms of memory consolidation. In rat hippocampal slices, propofol has been shown to transiently affect induction and maintenance of LTP in the CA1 region of the hippocampus (Nagashima et al., 2005; Takamatsu et al., 2005; Wei et al., 2002). In line with these findings, propofol infusion during memory consolidation impaired hippocampus-dependent spatial memory in rats and decreased recall performance in a word-list task relying on hippocampal integrity in humans (Moon et al., 2020; Zhang et al., 2013). Furthermore, a positron emission tomography (PET)-study in humans detected reduced hippocampal glucose-metabolism during propofol administration and fMRI experiments showed suppressed hippocampal activity during encoding of emotional pictures under continuous propofol infusion in sub-anesthetic doses (Pryor et al., 2015; Sun et al., 2008). Therefore, it appears likely that at least some of the observed memory effects of propofol are mediated by neural networks that include the hippocampus. However, since α5GABA$_A$-receptors can also be found in other regions of the brain, several of which are also relevant for spatial cognition (Sperk et al., 2020), it is possible that modulation of other regions, e.g., the striatum, may have contributed to our results.

Most theories address the mechanisms underlying memory consolidation either on a local synaptic level or on a large-scale (i.e., hippocampal-neocortical) systems level. These two groups of mechanisms are frequently considered to be associated with distinct time scales (Alvarez & Squire, 1994; McClelland et al., 1995). Synaptic consolidation is thought to operate for up to some hours, whereas systems consolidation may continue for years (Dudai et al., 2015; Squire et al., 2015). However, recent evidence shows that processes of systems level consolidation can already be observed in the immediate post-encoding period (Dudai et al., 2015; Tambini & Davachi, 2019). Reactivation of neural activity in the hippocampus in the post-encoding period was associated with activity across hippocampal-neocortical networks that determines later recall. For example, functional connectivity between the hippocampus and the lateral occipital complex during some minutes following encoding in a visual associative memory task correlated with later memory performance (Tambini et al., 2010). Likewise, multivoxel activity patterns in the human medial temporal lobe and retrosplenial cortex during encoding and the immediate post-encoding period have been shown to predict later recall in a similar task (Staresina et al., 2013). In a recent study, interference with hippocampal-neocortical interactions by transcranial magnetic stimulation over neocortex in a time window of up to 50 min following encoding of object–face associations led to a selective deficit in associative memory while item memory for objects and faces was spared (Tambini & D'Esposito, 2020). Our results complement these findings by suggesting that modulation of post-encoding neural activity in a time window of less than 1 h may causally affect systems consolidation, i.e., on a timescale that matches processes of synaptic memory consolidation (Dudai et al., 2015). Moreover, the pattern of impaired sequences of path segments and spatial relationships of landmarks with preserved path segments and landmarks is consistent with the hypothesis that neural activity in the early consolidation period is not a mere carry-over of encoding-related activity. Rather it is compatible with a post-encoding integration process that binds distinct items and distributes memory representations across hippocampal-neocortical networks for future behavior (Tambini & Davachi, 2019). Accordingly, a unified framework has been proposed recently that suggests that depending on the relevance of newly learned information, associated synapses are tagged (Cowan et al., 2021). These salience tags might facilitate LTP cascades that lead to selective reinforcement of synapses and their prioritization for system consolidation, thereby linking synaptic and systems consolidation already during the early-post encoding period.

Like in previous studies in animal models and humans, we used different conditions at retrieval to prompt the use of distinct spatial representations for memory-guided navigation. Removal of all landmarks was intended to prevent reorientation by landmarks and to force subjects to rely on representations of sequences of path segments that had been traveled in the pre-anesthesia session (egocentric trials). Shifting of starting points with landmarks present was intended to allow for additional orienting by using the spatial relationships between landmarks (allocentric trials) or to force subjects to solely rely on these relationships (novel allocentric trials). However, during natural behavior, these representational modes are almost always used in combination, with their relative contribution depending on individual preferences, abilities and contextual factors (Chersi & Burgess, 2015; Ekstrom et al., 2014, 2017; Johnsen & Rytter, 2021; Ladyka-Wojcik & Barense, 2021). Previous research suggests a corresponding interaction at the neural level between hippocampus and striatum, with the latter being mainly responsible for egocentric stimulus-response strategies and reinforcement learning (Chersi & Burgess, 2015; Iglói et al., 2010). Navigational impairments in egocentric and allocentric conditions may thus be attributable to modulation of neural activity in multiple brain regions, including hippocampus and striatum. On the other hand, neuronal populations in hippocampus and entorhinal cortex code a multitude of spatial, temporal and visual features required for memory-guided navigation (Eichenbaum, 2017; Moser et al., 2015), and recent evidence suggests that overlapping groups of hippocampal neurons can support allocentric as well as egocentric spatial representations (Alexander et al., 2020). Similarly, on the level of large-scale networks, largely overlapping brain regions including hippocampus, entorhinal cortex, parietal cortex, retrosplenial cortex and others may be involved in shared processing of information for egocentric and allocentric representations (Chrastil, 2013; Ekstrom et al., 2017). By this view, both representational modes may represent a continuum supported by an

extended network with changing hubs rather than by clearly separable neural substrates.

Consistent with the hypothesis of shared neural resources for egocentric and allocentric processing, rodent experiments employing the starmaze task demonstrated that both sequence- and landmark-based navigation rely on the integrity of hippocampal subregion CA1 (Rondi-Reig et al., 2006). Subsequent fMRI-experiments in humans with a highly similar task showed that sequence-based navigation activates the left hippocampus and landmark-based navigation activates the right hippocampus (Iglói et al., 2010). The impairments observed here fit these observations and may suggest that during the post-encoding period at least partially overlapping networks provide computations relevant to early consolidation of allocentric as well as egocentric memory representations (Johnsen & Rytter, 2021; Kunz et al., 2020; Samanta et al., 2021). Alternatively, at least in our task, administration of propofol may have affected a central spatio-temporal binding process that yields seemingly distinct behavioral manifestations – depending on the particular navigational context imposed by the experimenter. A common denominator behind the different deficits in our task may thus be a central impairment in associating navigational information in time (egocentric condition) and space (allocentric conditions). Confirmation of this hypothesis will however require a combination of our neuro-pharmacological approach with electrophysiological recordings in experimental animals.

In conclusion, our results provide additional evidence for a significant and specific role of the post-encoding period for later recall (Dudai et al., 2015; Tambini & Davachi, 2019). This role seems to extend to several aspects of spatial memory formation. Our findings are consistent with the hypothesis that neural activity in a brief time window following learning is more than the persistence of a punctual encoding process. Rather, the selectivity of the deficits point to a time-limited associative process that is necessary for the formation of integrated spatial representations that are critical for later memory-guided navigation – in particular those that require sequencing of path segments and flexible use of spatial relationships between landmarks. While our approach allows for no direct inferences on neural substrates, the known distribution of GABA-receptors together with previous behavioral and imaging evidence of propofol effects on the human brain (Moon et al., 2020; Pryor et al., 2015) make hippocampus-dependent networks a likely candidate for this process. Propofol anesthesia may provide a valuable tool to investigate causal relationships between post-encoding neural activity and memory-guided behavior in neurologically normal humans.

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Open practices

The study in this article earned an Open Data – Protected Access badge for transparent practices. Materials and data for the study are available at https://osf.io/ykcd8/.

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Supplementary data

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