Neural correlates for prospective memory decline in postpartum women

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Neural correlates for prospective memory decline in postpartum women

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<ABSTRACT>

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I. INTRODUCTION

Prospective memory (PM) refers to the ability to remember to execute delayed intention in appropriate situations. Although postpartum women have risk factors for decreased PM performance such as demanding ongoing tasks, depressive symptoms, and decreased serum levels of estrogen, there has been little research on PM in postpartum women. Therefore, the present study aimed to assess PM performance and to find out relevant functional and structural neural correlates in postpartum women. Variable clinical information was also obtained to establish possible causes for decreased PM performance in postpartum women.

II. MATERIALS AND METHODS

Twenty-five postpartum women aged 20-40 years in the 2nd - 4th month after parturition and 26 nulliparous women who were matched for age and education were prospectively enrolled. All participants underwent resting-state and PM task-based functional MRI (fMRI) and structural MRI, self-report questionnaires, neuropsychological tests, and hormone assays.

III. RESULTS

The postpartum women showed decreased PM performance compared to the controls, showing lower PM accuracy (P = .003) and longer reaction times (P = .003). On task-based fMRI analysis, the right hippocampus failed to show PM-related activation in postpartum women. On Psychophysiological Interaction analysis using the right hippocampus seed, postpartum women had decreased functional connectivity (FC) with ventral frontoparietal networks (FPN) in PM trials relative to PM ongoing trials (ongoing trials in the PM block), while the controls showed increased FC. Postpartum women also showed altered resting-state functional connectivity (RSFC) in the right hippocampus seed: decreased RSFC with the ventromedial prefrontal cortex, and increased RSFC with the ventrolateral prefrontal cortex, temporoparietal junction, and frontal eye field. No difference was found in cortical thickness or hippocampal volume between the groups. On multivariate analysis, the decreased FC between the right hippocampus and ventral FPN in PM trials relative to PM ongoing trials (odds ratio = 1.219, P = .035) and the higher number of nocturnal awakenings (odds ratio = 0.635, P < .001) were independent predictors for poor PM performance even after adjustments for age, duration of education, serum level of estrogen, and depressive symptoms.

IV. CONCLUSION

The present study showed decreased PM behavioral performance in postpartum women compared to the controls. Decreased FC within spontaneous retrieval-related regions including the right hippocampus and ventral FPN along with disrupted sleep rhythms may contribute to poor PM performance in postpartum women.

Key words : postpartum, prospective memory, functional MRI, structural MRI

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I. INTRODUCTION

More than half of pregnant women perceive a decline in their cognitive abilities compared to before pregnancy.[1] Postpartum women also complain of similar, but maybe a milder degree of cognitive change.[2] "Maternal amnesia", "momnesia" or "pregnancy brain" is used colloquially to describe this condition and the most frequent symptoms are forgetfulness and memory disturbances.[3-5] Recent meta-analysis studies show that these symptoms are not just subjective feelings, but objective cognitive impairments.[2,6]

Prospective memory (PM) refers to the ability to remember to execute delayed intention in appropriate situations.[7] PM requires intention planning and formation, maintaining memory of the intention, then cue detection and retrieval of the related intention, and carrying out this intention while performing an ongoing activity.[8] PM is essential when performing daily tasks, so its disturbance can cause inconvenience or more serious consequences in our day to day lives. For instance, forgetting to take medication (e.g., insulin) can result in serious health problems (e.g., hyperglycemia), forgetting to turn off the gas stove can cause fires, and forgetting a wedding anniversary can result in

arguments with your spouse. Increased background cognitive demands,[9] depressive symptoms,[10-12] and sleep disturbance have been suggested as factors that negatively affect PM,[13] while exposure to estrogen (e.g., estrogen replacement therapy[14] or cumulative life time estrogen exposure[15]) has been suggested to positively affect PM. Postpartum women might be vulnerable to PM dysfunction as they are dealing with additional demanding ongoing tasks (e.g., feeding their baby or changing their baby's diaper every couple of hours without sleep), while possibly suffering from depressive symptoms,[16] and because they are found to have decreased serum levels of estrogen. So far, a few studies have been conducted to define PM performance in pregnant or postpartum women using behavioral data,[5,17] showing decreased PM performance in these groups. However, as these studies mainly focused on pregnant women, there has been a lack of information about the effect of postpartum on PM. Moreover, no study has focused on revealing culprit regions related to PM performance in postpartum women using functional and structural MRI.

Therefore, the present study aimed to assess PM performance in postpartum women by comparing them with nulligravid women matched for age and duration of education and to find neural substrates associated with decreased PM performance in postpartum women using resting-state and PM task-based functional MRI (fMRI) and structural MRI. To establish possible causes for decreased PM performance in postpartum women, information on clinical characteristics was also obtained using self-report questionnaires, hormone assays, and cognitive assessment tests.

II. MATERIALS AND METHODS

1. Participants

Women aged 20-40 years in the 2nd - 4th month after parturition (Postpartum group) with normal pregnancies, uncomplicated term vaginal or Caesarean deliveries, and healthy babies were recruited. Women who were matched to these patients for age and duration of education and who had never been pregnant (Control group) were also recruited for comparison. Participants were excluded if they had been treated with hormonal preparations or with psychotropic drugs, had a history of head trauma that resulted in loss of consciousness or concussion, or had medical, psychiatric, or neurological comorbidities that might account for cognitive dysfunction. All participants were right-handed, native Koreans with normal or corrected-to-normal vision and received monetary compensation for their participation ($35). This prospective study was approved by the Institutional Review Board, and all participants provided written informed consent prior to all study procedures.

2. Experimental tasks & procedures

The present experiment consisted of four sessions: the (1) pre-scan session, (2) fMRI scanning session, (3) structural MRI scanning session, and (4) post-scan session. In the pre-scan session, participants were asked to fill out self-report questionnaires measuring demographic information, depressive symptoms, and subjective cognitive dysfunction. Then, blood samples were drawn for hormone assays. After that, participants completed a shorter practice version of the fMRI scanning session using a laptop computer to familiarize themselves with the tasks in the actual scanning session. The fMRI scanning

session included resting-state and prospective memory task sessions. Prior to the post-scan session, a 3-dimensional (3D) T1-weighted structural image and diffusion tensor imaging (DTI) data were acquired. In the post-scan session, a cognitive test battery was conducted to evaluate the objective cognitive status of the participants. The PM task performed in the fMRI scanning session was programmed using the Cogent 2000 toolbox (www.vislab.ucl.ac.uk/cogent.php) and MATLAB 7.12.0 (The MathWorks).

3. Self-report questionnaires

Self-report questionnaires were comprised of questions regarding demographic and clinical characteristics, total sleep time per day, number of nocturnal awakenings, and a scale of 10 to rate sleep deprivation, for which 0=absence and 10=very severe to indicate lack of sleep. It also contained the Beck Depression Inventory (BDI)[18] and the Edinburgh Postnatal Depression Scale (EPDS)[19] to assess depressive symptoms, and the Cognitive Failure Questionnaire (CFQ)[20] to assess subjective cognitive decline. Although the EPDS has not been validated for nulliparous women, it was used to quantify subjective depression for both the Postpartum and Control groups in order for consistency between the groups.

4. Neuropsychological tests

The cognitive test battery was comprised of the semantic Controlled Oral Word Association test (COWAT) and Trail Making Test (TMT) part B to assess executive function/verbal fluency, the Digit Span subset of the Korean version of the Wechsler Adult Intelligence Scale: forward, backward, and

sequencing recall tests to assess working memory, the 15-item Korean version of the modified Boston Naming Test (K-BNT) to assess language function, the Word List Memory to assess verbal learning, the Word List Recall and Recognition to assess verbal learning/memory function, and the TMT part A to assess speed of information processing.

5. Hormone assays

Blood samples were collected via venipuncture from the antecubital space and serum levels of estradiol, progesterone, prolactin, cortisol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were assayed at the Department of Laboratory Medicine and Nuclear Medicine, Severance Hospital, Yonsei University College of Medicine. Serum levels of estradiol, prolactin, cortisol, FSH, and LH were measured by an enzyme chemiluminescent immunoassay using a UniCel DxI 800 automated analyzer (Beckman Coulter, Inc, Fullerton, CA). The minimum sensitivity and range of the estradiol, prolactin, cortisol, FSH, and LH assay was 20-4800 pg/mL, 0.25-200 ng/mL, 0.4-60.0 μg/dL, 0.2-200 mIU/mL, and 0.2-200 mIU/mL, respectively. Serum progesterone was determined by radioimmunoassay using the Progesterone Coat-A-Count® RIA Kit (Diagnostic Products Corporation, Los Angeles, CA). The minimum sensitivity and range of the progesterone assay was 0.1–40 ng/mL. Blood was immediately centrifuged and serum was separated and stored at - 70 °C, and sent to an outside lab for a subsequent oxytocin assay. Serum levels of oxytocin were assayed by the Enzyme-Linked ImmunoSorbent Assay using the Spectramax 190 microplate reader (Molecular devices Corporation, Sunnyvale, CA). The minimum sensitivity and range of

the oxytocin assay was 10-400 uIU/mL.

6. fMRI paradigm for PM

The current study employed a PM task (Fig. 1) designed with alternating blocks of PM and control (CTRL) conditions, and each block was repeated 4 times.

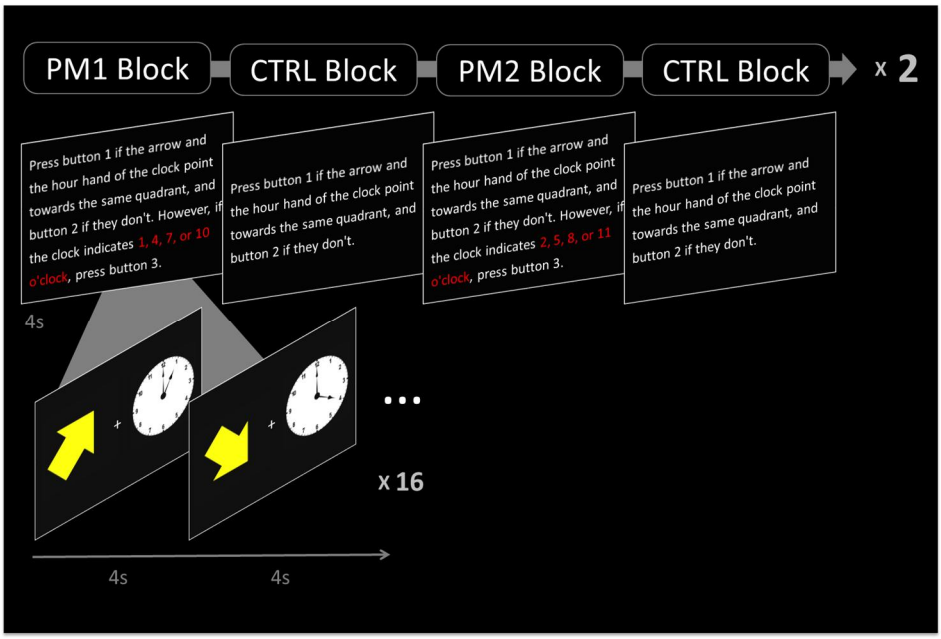

Figure 1. Schematic illustration of the PM task.

The stimuli consisted of an arrow and a clock presented in the left and right side of the screen, respectively. For the ongoing task, participants were instructed to respond using the keypad with their index or third finger depending on whether the arrow and the hour hand of the clock indicated the same quadrant or not. Both the arrow and the clock could indicate a direction from 1 to 11 o'clock. The CTRL blocks consisted of only ongoing trials (CTRL

ongoing) where participants did not have to maintain PM intentions (uncontaminated ongoing trials; not affected by PM intention). In the PM blocks, participants were asked to remember particular times (1, 4, 7, 10 or 2, 5, 8, 11; each set was the target of 2 PM blocks), and to press a third button with their ring finger whenever they saw that particular time on the clock (PM trial) while performing the ongoing task (PM ongoing; contaminated ongoing trials; affected by PM intention). Each block consisted of 16 trials, and half of the trials were PM trials for the PM block. At the beginning of each block, an instruction page was presented for 4000 ms which gave directions on the tasks of that certain block. Participants were given 4000 ms to perform each following task trial. Responses were categorized into correct response, wrong error, omission error, and commission error. Correct response was defined as pressing the correct button in each trial, wrong error as failure to respond or pressing the wrong button in ongoing trials, omission error as failure to press the third button in PM trials, and commission error as failure to inhibit PM response in ongoing trials.

7. Image acquisition

All scans were acquired by using a 3T MR imaging unit (Discovery MR750; GE Healthcare, Milwaukee, WI) with an 8-channel head coil. Functional images were acquired with the gradient-echo single-shot echoplanar imaging (GE-SS-EPI) sequence with the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 240 x 240 mm^2, voxel size = 3.75 x 3.75 x 4.0 mm^3, flip angle = 90°, 33 axial slices tilted 30° from the AC–PC plane, no gap, interleaved. First, resting-state MRI data were collected for 6 m 58s (209

volumes). During the resting-state data acquisition, participants were instructed to close their eyes while lying awake, and not to think of anything in a particular or systematic way. In the PM task run, stimuli were projected onto a black background screen at the end of the scanner, and participants viewed stimuli by way of a mirror mounted on the head coil. Responses made by participants were collected with a magnet-compatible button box placed under the participant's right hand. The scan time of the PM task run was 9m 14s including a dummy scan for 10s. At the end of the functional imaging session, high-resolution T1-weighted structural images (3D-T1-TFE sequence with the following parameters: sagittal acquisition with TR = 8.3 ms, TE = 3.3 ms, FOV = 198 x 220 mm^2, voxel size = 0.77 x 0.86 x 1.0 mm^3, 216 slices, flip angle = 12°, no gap) were also acquired for each subject.

8. Image analysis

A. PM task-based fMRI data analysis

The fMRI data were preprocessed and analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, U.K.). Slice-timing correction was done by resampling all slices relative to the middle slice (i.e., 17^{th} slice) in temporal order. The EPI data for each subject was realigned to the first volume for motion correction and only data sets with ≤ 2mm maximal displacement during the entire scan were included in this study. Next, the functional images were coregistered to the T1-weighted image and spatially normalized to the Montreal Neurological Institute (MNI) template provided with SPM8, then resampled into 3 x 3 x 3 mm voxels, followed by spatial smoothing using a Gaussian kernel with a full width at half maximum (FWHM)

of 8 mm. A high-pass filter of 1/128 Hz was used to remove low-frequency noise, and an AR (1) + white noise model corrected for temporal autocorrelation.

(A) PM task-related activation analysis

GLM analyses were then performed for both block- and event-related designs. These approaches allowed us to examine not only sustained brain activity differences but transient differences between the groups. In block design analysis, regressors were created for PM blocks and CTRL blocks by convolving the boxcar function with the hemodynamic response function (HRF) implemented in SPM. The length of each block in the regressors was 68s which included 4s for presentation of the instruction page. Transient effect (event-related) was estimated by including regressors for each type of trial by convolving neural input functions with the HRF. Trial types were PM trials, PM ongoing trials, and CTRL ongoing trials. All error trials were separately modeled with a single regressor and excluded from further analyses. Additionally, another GLM analysis was conducted only for the instruction periods to investigate group differences during encoding of intentions. A total of 8 instruction events were modeled with one regressor for this analysis. Six movement parameters extracted from the realignment process were included as confounders, as well as a single covariate representing the mean session effect. Random-effects group analyses were performed in full-factorial design with within-subject factors (block design: PM block vs. CTRL block, event-related design: PM vs. PM ongoing vs. CTRL ongoing) and between-subject factors (group: PP vs. Control) using beta estimates for each regressor. To identify

specific patterns of activity across conditions in regions which showed significant differences between the Postpartum and Control groups, ROI analyses were conducted using the MarsBar plug-in for SPM (http://marsbar.sourceforge.net/). The ROIs were converted 4mm sphere masks centered at the peak, and percent signal changes which were extracted from each ROI for each participant were entered into second level analysis. Unless stated otherwise, all statistical analyses were corrected for multiple comparisons based on Monte Carlo simulation corresponding to an alpha level of $P < .05$ [21].

(B) PM task-related functional connectivity (FC) analysis

To identify group differences in PM task-related FC, a generalized Psycho-Physiological Interaction (gPPI) analysis[22] was conducted. A right hippocampus seed was obtained from the overlapping area between significant clusters with group x task interaction from the block- and event-related design analyses. The physiological variable was made by deconvolving the mean BOLD signal within the seed, and the psychological variable was created by convolving each task regressor (PM, PMongoing, and CTRLongoing trials) with the HRF. The physiological variable was multiplied by the psychological regressors to form the interaction term (PPIs). Individual beta images for each PPI regressor were then entered into a group-level analysis which had a procedure identical to that used in event-related design analyses. The activation threshold for gPPI analysis was set at an alpha level of $P < .05$ in accordance with Monte Carlo simulation.

B. Resting-state fMRI data analysis

(A) Seed-based analysis

Data were first preprocessed according to the Data Processing Assistant for Resting-State fMRI toolbox (http://www.restfmri.net) preprocessing pipeline implemented in Matlab (MathWorks, Natick, Massachusetts). Images were corrected for section timing, realigned, normalized by using the EPI template provided by SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12), and smoothed by using a 4-mm full width at half maximum (FWHM) Gaussian kernel. After normalization, to remove long-term drift and irrelevant oscillations in the signal, the data were detrended and bandpass filtered (0.01– 0.08 Hz). Nuisance covariates, including head-motion parameters, global mean signals, WM signals, and CSF signals, were regressed out. To perform seed-based analysis, the right hippocampus seed which was used in PPI analysis was also selected to evaluate the difference in resting-state functional connectivity (RSFC) between the groups. The RSFC from the right hippocampus seed was estimated and used to configure a statistical map. Two sample *t*-tests were performed on the group's statistical images with the SPM8 toolbox. The assumptions of unequal variance and independence among all groups were made on the *t*-tests. All statistical analyses were corrected for multiple comparisons based on Monte Carlo simulation corresponding to an alpha level of $P < .05$.[21]

(B) Independent Component Analysis (ICA) and Dual Regression

To define alterations in the RSFC patterns in well-known intrinsic connectivity networks (ICNs), data-driven ICA was conducted. Data were

preprocessed using FSL version 5.0.9 (http://www.fmrib.ox.ac.uk/fsl/). For signal stabilization, the first five volumes of each individual's functional scan were removed, yielding 204 volumes per subject for subsequent analysis. The functional images were corrected for head motion using FSL's MCFLIRT and Brain extraction (BET) was used to remove unwanted non-brain tissue. Then, the functional images were smoothed with 5mm FWHM, and high-pass filtered with a cut-off frequency of 0.01 Hz. FSL's FLIRT was used to perform a boundary-based registration of functional images to subject-specific T1-weighted images and then to the MNI152 template using a 12 degrees of freedom affine transformation. Finally, the scans were resampled to 4mm voxel size.

MELODIC ICA version 3.14 was used to obtain ICNs from the preprocessed images using a temporal-concatenation spatial ICA approach.[23] To create a single 4D dataset, functional images of all participants were concatenated in the temporal domain. Then, this concatenated dataset was decomposed into 25 spatially independent components (ICs). To analyze differences between the two groups, a dual-regression was performed using the selected 10 ICs.[24] With this approach, each group component was used to generate a subject- and component-specific spatial map and an associated mean time course using two-step sequential multiple regressions. First, each group-level spatial map was used as a spatial regressor against each subject's functional images to extract a set of 25 subject-specific time courses corresponding to each group-level IC. Then, each subject-specific time course was variance-normalized and used as a temporal regressor against each subject's functional images to obtain subject-specific spatial maps for each of the 25 ICs.

To select the ICNs of interest, each of the 25 extracted components was spatially correlated with 10 resting-state ICN templates reported in a previous study.[25] Among the 13 group ICs which showed high spatial correspondence ($r > 0.4$) with the 10 ICN templates, 10 group ICs were confirmed by visual inspection of the templates.[25]

To evaluate group differences within the 10 ICNs of interest, the subjects' regression maps for each ICN of interest were compared using a voxel-wise general linear model. To do this, non-parametric permutation testing (5,000 permutations) with Threshold-Free Cluster Enhancement (TFCE) for multiple comparison corrections using FSL's nonparametric permutation testing tool was used and a TFCE-corrected $P < 0.05$ was considered significant.

C. Cortical thickness analysis

Structural MRI data were analyzed to explore cortical thickness and cortical volume using Freesurfer (version 5.3.0, http://surfer.nmr.mgh.harvard.edu), as previously published [30]. After normalization of image intensity variations due to magnetic field inhomogeneities, the skull was removed from the normalized image. Then, an estimate of the GM/WM boundary was constructed by classifying all WM voxels in the MRI volume. The surface of the WM voxels was refined to obtain better accuracy in the GM/WM boundary and then subsequently deformed outward to find the pial surface, according to methods explained by Fischl and Dale [33]. The surface deformation was based on a local adaptive estimation of the MRI values at different surfaces by minimizing the constrained energy function. Cortical thickness estimates were then obtained with the shortest

distance between the WM and the pial surface at each location in the brain. Statistical maps were generated using Freesurfer's QDEC 1.5 (Query, Design, Estimate, Contrast) application. QDEC fitted a general linear model (GLM) at each surface vertex to explain the data from all subjects in the study. The results were obtained with a FWHM (full-width/half max) of 10 mm. Significant differences were considered for clusters with a P value < 0.05 with correction for multiple comparisons using Monte Carlo Simulation. The results were visualized in inflated surfaces for better visualization of sulcal regions while maintaining topology. Freesurfer has the capability to parcellate the cerebral cortex based on arbitrary maps defined on a standard template. For this analysis, the Desikan-Killiany cortical atlas that parcellates the cerebral cortex into 34 cortical regions per hemisphere was used.

9. Statistical analysis

Clinical characteristics and neuropsychological data were compared between the two groups. The Kolmogorov-Smirnov test was used to determine whether data were normally distributed. Accordingly, data that had normal distribution were presented as means ± SDs, and quantitative variables were compared by using a two sample *t*-test. Otherwise, for comparing quantitative values, data were presented as medians with ranges and the Mann-Whitney *U*-test was used. Qualitative data were analyzed by using the χ^2 test or Fisher's exact test when appropriate. Two-tailed Spearman correlation analyses were performed to assess the relationship between PM accuracy and clinical and imaging results which either showed significant differences between the groups or were suggested to be related to PM performance (e.g., depressive symptoms).

A univariate generalized linear model analysis was performed to evaluate the association between PM accuracy and the significantly correlated variables in the above-mentioned Spearman correlation analysis. Then, a multivariate generalized linear model was used to identify independent factors for PM accuracy. Variables significantly associated with PM accuracy in the univariate model ($P < .05$), other variables of interest (e.g., depressive symptoms and serum levels of estradiol), and possible confounding factors (e.g., age and duration of education) were included in the multivariate model. Statistical analyses were performed by using SPSS, Version 19.0 (IBM, Armonk, New York), and a 2-tailed $P < .05$ was considered significant.

III. RESULTS

1. Participant characteristics

Initially, 25 women were recruited for the Postpartum group and 30 women were recruited for the Control group. Among the Control group, one participant was excluded due to excessive imaging artifacts, two were excluded due to movements exceeding a prior maximum movement of 2 mm, and one was excluded due to an incidentally found old infarct. No participant in the Postpartum group was excluded. Therefore, 25 women in the Postpartum group and 26 women in the Control group were included for final analysis. The demographic and clinical data of the participants are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the participants

	Control group (n=26)	Postpartum group (n=25)	*P* value
Demographic characteristics			
Age (y)	29.8 ± 4.0	30.9 ± 3.0	.267
Duration of education (y)	19 (16-19)	16 (16-19)	.160
Married	6 (23.1%)	25 (100%)	<.001
Normal delivery / C-sec	N/A	17/8	N/A
Interval between MRI scan and delivery date (d)	N/A	103.7 ± 16.2	N/A
Self-report questionnaires			
Number of awakenings	0.0 (0.0-0.0)	1.5 (0.0-2.0)	<.001
Total sleep time per day (h)	6.0 (6.0-6.8)	6.8 (6.0-8.0)	.084
Lack of sleep	4.5 (2.0-7.0)	5.0 (3.0-6.0)	.681
EPDS	6.1 ± 4.0	7.3 ± 5.6	.446
BDI	6.2 ± 5.6	9.0 ± 6.0	.092
CFQ	27.5 ± 9.3	34.9 ± 12.9	.021
Hormone assays			
Estradiol (pg/mL)	87.0 (52.0-201.0)	40.0 (24.8-65.5)	.004
Progesterone (ng/mL)	1.0 (0.6-5.4)	0.3 (0.3-0.6)	.012
LH (mIU/mL)	6.1 (3.5-13.6)	5.2 (3.4-6.2)	.166
FSH (mIU/mL)	6.6 (3.8-8.5)	7.3 (6.1-9.2)	.228
Prolactin (ng/mL)	12.6 (9.3-16.6)	16.7 (7.0-42.9)	.197
Oxytocin (uIU/mL)	94.9 ± 27.8	116.6 ± 85.0	.434
Cortisol (μg/dL)	9.8 ± 3.9	7.3 ± 3.2	.095
Neuropsychological tests			
COWAT (Animal)	21.0 ±4.0	20.5 ± 5.8	.725
15-item K-BNT	14.5 (14.0-15.0)	14.5 (14.0-15.0)	.573
Digit span forward	15.0 (14.0-16.0)	14.0 (13.0-15.0)	.127
Digit span backward	12.4 ± 2.8	11.6 ± 2.8	.269
Digit span sequencing	9.5 ± 2.2	8.0 ± 2.5	.033
Word List Memory	25.9 ± 2.9	24.9 ± 3.6	.281
Word List Recall	90.0 (89.0-100.0)	100.0 (90.0-100.0)	.141
Word List Recognition	10.0 (10.0-10.0)	10.0 (10.0-10.0)	.579
TMT_A	20.0 (19.0-23.0)	20.0 (17.8-28.0)	.962
TMT_B	62.3 ± 26.7	54.1 ± 22.4	.242

Values that have normal distribution are expressed as means; otherwise, values are expressed as medians (interquartile range).

BDI, Beck Depression Inventory; CFQ, Cognitive Failure Questionnaire; COWAT, Controlled Oral Word Association test; EPDS, Edinburgh Postnatal Depression Scale; FSH, follicle-stimulating hormone; 15-item K-BNT, 15-item Korean version of the modified Boston Naming Test; LH, luteinizing hormone; and TMT, Trail Making Test.

There was no significant difference in age and duration of education between the two groups. Compared with the Control group, the Postpartum

group showed significantly higher scores in CFQ (34.9 ± 12.9 vs. 27.5 ± 9.3, P = .021), which means severer subjective cognitive decline. Although the Postpartum group tended to sleep longer per day (6.8 vs. 6.0 hours, P = .084), they awakened more frequently during the night (1.5 vs. 0, P < .001) than the Control group and no difference was found in the self-rated scale on lack of sleep. The degree of depressive symptoms also showed no significant differences between the two groups. The Postpartum group exhibited poorer performance only in the digit span sequencing test compared with the Control group (8.0 ± 2.5 vs. 9.5 ± 2.2, P = .033). The results for the other cognitive assessment tests did not differ between the two groups. The serum levels of estradiol (40.0 vs. 87.0 pg/ml, P = .004) and progesterone (0.3 vs. 1.0 ng/ml, P = .012) were significantly lower in the Postpartum group. No other hormones showed significant differences between the two groups.

2. PM task behavioral performance

All participants successfully performed PM tasks for nearly all the trials, as measured by the proportion of correct responses (mean=.95, standard deviation=.05). The summary of correct responses and errors in the prospective memory task are presented in Table 2.

Table 2. Correct responses and errors in the PM task

	PM Block						CTRL Block		
	PM trial			PM ongoing trial			CTRL ongoing trial		
	Control	PP	*P* value	Control	PP	*P* value	Control	PP	*P* value
Correct response	31.0 (30.0-32.0)	29.0 (26.8-31.0)	.003	32.0 (31.0-32.0)	31.0 (29.0-31.3)	.033	63.0 (62.0-64.0)	62.0 (61.0-64.0)	.107
Type of error									
Wrong	-	-	-	0.0 (0.0-1.0)	1.0 (0.8-3.0)	.033	1.0 (0.0-2.0)	2.0 (0.0-3.0)	.107
Omission	1.0 (0.0-0.2)	3.0 (1.0-5.3)	.003				-	-	-
Commission	-	-	-	0.0 (0.0-0.0)	0.0 (0.0-1.0)	.361	-	-	-
Reaction time (ms)	1248.0 ± 250.4	1460.7 ± 243.9	.003	1829.8 ± 332.4	1948.3 ± 278.9	.175	1132.8 ± 220.6	1248.6 ± 213.2	.063

PP, postpartum group

Compared to the Control group, the Postpartum group showed poorer performance in tasks requiring delayed intention. The Postpartum group gave fewer correct answers (P = 0.003) and had more omission errors (P = 0.003) with longer reaction times (P = 0.003) in the PM trials, and fewer correct answers (P = 0.033) and more wrong errors (P = 0.033) in the PM ongoing trials. No significant differences were observed in the number of commission errors and reaction times in the PM ongoing trials. Although, there were no significant differences in performance at all in the CTRL ongoing trials, the Postpartum group tended to need more time to perform the CTRL ongoing trials (P = 0.063).

3. PM task-based fMRI Results

A. Main effect of task

In block design analysis, clusters in the bilateral rostrolateral prefrontal cortex (rlPFC), superior medial frontal gyrus, and lateral parietal cortex, areas which have been known to be associated with PM,[26] were found for the main effect of "task" with contrast between the PM block and CTRL block (FWE-corrected $P < .05$; Fig. 2A and Table 3).

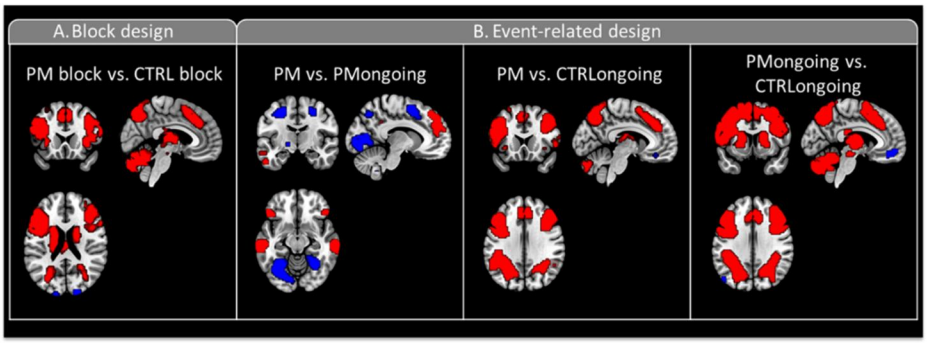

Figure 2. Main effect of tasks across all participants (FWE-corrected $P < .05$). (A) Block design analysis. Red clusters indicate increased activation, while blue clusters indicate decreased activation in the PM block compared to the CTRL block. (B) Event-related design analysis. Red clusters indicate increased activation, while blue clusters indicate decreased activation in the PM trials compared to the PM ongoing trials, the PM trials compared to the CTRL ongoing trials, and the PM ongoing trials compared to the CTRL ongoing trials, respectively. Images are oriented according to neurological convention (right is right).

Table 3. Significant regions for the main effect of the task

Design	Contrast	Region	Side	MNI coordinates			Maximum *t*	No. of voxels	*P* value
				x	y	z			
Block	PM block > CTRL block	Inferior parietal lobule	left	-33	-55	37	11.06	3341	< .001
		Frontal inferior operculum	left	-48	8	28	9.37	3425	< .001
		Supplementary motor area/superior medial frontal gyrus	left	-3	17	49	8.46	555	< .001
		Frontal inferior operculum	right	42	32	28	8.12	1208	< .001
		Cerebellum	right	9	-73	-32	7.55	2217	< .001
		Inferior temporal gyrus	left	-45	-55	-11	5.33	35	< .001
		Cerebellum	left	-21	-40	-44	4.97	6	< .001
	PM block < CTRL block	Superior occipital gyrus	right	18	-100	16	6.62	75	< .001
		Middle occipital gyrus	left	-15	-100	13	5.88	44	< .001
Event-related	PM > PMongoing	Middle temporal gyrus	left	-54	-58	34	8.74	362	< .001
		Angular gyrus	right	57	-55	37	7.21	165	< .001
		Middle temporal gyrus	left	-63	-25	-11	7	200	< .001
		Middle temporal gyrus	right	69	-31	-11	6.94	155	< .001
		Postcentral gyrus	left	-45	-28	61	6.58	86	< .001
		Superiomedial frontal gyrus	left	-6	47	25	6.21	393	< .001
		Inferior temporal gyrus	left	-54	-1	-35	6.06	55	< .001
		Orbitoinferior frontal gyrus	right	45	29	-14	5.38	36	< .001
		Orbitoinferior frontal gyrus	left	-48	32	-14	5.31	62	< .001
		Inferior temporal gyrus	right	54	-4	-35	4.91	6	< .001
	PM < PMongoing	Supplementary motor area	left	-24	-4	52	9.1	672	< .001
		Middle frontal gyrus	right	24	-1	49	8.8	271	< .001
		Lingual gyrus	right	27	-55	-8	7.07	1616	< .001
		Superior parietal gyrus	right	18	-70	46	6.18	155	< .001
		Vermis		0	-55	-38	6.13	67	< .001
		Insula	right	33	20	7	5.88	121	< .001

	Precentral gyrus	left	-57	8	28	5.84	95	< .001
	Superior parietal gyrus	left	-15	-67	46	5.75	75	< .001
	Putamen	left	-21	8	1	5.55	34	< .001
	Inferior frontal operculum	right	45	8	28	5.41	24	< .001
	Supramarginal gyrus	right	39	-40	43	5.33	49	< .001
	Cerebellum	left	-15	-55	-50	5.03	7	< .001
	Middle frontal gyrus	left	-39	59	16	4.98	10	< .001
	Inferior parietal gyrus	left	-42	-40	43	4.97	17	< .001
	Inferior frontal triangularis	left	-51	29	25	4.73	9	< .001
PM > CTRLongoing	Inferior parietal gyrus	left	-33	-58	40	10.33	2861	< .001
	Inferior frontal operculum	right	42	29	31	7.54	714	< .001
	Orbitomedial frontal gyrus	left	-45	20	28	7.49	2147	< .001
	Superior medial frontal gyrus		0	38	34	7.46	470	< .001
	Cerebellum	right	9	-76	-32	6.83	771	< .001
	Inferior temporal gyrus	left	-63	-25	-14	5.94	170	< .001
	Orbitomiddle frontal gyrus	right	48	38	-20	5.7	38	< .001
	Inferior temporal gyrus	right	63	-22	-17	5.7	131	< .001
	Caudate	right	21	-1	22	5.36	81	< .001
	Cerebellum	left	-39	-67	-35	5.35	66	< .001
	Inferior temporal gyrus	left	-51	-49	-14	5.26	21	< .001
	Insula	right	33	23	-5	5.14	22	< .001
	Insula	left	-33	23	-5	5.06	13	< .001
	Middle frontal gyrus	right	30	56	13	5.05	14	< .001
	Inferior frontal triangularis	right	54	20	-2	4.87	27	< .001
	Vermis	right	3	-58	-29	4.84	9	< .001
	Vermis		0	-61	-17	4.7	2	< .001
	Inferior occipital gyrus	left	-33	-91	-11	4.63	2	< .001
	Supramarginal gyrus	left	-60	-22	19	4.6	3	< .001
PM < CTRLongoing	Rectus gyrus	left	-12	35	-17	5.3	10	< .001
	Middle occipital gyrus	left	-18	-97	13	5.23	29	< .001
	Superior occipital gyrus	right	18	-97	16	4.62	1	< .001
PMongoing > CTRLongoing	Inferior parietal lobule	left	-30	-58	40	12.63	7486	< .001

	Supplementary motor area/superior medial frontal gyrus	left	-6	8	55	10.7	7762	< .001
PMongoing < CTRLongoing	Rectus gyrus	left	-12	35	-17	5.56	79	< .001
	Superior frontal gyrus	left	-18	41	52	5.11	9	< .001
	Anterior cingulum	right	6	35	-8	4.71	3	< .001

To further assess the main effect of the "task" with each contrast between the PM trials, PM ongoing trials, and CTRL ongoing trials, an event-related design analysis was performed. Compared to the CTRL ongoing trials, both the PM and PM ongoing trials had higher BOLD activity in the bilateral rlPFC, dorsolateral prefrontal cortex (dlPFC), lateral parietal cortex, superior medial frontal gyrus/anterior cingulum, anterior insula, and putamen. The PM ongoing trials showed lower BOLD activity in the rostromedial PFC (rmPFC) compared to the CTRL ongoing trials. In a direct comparison between the PM and PM ongoing trials, the PM trials showed higher activity in the bilateral orbitofrontal gyri, temporal lobe, and anterior cingulum/rmPFC, while showing lower activity in the bilateral dlPFC, lateral parietal cortex, putamen, anterior cingulum, and cuneus (FWE-corrected $P < .05$; Fig. 2B and Table 3).

B. Interaction of group x task

In the block design analysis, the right hippocampus and bilateral superior temporal gyri showed significant group x task interaction. Percent signal changes for the clusters which had significant interaction revealed that the interaction was based on a significant percent signal increase in the PM block in the Control group, while there was no significant change in the Postpartum group (Fig. 3A and Table 4).

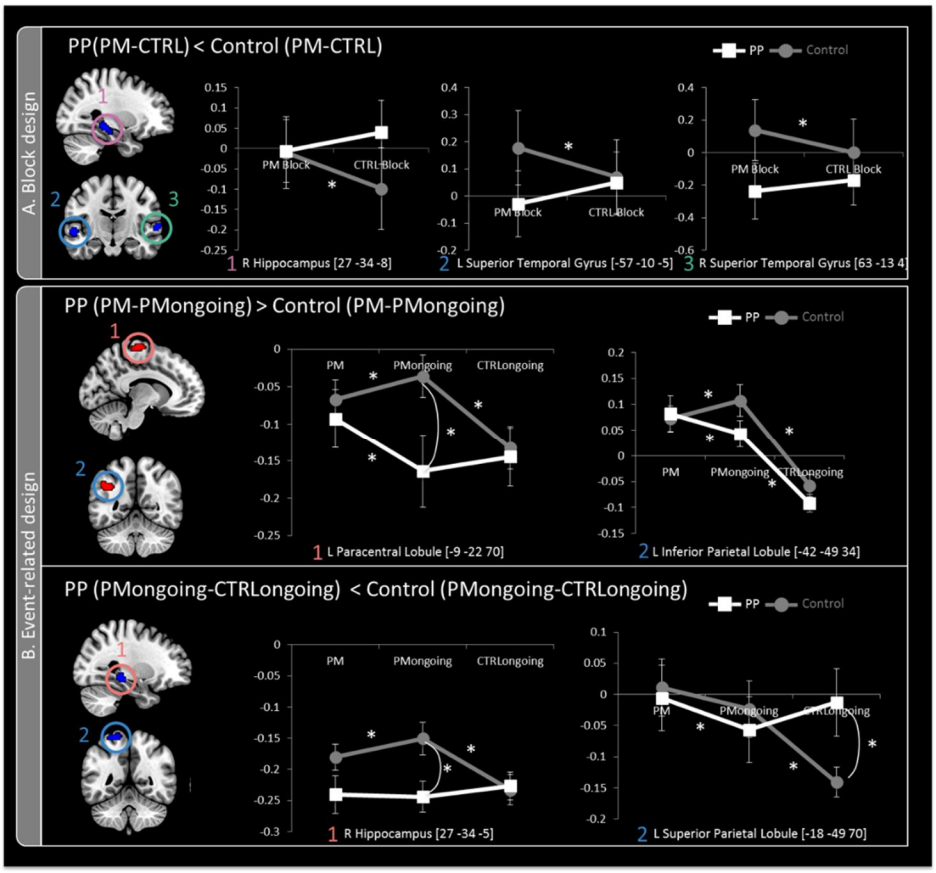

Figure 3. Group x task interaction. Clusters which had significant interaction and percent signal changes extracted from the clusters according to the trial. (A) Block design analysis. (B) Event-related design analysis. PP, Postpartum group. Images are oriented according to neurological convention (right is right).

Table 4. Significant regions for group x task interaction

Design	Contrast	Region	Side	MNI coordinates			Maximum *t*	No. of voxels	*P* value
				x	y	z			
Block	PP (PM-CTRL) < Control (PM-CTRL)	Superior temporal gyrus	left	-57	-10	-5	3.19	69	.001
		Hippocampus	right	27	-34	-8	3.13	28	.001
		Superiror temporal gyrus	right	63	-13	4	2.95	25	.002
Event-related	PP (PM-PMongoing) > Control (PM-PMongoing)	Supramarginal gyrus	left	-42	-49	34	3.52	74	< .001
		Paracentral lobule	left	-9	-22	70	3.45	38	< .001
	PP (PM-CTRLongoing) > Control (PM-CTRLongoing)	Superior occipital gyrus	left	-27	-82	46	3.14	32	.001
	PP (PMongoing-CTRLongoing) < Control (PMongoing-CTRLongoing)	Superior parietal lobule	left	-18	-49	70	3.18	35	.001
		Hippocampus	right	27	-34	-5	3.1	26	.001

PP, postpartum group

In the event-related analysis, four clusters were found for the group x task interactions. The Postpartum group showed lesser increase in BOLD activity in the right hippocampus and left precuneus in the PM ongoing trials compared to the CTRL ongoing trials. In contrast, the Postpartum group demonstrated greater increase in BOLD activity in the left IPL and right paracentral lobule in the PM trials compared to the PM ongoing trials. The percent signal change for the clusters, except for the left precuneus, revealed that interaction was based on the lower BOLD activity in the PM ongoing trials in the Postpartum group compared to the Control group. The percent signal change for the left precuneus revealed that the interaction was based on the higher BOLD activity in the CTRL ongoing trials in the Postpartum group compared to the Control group (Fig. 4B and Table 5).

C. PPI analysis

As right hippocampal clusters were found to be significant in group x task interactions on both block- and event-related design analyses, I considered the possibility that this region might play a critical role in the decreased PM performance observed in the Postpartum group. So, I conducted a conjunction analysis with two clusters and selected the overlapping region as a seed for PPI analysis (Fig. 4). Moreover, meta-analysis results using the Neurosynth framework (http://neurosynth.org/) which is a platform for automated meta-analysis and available via a web interface showed that this region was selectively related with PM, supporting my assumption. The Postpartum group revealed lesser increase in FC in the bilateral inferior parietal lobules (IPL), posterior cingulate cortex (PCC), and mPFC/anterior cingulate cortex (ACC) in PM trials relative to PM ongoing trials (Fig. 4 and Table 5).

The significant regions substantially overlapped with the retrieval-related ventral frontoparietal network (FPN) discussed in a recent meta-analysis study[27]. Beta estimates, representing the strength of FC with the hippocampus seed, were extracted from the four main clusters included in this network (PCC, mPFC/ACC, right and left IPLs), and this revealed that the interaction was based on a significant decrease in FC in the PM trials compared with the PM ongoing trials in the Postpartum group (P <.001), while there was a significant increase in FC in the PM trials compared with the PM ongoing trials in the Control group (P = .005). In PM trials relative to CTRL ongoing trials, the Postpartum group showed lesser increase in FC mainly in the occipital and temporal areas. However, in PM ongoing trials relative to CTRL ongoing trials, the Postpartum group showed an increase in FC in ventromedial PFC (Table 5).

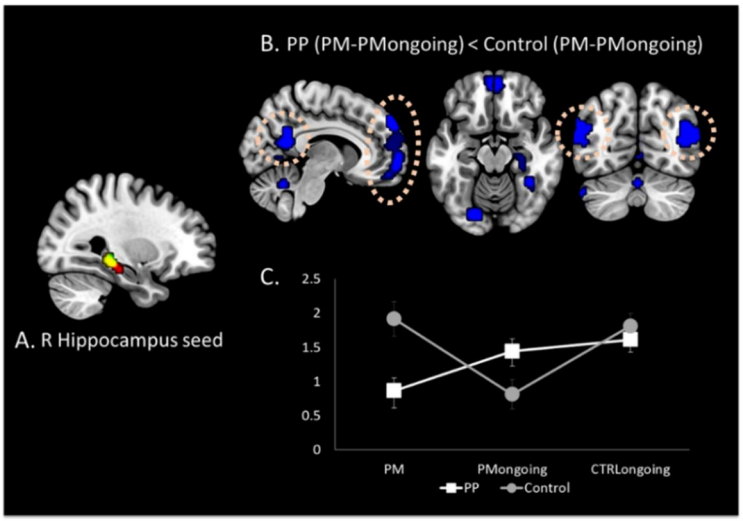

Figure 4. PM task-based FC analysis using the right hippocampus seed. (A) Right hippocampus seed (yellow cluster) which is a conjunction overlapping area between significant clusters with group x task interactions on block- (red cluster) and event- related (green cluster) design analyses. (B) Clusters showing lesser increase in FC in PM trials relative to PM ongoing trials in the Postpartum group. (C) Changes in beta estimates extracted from the four main clusters (dotted circle in (B); right and left inferior parietal lobules, medial prefrontal cortex/anterior cingulate cortex, and posterior cingulate cortex) according to the trial.

Table 5. Significant group x task interaction regions for PPI analysis

Contrast	Region	Side	MNI coordinates			Maximum t	No. of voxels	*P* value
			x	y	z			
PP (PM-PMongoing) < Control (PM-PMongoing)	Superior occipital gyrus	left	-36	-97	16	4.47	369	< .001
	Superior medial frontal gyrus		0	59	-11	4.41	582	< .001
	Superior temporal gyrus	right	45	-64	25	4.02	172	< .001
	Cerebellum	left	-12	-73	-35	3.52	115	< .001
	Precuneus	right	9	-52	16	3.50	120	< .001
	Hippocampus	right	21	-22	-8	3.41	56	< .001
	Inferior parietal lobule	right	30	-40	52	3.40	96	< .001
	Fusiform gyrus	right	36	-46	-14	3.32	28	.001
	Cerebellum	left	-48	-61	-47	3.30	34	.001
	Cerebellum	left	-18	-79	-17	3.23	78	.001
	Middle occipital gyrus	right	27	-88	34	3.07	45	.001
PP (PM-CTRLongoing) < Control (PM-CTRLongoing)	Middle occipital gyrus	left	-48	-85	16	3.99	472	< .001
	Middle temporal pole	left	-30	5	-38	3.77	51	< .001
	Middle frontal gyrus	right	48	-7	58	3.54	40	< .001
	Vernis		0	-58	-50	3.39	40	< .001
	Lingual gyrus	right	15	-58	-2	3.29	77	.001
	Inferior temporal gyrus	left	-51	-1	-32	3.17	30	.001
	Superior frontal gyrus	right	24	-13	67	3.04	27	.001
	Middle temporal gyrus	right	51	-67	16	2.98	29	.002
PP (PMongoing-CTRLongoing) > Control (PMongoing-CTRLongoing)	Rectus gyrus	left	-3	53	-23	3.33	42	.001

PP, postpartum group

4. Resting-state fMRI results

A. RSFC analysis using the right hippocampus as a seed

Compared with the Control group, the Postpartum group exhibited decreased RSFC in the ventromedial PFC (vmPFC) and increased RSFC in the left ventrolateal PFC (vlPFC) and right temporoparietal junction (Fig 5 and Table 6).

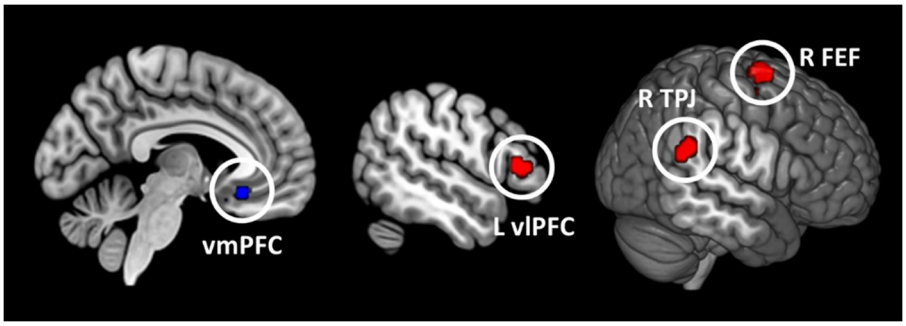

Figure 5. RSFC analysis using the right hippocampus seed. Red clusters indicate increased connectivity and the blue cluster indicates decreased connectivity in the Postpartum group compared with the Control group. vmPFC, ventromedial prefrontal cortex; L vlPFC, left ventrolateral prefrontal cortex, R TPJ, right temporo-parietal junction, and R FEF, right frontal eye field.

Table 6. Regions showing significant differences in FC when the right hippocampus was used as a seed

Contrast	Connected region	Side	MNI coordinates			Maximum t	No. of voxels	*P* value
			x	y	z			
PP > Control	Superior frontal gyrus	right	24	0	72	4.76	76	< .001
	Inferior frontal triangularis	left	-54	27	9	4.20	26	< .001
	Supramarginal gyrus	right	60	-42	27	3.19	39	.001
PP < Control	Superior frontal gyrus	left	-21	36	54	3.81	35	< .001
	Orbitomedial frontal gyrus	right	3	15	-18	3.49	32	0.001

PP, Postpartum group

B. ICA with dual regression

No significant difference was found in the FC patterns of default mode, executive control, right and left fronto-parietal, sensorimotor, visual, and auditory networks.

5. Cortical thickness results

No significant difference in cortical thickness was found between the two groups.

6. Clinical and imaging variables correlated with PM accuracy

A higher BDI score (greater depressive symptoms, ρ = -.320, *P* = .024) and a higher number of nocturnal awakenings (ρ = -.393, *P* = .005) were associated with decreased PM accuracy. Meanwhile, when FC between the right hippocampus and retrieval-related ventral FPN was stronger in PM trials compared to PM ongoing trials, the PM accuracy was higher (ρ = .306, *P* = .029). Although the BDI score was correlated with the number of nocturnal awakenings (ρ = .510, *P* < .001), no significant correlation was found between the FC of PM trials relative to PM ongoing trials and these two variables. Additionally, higher scores on the Digit span sequencing test were correlated with higher PM accuracy (ρ = .322, *P* = .021) and higher CFQ scores (greater subjective cognitive decline) tended to be higher with lower PM accuracy (ρ = -.268, *P* = .057). On the generalized linear model analysis, the number of awakenings (odds ratio [OR] = .635 [.499-.809]; *P* < .001) and FC between the right hippocampus and ventral FPN in PM trials relative to PM ongoing trials (OR = 1.346 [1.184-1.531]; *P* < .001) were independent predictors for PM

accuracy even after adjustment for age, duration of education, serum level of estradiol, and the BDI score (Table 7).

Table 7. Multivariate analyses of factors predicting PM accuracy

Variable	Odds ratio	95% CI	*P* value
Age (y)	1.039	0.981-1.101	.195
Duration of education (y)	1.014	0.911-1.130	.799
Number of awakenings	0.635	0.499-0.809	<.001
BDI	1.042	0.998-1.088	.061
Estradiol (pg/mL)	1.001	0.998-1.088	.541
PPI_PM>PM ongoing	1.219	1.014-1.464	.035

PPI_PM>PM ongoing, functional connectivity between the right hippocampus and retrieval-related ventral fronto-parietal network in PM trials compared to PM ongoing trials

IV. DISCUSSION

This is the first study to assess PM performance and its neural correlates in postpartum women who were compared with age- and education-matched nulliparous control subjects. Decreased PM performance and altered resting-state as well as PM task-related brain activity without structural brain change were found in the Postpartum group. The right hippocampus failed to show significant increase in PM-related brain activation and had decreased FC with ventral PFC in PM trials relative to PM ongoing trials in this group. Furthermore, along with the number of nocturnal awakenings, FC between the right hippocampus and ventral FPN in PM trials relative to PM ongoing trials was an independent predictor for PM performance. These findings suggest that the right hippocampus and its connectivity with ventral FPN might be the culprit neural correlates for decreased PM

performance in postpartum women.[27,28]

PM requires multi-componential cognitive ability. According to the multiprocess framework, largely two kinds of processes may support PM: top-down strategic monitoring and bottom-up spontaneous retrieval processes.[28] Top-down strategic monitoring refers to the sustained attentional control process that maintains the intention active in the mind while a person is performing other ongoing tasks[29] and that monitors the environment for intention relevant stimuli (PM cues).[30] Rostro-lateral PFC and dorsal FPN (i.e., dorsolateral PFC, precuneus, and superior parietal lobule) have been suggested to subserve these processes.[26,27,31] Sometimes, retrieval of PM intention is spontaneously and automatically triggered by certain PM cues without any efforts to keep the PM intention active. This is referred to as the bottom-up spontaneous retrieval process.[32] According to a recent meta-analysis study,[27] the ventral FPN (i.e., ventrolateral PFC, anterior and posterior cingulate cortex, inferior parietal lobule, and insula) and ventromedial aspects of rostro-lateral PFC might be neural correlates for this process.

In this study, postpartum women were found with altered activation in the right hippocampus. Although inconclusive,[18,33] the medial temporal lobe (MTL) including the hippocampus has also been suggested to be involved with the retrieval process, but is thought to be limited to a more reflexive and automatic retrieval process recruited only by particular PM cues (i.e., focal PM cues, for which required cognitive processes are similar to those required during ongoing tasks).[18,34] In the present study, as focal PM cues (i.e., both PM and ongoing tasks required judgement on the direction of the hour hand of the clock) were used, the right hippocampus might have been consequentially recruited in

the retrieval process, thereby causing group differences. There have been several studies which show that the right hippocampus, particularly its posterior portion as shown in the present study, is associated with PM. Some studies reported associations between the right hippocampus and successful prospective memory[35] and future event construction.[36] Moreover, a meta-analysis result using the Neurosynth framework (http://neurosynth.org/) showed a right hippocampal area that was selectively related to PM which was located in a very similar location to the one found in this study.

For successful PM performance, the regions relevant to each process must connect well at appropriate moments. Therefore, PPI analysis was conducted to evaluate PM-related FC patterns in each trial and decreased FC was observed between the right hippocampus and ventral FPN in PM trials relative to PM ongoing trials in the Postpartum group, while increased FC was observed in the Control group. Because intention retrieval is a more predominant process in the PM trial compared to the PM ongoing trial, FC between regions relevant to the retrieval process is expected to increase, as shown in the Control group. In contrast to the Control group, however, the Postpartum group showed decreased FC between retrieval-related regions (i.e., the right hippocampus and ventral FPN) and this might be the reason behind poor PM performance in postpartum women. Supporting this assumption, the FC between the right hippocampus and ventral FPN in PM trials relative to PM ongoing trials was an independent predictor for PM performance even after adjustment of possible confounding factors including age, duration of education, quality of sleep, serum level of estradiol, and depressive symptoms.

Taken together, the decreased PM performance in postpartum women

might be due to disturbed bottom-up spontaneous retrieval processes rather than alterations of top-down strategic monitoring processes. Individuals rely on top-down strategic monitoring and bottom-up spontaneous retrieval processes to varying extents depending on the characteristics of PM and ongoing tasks (i.e., importance and cognitive burden of PM and ongoing tasks, and salience, focality, and valence of PM cues) as well as individual factors.[28,37,38] When the PM cue is focal and salient, it can be detected without a great deal of effort and when a person is performing very important and demanding ongoing tasks, cognitive resources are not enough for sustained attentional control; thus, in these cases, individuals tend to depend more on the spontaneous retrieval process.[28,38] Postpartum women might rely more on the spontaneous retrieval process for PM due to the sudden increase in demanding ongoing tasks (i.e., taking care of their babies). Nonetheless, postpartum women are more likely to perform PM poorly in daily life because neural correlates for the retrieval process are disturbed.

The Postpartum group also showed decreased RSFC between the right hippocampus and vmPFC. The hippocampus and vmPFC have strongly connected structures. vmPFC has been suggested to contribute to the inhibitory control of interference (i.e., ongoing stimuli) and the changing of the action 'set' (i.e., from ongoing task set to PM task set) when the hippocampus signals the need to alter the active working 'set'.[39] Maintaining a critical balance between internal intention and external ongoing stimuli by changing action mode is requisite for successful performance of PM. Therefore, decreased RSFC between the right hippocampus and vmPFC might be a poor preparatory state for PM. Increased RSFC between the right hippocampus and left vlPFC, right

TPJ, and right FEF was also found in the Postpartum group. vlPFC and FEF have been associated with top-down memory and attention control in previous studies[40,41] and TPJ with identification and processing of external cues.[42] Therefore, hyper-connectivity might be a compensation mechanism to overcome decreased RSFC of the right hippocampus and vmPFC.

Several studies[13,43] suggesting an association between sleep and PM have been reported. Individuals with sleep deprivation[43] and bad sleeping habits[13] had decreased PM performances. In line with previous results, a higher number of nocturnal awakenings was an independent predictor for poor PM performance in this study. Depressive symptoms were also an important predictor of PM performance although clinically evident depressive patients were not recruited. Interestingly, participants who woke up more often during the night had more depressive symptoms. This is also in line with previous reports showing an association between disrupted sleep rhythms and depression during the postpartum period.[44,45] Accordingly, disrupted sleep rhythms during the postpartum period might contribute to subclinical depressive symptoms and decreased PM performance. Sleep disturbance is a modifiable factor, so appropriate interventions to improve quality of sleep might help postpartum women achieve better PM performance.

The serum level of estradiol was not correlated with PM performance and could not predict PM performance as well, which was not consistent with previous results showing a positive effect of estrogen on PM performance.[15] The use of different markers for estrogen might possibly explain why these previous results were discrepant with the present result. In the previous study,[15] the authors used the Index for Cumulative Estrogen Exposure, not the serum level

of estrogen which represents a brief moment in time. Other previous studies also showed no association between the serum level of estradiol and cognitive function[46] and researchers suggested that a marker which showed the cumulative exposure of estrogen across a subject's life time was better because it showed the consistent effect of estrogen on cognition than the serum level of estradiol.[47]

The present study has several limitations. First, the PM task given in this study was easy and most participants successfully performed the task for nearly all trials. Therefore, brain activation patterns corresponding for error trials and correct trials could not be evaluated. Future studies with more difficult tasks are needed to define which brain regions are associated with error trials and whether postpartum women show different activation patterns in error trials compared to the control subjects. Second, only a focal event-based PM task was performed in this study and the attentional control process was not required as much as the retrieval process for this task. Lack of differences in attention control-related brain activity might result in false-negative findings. Therefore, studies using more cognitively demanding, non-focal or time-based PM tasks would be helpful to elucidate the presence of altered top-down attention control-related brain activity during PM tasks in postpartum women. Finally, a relatively crude method was used to obtain information about each participant's quality of sleep as this study primarily aimed to define neural correlates for decreased PM performance in postpartum women. However, the present results demonstrated the association between disrupted sleep rhythms and PM performance, so a future study with a more delicate and standardized approach regarding quality of sleep is warranted.

V. CONCLUSION

The present study showed decreased PM behavioral performance in postpartum women compared to nulligravid control subjects matched for age and duration of education. Decreased FC within spontaneous retrieval-related regions including the right hippocampus and ventral FPN along with disrupted sleep rhythms may contribute to poor PM performance in postpartum women.

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ABSTRACT(IN KOREAN)

출산 후 여성에서의 미래기억 능력 저하와 연관된 뇌활성화 변화

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신나영

I. 목적

미래기억이란 미래의 특정 상황에서 특정 행동을 수행하고자 하는 의도를 기억하는 능력을 말한다. 출산 후 여성의 경우, 미래기억을 저하시킬 수 있는 과도한 동시 과제, 우울감, 및 에스트로겐 저하와 같은 위험 요소가 있음에도 불구하고, 아직 해당 그룹에서의 미래기억 수행력 평가 및 관련된 뇌영역에 대한 연구가 없다. 따라서, 본 연구는 출산 기왕력이 없는 대조군과의 비교를 통해, 출산 후 여성에서의 미래기억 능력을 평가하고, 기능 및 구조적 영상을 통해 관련 뇌영역을 찾고자 하였다. 또한, 다양한 임상적 정보 획득을 통해 미래기억 능력 변화를 야기하는 인자를 밝히고자 하였다.

II. 대상 및 방법

정상 출산 후 2-4개월 사이의 20-40세 여성 25명과, 출산 기왕력이 없고 나이와 교육연수를 매칭한 26명의 대조군을 전향적으로 모집하였다. 모든 참가자는 휴지기 및 미래기억과제 기능적 자기공명영상 및 구조적 자기공명영상을 촬영하였으며 설문지, 인지기능 검사, 및 호르몬 검사를 같은 날 수행하였다.

III. 결과

출산 후 여성군은 대조군에 비해 미래기억 과제의 정확도가 유의하게 낮고, 과제 수행 시 더 오랜 시간이 걸렸다. 미래기억과제 기능적 자기공명영상 분석 결과, 우측 해마에서 대조군과는 달리 미래기억과제와 관련된 유의한 활성화 증가가 출산 후 여성에서는 관찰되지 않았다. 또한, 우측 해마 영역을 이용하여 과제관련 기능적 연결성 분석을 시행한 결과, 배측 전두-두정 네트워크와의 연결성이 미래기억 동시과제 시행 시에 비해 미래기억과제 시행 시, 출산 후 여성에서는 유의한 감소를, 반면 대조군에서는 유의한 증가를 보였다. 동일한 우측 해마영역을 이용한 휴지기 기능적 연결성 분석에서 역시 출산 후 여성에서 유의한 차이를 보였다. 배측내측전두피질과의 연결성은 감소하였으며, 배측외측전두피질, 측두두정경계, 및 전두안구영역과의 연결성은 증가하였다. 대뇌피질두께 및 해마 용적에는 유의한 그룹 간 차이는 없었다. 다변량분석 결과, 미래기억 동시과제 시행 시에 비해 미래기억과제 시행 시 우측 해마와 배측 전두-두정 네트워크와의 연결성과 수면 중 일어나는 횟수가 미래기억 수행력을 예측할 수 있는 인자였다.

IV. 결론

출산 후 여성에서 미래기억과제 수행력이 유의하게 저하되며, 이는 해마와 배측 전두-두정 네트워크를 포함하는 미래기억 의도의 자발적으로 회상과 관련된 영역간의 뇌연결성 변화 및 수면 질 저하에 기인한 것이다.

핵심되는 말 : 출산 후, 미래기억, 기능적 자기공명영상, 구조적 자기공명영상