이학석사학위논문

Neural response to stimulus repetition in the rat perirhinal and postrhinal cortex

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Abstract

It has been suggested that the perirhinal and postrhinal cortex plays key roles in recognition memory. A possible neural mechanism for the recognition memory is phenomenon called repetition suppression, which refers to decremental change in the response of neuron when a stimulus is repeated. Monkey studies have found a proportion of perirhinal cortex neurons that changed with changes in stimulus familiarity. However, there were few comparable studies in rodent literature. Furthermore, there has been a conflict between existing rat physiological studies. For this reason, recordings of single neuronal activity were made from the perirhinal and postrhinal cortex of rats while performing object cued response selection (OCRS) task. The neural responsiveness to familiar and unfamiliar stimuli were compared in each regions. The postrhinal cortex neurons show a large proportion of (79%) decremental response change across multiple repetition of familiar stimulus and greater decremental response change when unfamiliar stimulus was repeated between the first trial and subsequent trial, but no such response changes were found in the perirhinal cortex. When the learning state of animals were accounted for neural response changes, both perirhinal and postrhinal cortex show a greater decremental response to the

unfamiliar stimulus during learned state than during acquisition phase. This result suggests that both perirhinal and postrhinal cortex process relative familiarity of unfamiliar stimulus, but not of highly familiar stimulus, only when the rat successfully acquired recognition memory. This finding is the first to show decremental neural response changes in the perirhinal and postrhinal cortex that were modulated by object-response associative recognition memory in rodents.

Keyword : Object recognition, associative recognition memory , perirhinal cortex, postrhinal cortex, familiarity.
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Chapter 1. Introduction

1.1. Study Background

The medial temporal lobe, which includes the hippocampus, perirhinal and postrhinal cortex, has been known for its involvement in memory since the memory deficit was reported from the case study of patient HM (Scovile and Milner,1957). HM surgically removed parts of the medial temporal lobe bilaterally to relieve intractable epileptic seizures. HM suffered from both severe retrograde and anterograde amnesia. While the damage to hippocampus identified as critical lesion responsible for the memory loss, little was known about the perirhinal cortex and its role in recognition memory until 1980s (Zola-Morgan et al., 1989).

Mishkin (1978) was one of the first researchers to replicate the HM's lesion in monkeys to produce animal model of amnesia. Initially, Mishkin reported that the major deficit was found only when the combined lesion of the hippocampus and the amygdala was made, but the recognition memory was relatively spared when the lesion was made only to the hippocampus or to the amygdala alone (Mishkin, 1978). However, subsequent studies refuted the initial report and demonstrated that the memory deficit observed after extensive medial temporal lobe lesions was due to damage to regions adjacent to the hippocampus rather than to the hippocampus and amygdala.

Particularly, the damage to the perirhinal cortex produced major impairment in recognition memory (Zola-Morgan et al., 1989; Meunier et al, 1993; Suzuki et al., 1993). Also, animals with lesion to the hippocampus, but with spared perirhinal cortex did not show memory deficit (Aggleton and Brown, 1999). Similar observations were found in rat recognition memory literature. Object recognition memory in rat was severely impaired following perirhinal lesions or inactivation (Mumby et al., 1994; Ennaceur et al. 1996 ; Winters et al., 2004; Winters and Bussey, 2005), but only show minor deficit with hippocampal lesions (Winters et al., 2004; Forwood et al.,2005).

Based on the findings from perturbation studies of perirhinal cortex, it is strongly suggested that perirhinal cortex plays essential role in recognition memory. Although the perturbation studies were useful for establishing the necessity of perirhinal cortex for object recognition memory, those studies could not provide information about mechanisms of how this region performs such task. Findings from monkey electrophysiological studies (Brown et al., 1987; Fahy et al., 1993; Li et al., 1993; Miller et al., 1993; Miler and Desimone, 1994) revealed possible neural mechanism for recognition memory. The possible core mechanism is a phenomenon called repetition suppression. The repetition suppression refers to decremental change in the response of neuron when a stimulus is repeated.

First evidence of such neuronal response was reported when Brown et al. (1987) explored the inferomedial temporal cortex of monkeys, which also includes perirhinal cortex. A proportion of single units from the inferomedial temporal cortex shows stronger response to first presentation of the stimulus than to repeated stimulus (see figure 1), but no such response was detected in the hippocampus. Most subsequent studies are in agreement with the initial finding that a proportion repetition sensitive neurons (though not only the repetition suppression but also repetition enchantment has been reported) are highest in the perirhinal cortex and in its adjacent areas (Fahy et al., 1993; Li et al., 1993; Miller et al., 1993; Miler and Desimone, 1994). On the basis of these collective evidences from monkey electrophysiology studies, it has been proposed that such responses sensitive to the repetition of a stimulus carry critical and sufficient information to recognition memory concerning the relative familiarity and prior occurrence of particular stimulus (Brown and Xiang, 1998).

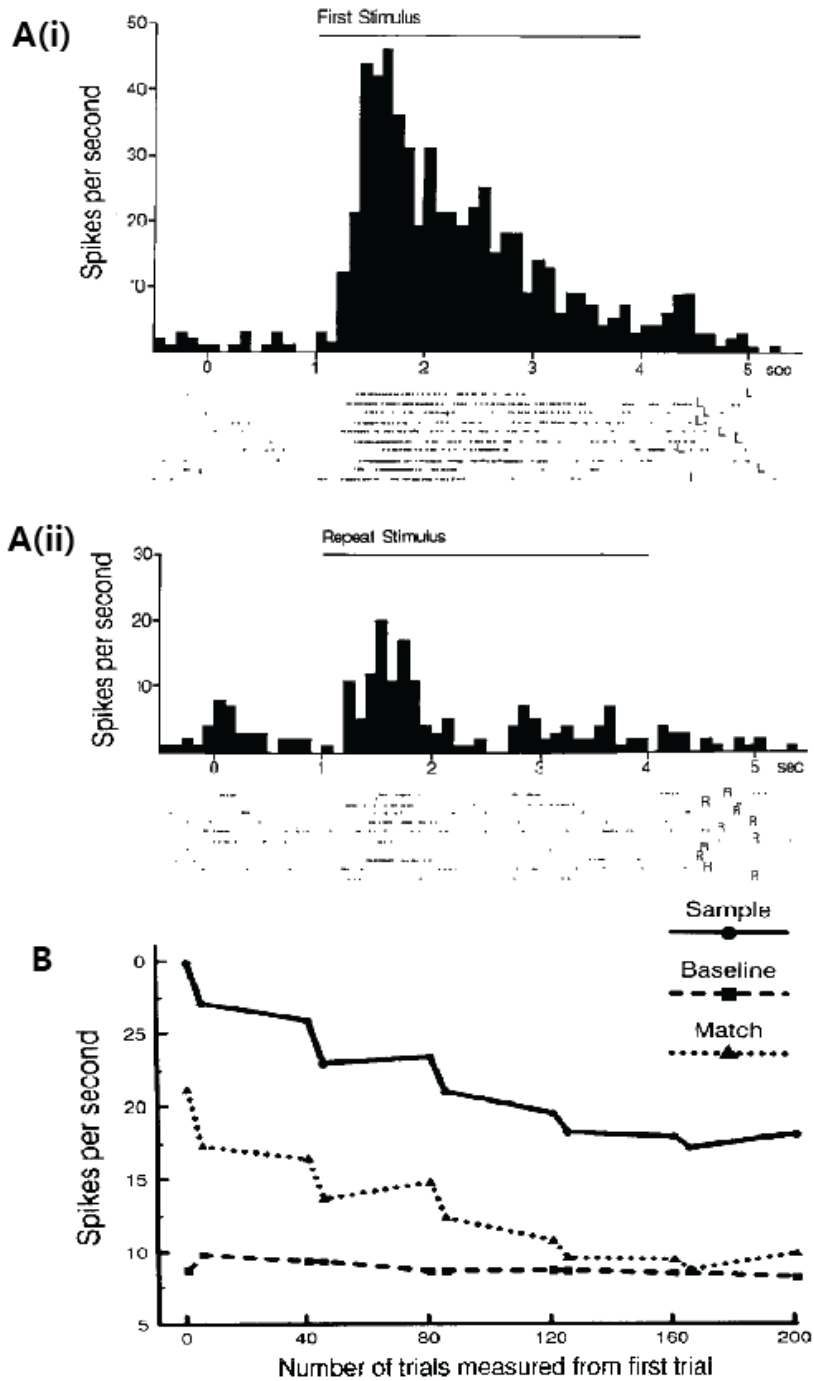

Figure 1. Examples of decremental neuronal response change. **A.** example of neuron that shows strong response to the first (i) presentation than to repeated presentation (ii). Note the smaller response for the repeated stimuli.

Adapted from Fahy et al. (1993). **B.** average neuronal response that declined significantly with increasing stimulus familiarity over the session. Adapted from Li et al. (1993)

In contrast to data concerning neurophysiology of monkey, there are only few comparable studies regarding the neuronal response change in perirhinal cortex that changes with stimulus relative familiarity in the rodent literature (Zhu and Brown, 1995; Zhu et al., 1995; Burke et al., 2012; Deshmukh et al., 2012; Roloff et al., 2016). Furthermore, there are conflicts among the existing physiological studies. While the studies using "passive-viewing' paradigm reported the presence of repetition sensitive neurons (Zhu and Brown, 1995; Zhu et al., 1995), the studies based on exploration of objects failed to find evidence of such neuronal activities in perirhinal cortex (Burke et al., 2012; Deshmukh et al., 2012). To address this issue in the rodent literature, the current study aim to investigate the neural response change to stimulus repetition in rat perirhinal cortex and its neighboring regions in recognition memory.

1.2. Purpose of Research

The main purpose of the current thesis is to investigate the presence of repetition sensitive neurons that changes with relative familiarity of stimulus in the perirhinal cortex and postrhinal cortex. All of the previous studies used either variant of passive viewing procedure (Aggleton et al.,

1999) or spontaneous object recognition (SOR) task (Ennaceur and Delacour, 1988). Both behavioral paradigm have their limitations in investigating the recognition memory. For this reason, a newly developed behavioral testing paradigm called 'object cued response selection (OCRS)' task was used to address limitations from the previous physiological studies.

In the passive viewing procedure, the rat was either head fixed in a stereotaxic frame or was required to hold its head in position, and a stimulus were presented while the rat did not have to make any response to receive reward (Zhu and Brown, 1995; Zhu et al., 1995). Since the reward was delivered in regular interval regardless of the rat's behavior, there is a possibility that the rat might not be engaged in recognition behavior at all. Unlike passive viewing paradigm, OCRS task required the rat to make a correct response selection that is associated with object or visual scene stimulus. This paradigm allows the rat to move in a more natural manner, and demands active engagement in the recognition process to receive reward. There are also several weaknesses using SOR task (Burke et al., 2012; Deshmukh et al., 2012). One weakness is that the experimenter do not have strong control over stimulus presentation. Since the rat is allowed to move freely and explore the object at its will, it is unclear when the rat initiate or stop engaging in recognition process. Another weakness is that, even though the SOR paradigm can quantitatively measure indirect performance by

calculating time the rat spent in exploration zone, it cannot yielded a direct measurement of performance. On the contrary, the OCRS paradigm is free from both issues recurring in the SOR paradigm. In OCRS task, the timing of stimulus presentation is strictly controlled by infrared light sensors, so the experimenter can have a better understanding of when the rat samples the stimulus, and since the rat is required to make correct response selection, the direct behavioral performance of recognition memory can be assessed.

In addition to introducing a new behavioral paradigm that could help solve conflicting results in rodent perirhinal cortex literature, the current study could possibly bring some insight into the role of postrhinal cortex in recognition memory. The medial temporal lobe is theorized to be organized in hierarchal manner in which the perirhinal cortex and parahippocampal (postrhinal cortex in rats) cortex provide non-spatial (ex. items, objects) and spatial (ex. spatial frame of context, scene) information to hippocampus both directly and indirectly via entorhinal cortex (Knierim et al., 2014). Although the parahippocampal gyrus has been reported to be necessary for recognition memory of locations (Nemanic et al., 2004; Bachevalier and Nemanic, 2008), there has been no electrophysiological study of postrhinal cortex concerning the recognition memory.

In present thesis, I sought to resolve the conflicting issues among the previous rat neurophysiological studies by investigating the presence of

repetition sensitive neurons that changes with relative familiarity of stimulus in perirhinal and postrhinal cortex. Single unit activities from the perirhinal and postrhinal cortex were recorded simultaneously while the rat performed OCRS task, a newly developed recognition memory task that could overcome several limitations posed by previous studies. Previously unexplored role of postrhinal cortex in rat recognition memory is also explored by comparing the repetition sensitive neurons between the perirhinal and postrhinal cortex

Chapter 2. Materials and Methods

2.1. Subjects

Four male Long-Evans rats (350g-450g) were used in this study. Water was available *ad libitum*, but the food was restricted to maintain the ~80% of the free-feeding weight. The animals were individually housed and maintained on a 12 h light/dark cycle, and all the experiments were conducted in the light phase of the cycle. All protocols and procedures conformed to the guidelines determined by the Institutional Animal Care and Use Committee at the Seoul National University.

2.2. Behavioral apparatus

A customized response selection jar (13 x 6 x 13cm) on a linear track (46 x 7.5 cm; 94cm above the floor) elevated 94 cm above from the floor was used in present study. The track was equipped with a guillotine door-operated start box (22 x 16 x 31 cm) at one end and the response selection jar at the other end (Figure 2). The apparatus has two food wells where the rat can receive a quarter piece of cereal (Froot Loops, Kellogg's, USA) as a reward. The bottom food well (diameter 2cm) is placed under the response jar, and can be accessed by pushing forward the jar. The upper food well (diameter with 4cm) is located 10 cm above the linear track ground, and can be accessed by standing up and poking nose into the well. Four different 3

dimensional toy object were used as stimuli (Figure 2B): Ice cream (6 x 3 x 2 cm), House (5 x 3.5 x 2.3 cm), Phone (5.5 x 3 x 1.5cm), Owl (4.2 x 3 x 2cm) shaped toys. There is an indented rectangular area (6cm x 5cm x 3cm) in front of the jar where the stimulus object can be attached. A magnet was attached to this area so the object could be attached to the jar during the task.

Two LED light bulbs are installed at left and right top corner of the area. The LED lights are turned on only during the time of the stimulus presentation. The time of stimulus presentation was controlled by activations of the optic fibers installed over the behavioral apparatus. One optic fiber sensor is installed in middle of the linear track (22cm from the start box). The activation of this optic fiber sensor triggered the onset of the object stimulus by turning on the light from the LED light bulbs. Optics sensors are also installed at the food wells. Once the rat pushed the jar or poke into the upper-wells, these optic sensors signaled the LED light to turn off. The apparatus was surrounded with black curtains to block external visual cues. The ceiling light was turned off, and the experimental room was completely dark except during the time of stimulus presentation when light from the stimulus cue was available. The luminal intensity of LED light was 0.8 lux at 24cm away from the jar.

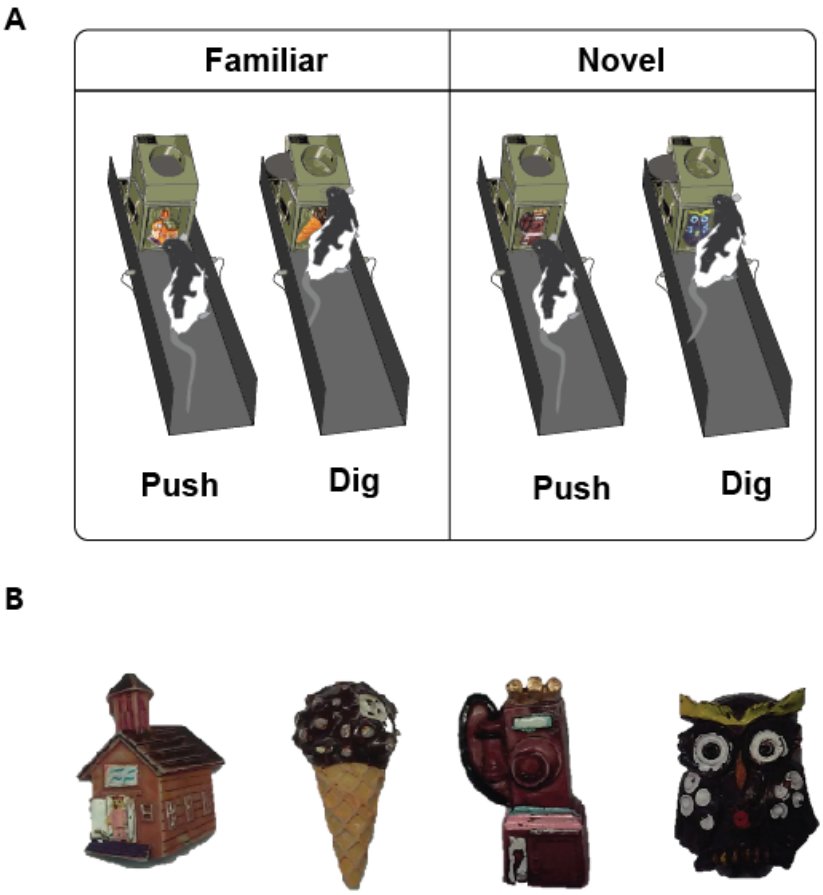

Figure 2. Object cued response selection (OCRS) task. **A.** the rat exited the start box (not shown) and travel along the track. The response selection jar was at the end of the track. An object stimulus was attached in front of the jar. The rat was required to make appropriated response associated with object stimulus (e.g., poked nose into upper food well if ice cream shaped object stimulus was presented and push forward the jar if house shaped object stimulus was presented). **B.** stimulus objects. Two objects stimuli (first two in left) were used during the pre-surgical training and four objects (two additional objects in right) stimuli were used during the main recording sessions.

2.3. Behavioral Paradigm

Handling and familiarization

Naïve rats were handled by an experimenter for 30 minutes a day for 3 days. Following the handling phase, rats were acclimated to open field exposure by allowing them to forage for multiple pieces of cereal scattered on the top of a lab cart (99 x 45 x 84 cm) for 3 days. Rats were then familiarized to the experimental room and the behavioral apparatus. During this familiarization phase, rats were allowed to freely explore the apparatus while consuming cereal pieces scattered over the track and in the food wells. Once rats consumed over 80 pieces of cereal within 30 minutes for two consecutive days, the shaping phase began.

Shaping

Once a trial started by the opening of the start box, the rat exited the start box and moved toward the jar. A quarter piece of Fruit Loop was placed in either upper or bottom food wells. Initially, the jar was located behind the bottom food well and the upper food well was open. The rat could easily obtain the reward since both food wells were wide open. The bottom food well was gradually covered by moving the jar forward, and the food well was fully covered as the rat learned to push the jar back to retrieve the reward. The rat was gently guided back to start box once it obtained the reward. The rats were trained until they were able to naturally push the jar and poke nose into upper well to obtain the reward. A daily session was finished when the rat proceeded 40 trials or when 30 minutes had passed, whichever came first.

Pre-surgical training

The rats were trained to perform object cued response selection (OCRS) task with two object stimulus during pre-surgical training phase. The experimental room was dark as the trials was started by the opening of the start box. The LED lights were turn on and the object stimulus was visible once the rat passed the optic sensor in the middle of the linear track. The food wells were fully covered. In order to obtain the reward, the rat had to make appropriate response selection associated with the object stimulus. Two object stimuli were used in this task. When the ice cream object was presented, the rat had to poke the nose into the upper-well to obtain the reward. The upper-well was automatically opened once the rat activated the optic sensor at the upper well by poking into the well. When the house object was presented the rat had to push the jar to uncover the bottom food well and obtain the reward. The responses associated with the objects were counterbalanced among rats. Thus, 2 rats were trained as the description above, but the other 2 rats were trained to push the jar when the ice cream object was presented and poke nose into upper-well when the house object was presented. A session was consisted of total of 40 trials per a day. Each stimulus appeared in a pseudo-randomized fashion for 20 trials in a daily session. Once the rats reached the performance criterion for the two objects task for two consecutive days, rats were trained with scene stimulus pair.

The data regarding scene stimulus is not included in present study. The performance criterion was greater than 80% correct responses per stimulus or greater than 75% correct responses for the overall stimuli, with a response bias of less than 0.15. The rats completed the pre-surgical OCRS (two objects) training in 7.71 days on average. The rats received hyperdrive implantation surgery after meeting the performance criterion for scene stimulus for one day.

Main recording

After recovery from the surgery, rats were behaviorally retrained in OCRS task with two objects, while the experimenter advanced the tetrodes to reach the perirhinal and postrhinal cortex. Once the experimenter deemed the tetrodes reached targeted area, rats were introduced to OCRS task with four object stimulus. Additional two objects, owl and phone shaped toys, were introduced. Same rule was applied to the newly introduced stimulus. The rat could obtain the reward by pushing the jar when phone object stimulus was presented or poke nose into the upper-well when owl object stimulus was presented. Previously taught stimulus pair (familiar pair) was presented along with newly introduced stimulus pair (unfamiliar pair) within a session in a pseudo-randomized fashion. A session terminated when the rat became exhausted and would not come out of the start box voluntarily (136.7 trials per session on average). The responses associated with the objects were

counterbalanced.

2.4. Hyperdrive Implantation

Hyperdrive

A custom-made recording drive (hyperdrive) with twenty seven tetrodes was used for electrophysiological recordings. Nichrome wires (17.8 μm diameter) were twisted and heat-bonded to make a tetrode. The final impedance of each wire was lowered to ~150 kΩ (measured in gold solution at 1 kHz with a Nano-Z) before implantation. Twenty four tetrodes were used for recordings of single units and three other tetrodes were used as reference electrodes.

Surgery

Each rat was anesthetized by an injection of Nembutal (70 mg/kg) before being placed in a stereotaxic frame. The anesthesia was maintained by isoflurane (1–3%) throughout surgery. The skull was exposed and the temporalis muscles on the right were partially retracted to place the hyperdrive as closely as possible to target area with minimal damage to unwanted cortical areas. The hyperdrive was implanted in right hemisphere of the brain, targeting the intermediate hippocampus, perirhinal and postrhinal cortex. The tetrode bundle was positioned ~6.8mm posterior to bregma, ~4.5mm-5.8mm lateral, and angled laterally at 10-15°. A hole was

drilled on the skull surface, matching the size of the diameter of the bundle tip. The drive was chronically affixed to the skull with eight anchoring screws and bone cement. All tetrodes were lowered down by ~1.6-1.9 mm immediately after the hyperdrive implantation. The rats were given 6-7 days of recovery periods before post-surgical experiments.

2.5. Electrophysiological recordings

After recovery from the surgery, individual tetrodes were lowered daily by small increments to the target regions over several days while the rat slept in a custom-built recording booth located outside the experimental room. Neural signals from tetrodes were amplified (1000~10000 times) and digitized (sampled at 32 kHz and filtered at 300~6000 Hz) using a Digital Lynx data acquisition system (Neuralynx). In the experimental room, neural signals were transferred to the data acquisition system through a slip-ring commutator (Neuralynx). For tracking the position of the animal, an array of red and green LEDs was attached to a preamplifier connected to the hyperdrive. The LED signal was captured by a digital ceiling camera and was fed to the acquisition system simultaneously via a frame grabber at 30 Hz. Spiking data from single units and position information were time-stamped and stored by the data acquisition machine for offline analyses.

2.6. Unit isolation

Single units were isolated offline using a Window based cluster-cutting software based on various parameters associated with the waveforms from four wires of a tetrode, including peak, energy, and valley (Ahn and Lee, 2015). Single units recorded from the tetrodes whose tips were located in the intermediate hippocampus, perirhinal and postrhinal cortex were only included. The isolated units were used in final analyses only if the following conditions were met: (1) proportion of the spikes within the refractory period is less than 2%, (2) average firing rate from the onset of the stimulus presentation to behavioral choice is higher than 0.5 Hz, (3) number of zero spikes trials is less than 30% of total trials and the average amplitude of single unit does not change significantly between 1st half and 2nd half of the session.

2.7. Histological verification of electrode position

Tetrode locations were histologically verified after the completion of last recording session. The positions of individual tetrodes were marked by passing small electrical current(10 μA for 10 s) through the tetrodes. The rat was killed by an overdose of CO2, and the brain was transcardially perfused with 0.1 M PBS solution followed by 4% v/v solution of formaldehyde. The brain was extracted and stored in 30% sucrose-formalin solution at 4° for approximately 24 hours. The brain was embedded in gelatin solution

afterwards. The brain was frozen and sectioned at a thickness of 30 μm using a sliding microtome. Then, brain tissues were stained with three different staining methods to clearly distinguish boarders among perirhinal cortex and its adjacent regions. Two rats were stained with only thionin solution. Three rats were stained with gold chloride solution and thionin solution. The other two rats were stained with thionin, gold chloride, and Timm's staining solution. For rats with only thionin staining, brain slices were mounted and stained with thionin for Nissl bodies. For rats with myelin and thionin staining, every first slice was stained with thionin and every second section was stained for myelin with a 0.2% buffered gold chloride solution followed by fixation (5 min) in a 2.5% sodium thiosulfate solution. For Timm's staining, a sulfide perfusate solution was circulated before the perfusion of 4% v/v formaldehyde solution. The brain was stored in 10% buffer formalin instead of 30% sucrose-formalin solution. Every first and second slices were stained thionin and myelin staining and every third section was stained with Timm's staining solution. Photomicrographs were taken, and the positions of individual tetrodes were reconstructed based on the histological data and physiological depth profiles recorded during data acquisition Boundary between perirhinal and postrhinal cortex was distinguished by the presence of angular bundle with CA1 pyramidal layers. Area posterior to caudal limits of this landmark classified as postrhinal cortex.

2.8. Data analysis

Behavioral data analysis

The performance of each rat was measured by calculating the proportion of correct trials in a session. The latency is measured by the time the rat took to make response selection from the onset stimulus presentation in each trials. The mean latency of sessions is calculated by averaging the latency of each trials in a sessions. The percent correct and mean latency for familiar and unfamiliar stimulus pair were calculated. The effects of relative familiarity on behavioral performance were tested by comparing the percent correct and mean latency of familiar and unfamiliar stimulus pair with two way ANOVA and paired-samples t-test.

The performance of unfamiliar stimulus pair was analyzed additionally in details. The performance learning curves of the unfamiliar stimulus pair were estimated based on state-space model (Smith et al., 2004; Smith et al., 2007). The behavioral performances of each session were classified into acquisition phase and learned state. The session was classified as acquisition phase if the lower confidence bound did not exceed the chance level performance at the beginning of the session, and the session was classified as learned state if the lower confidence bound reliably exceed the chance level performance across the trials.

Cell characteristic analysis

Cells are classified into interneuron and pyramidal neurons by using JMP hierarchical clustering method. Cells with spike width above 250μs are classified as putative pyramidal neurons and other cells are classified as putative interneurons. Firing pattern of the cells are categorized into busting, regular and unclassified neurons based on autocorrelograms (Barthó et al., 2004). The bursting neuron was characterized by a sharp and large peak at 3–6 ms with an exponential decay afterward. Regular spiking neurons exhibited an exponential rise from 0 to tens of milliseconds, and the maximum bin value was detected at < 35 ms in the autocorrelogram. Cells that did not meet any of these criteria were labeled as unclassified.

Repetition sensitive slope

For each trial, an event epoch was defined as period between the onset of the stimulus and the time of response choice. The mean firing rate of each trial was calculated by the number of spikes in epoch period divided by the trial latency. Only the firing rates in correct response trials were used in the analysis. The firing rates were normalized into 0 to 10 scale with maximum firing rate being 10. Three trials of the normalized firing rates of each stimulus pair were averaged into one block trial. A scatter plot showing the relationship between the normalized firing rate of cells and number of blocked trials was created. A slope was acquired by finding a linear line that best fitted into the scattered points. Correlation coefficients between the

mean normalized firing rates of blocked trials and the number of blocked trials were calculated. The correlation coefficient yielded p-value and corresponding correlation in R. Cells with significant p-value ($P<0.05$) were used for further analysis. The proportion of negative and positive slopes in each region are compared by Chi-squared test, and the mean slopes of each region were test with unpaired-samples t-test.

Neural response change to single trial repeat

The normalized firing rate (FR) in epoch period during the first and second presentation (trial) of each stimulus was calculated. Normalized firing rate difference (NFD) between 1st and 2nd presentation was calculated by following equation.

$$\mathrm{NFD} = \frac{(1\mathrm{st\ FR} - 2\mathrm{nd\ FR})}{(1\mathrm{st\ FR} + 2\mathrm{nd\ FR})}$$

The average NFDs of perirhinal and postrhinal cortex neurons in familiar and unfamiliar stimulus trials were compared with two way repeated measures of ANOVA. The responses of cells were categorized into decremental and incremental responses. The response was categorized as decremental if the second trial firing rate was smaller than first trial firing rate, and the response was categorized as incremental if the second trial firing rate was larger than first trial firing rate. The NFD of decremental and incremental responses were separately compared. A two ANOVA with region and stimulus type as independent variables was performed. The response to unfamiliar stimulus

pair was further divided with behavioral state. The neural responses during and acquisition phase and learned state were compared

Chapter 3. Results

3.1. Behavioral Performance

The overall performance of familiar object pair was significantly greater than the overall performance of unfamiliar pair ($p<0.001$, paired-samples t-test). The overall percent correct significantly increased across the sessions ($p<0.001$, repeated-measures ANOVA). The percent corrects of familiar stimulus pair object trials were above the pre-surgical criterion level (80% correct percent) from the first to last session. The percent corrects of unfamiliar stimulus pair trials gradually increased across the sessions. The performance was significantly lower than the criterion level in first two sessions ($p=0.0068$ and 0.0062, one sample t-test, one-tailed) (Figure 3A). The overall latency did not significantly changed across the sessions. The mean latency of the unfamiliar stimulus trials was significantly greater than that of familiar stimulus trials ($p=0.0112$, repeated measures ANOVA)(Figure3B).

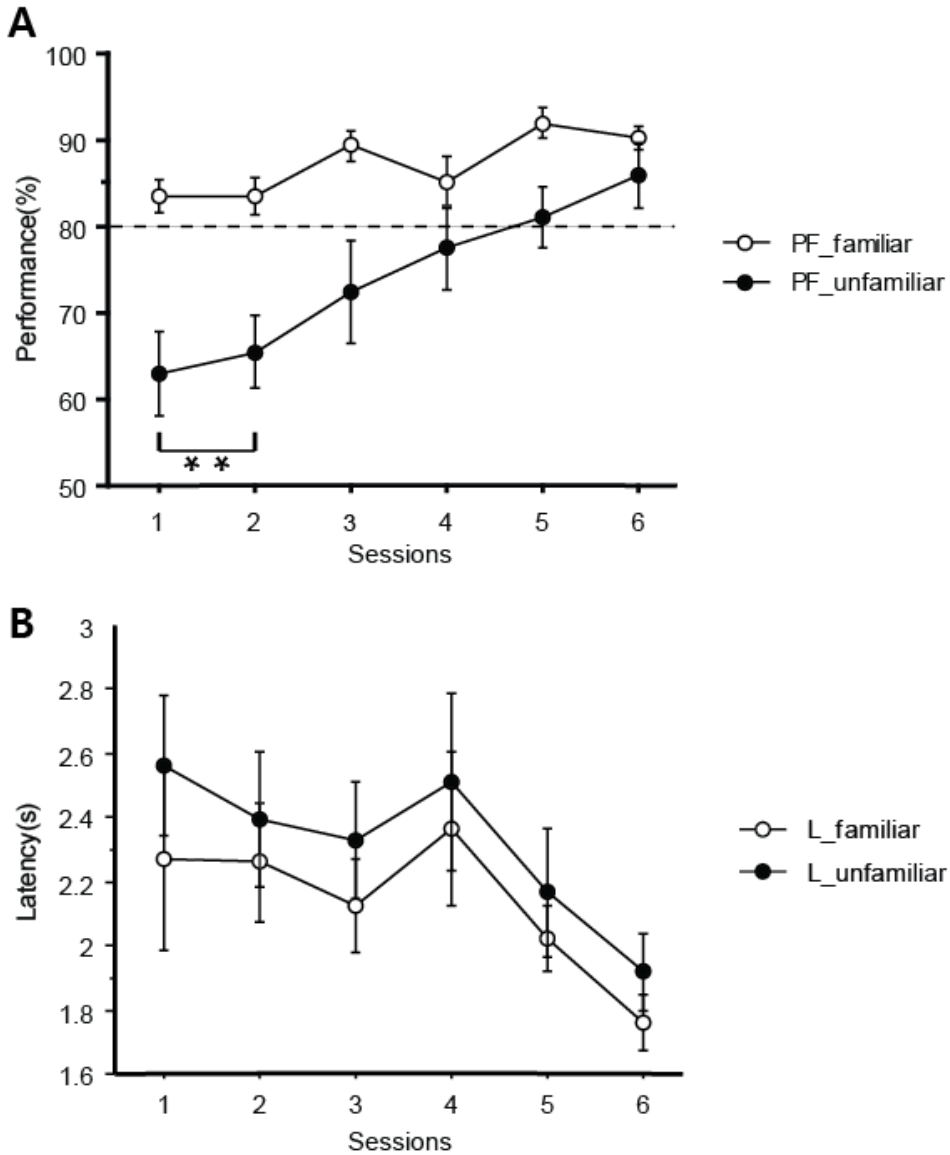

Figure 3. Behavioral Performance. **A.** Percent correct performance in OCRS with four objects across daily sessions. White open circles indicate percent correct in familiar object pair trials, and dark circles indicate percent correct in unfamiliar object pair trials. Dashed line indicates pre-surgical performance criterion for surgery (80% correctness average). The performance in familiar pair object trials are above the pre-surgical criterion from the first to last sessions. The performance in unfamiliar object pair trials significantly increased across the sessions ($p < 0.001$, repeated-

measures ANOVA). The performance of first two sessions are significantly lower than the criterion level ($p = 0.0068$ and $p = 0.0062$ one sample t-test, one tailed). $^{**}p < 0.01$. **B.** Latency by daily sessions. The mean latency in familiar object trials was significantly lower than those of unfamiliar object trials ($p = 0.0112$, repeated-measures ANOVA).

The performance graph showed that the rats reliably demonstrated associative recognition memory between correct responses and familiar stimulus pair across the sessions. The rats showed below chance level of correct percent when the unfamiliar stimulus pair were newly introduced. The rats successfully learned to recognized the unfamiliar stimulus and make correct response over the sessions. However, the error bars (standard error) at sessions 3 and 4 of unfamiliar stimulus pair were visibly larger than those of other sessions (Figure 3A). This suggested that the learning might occurred at different speed among rats. Thus, the individual rat performances of unfamiliar stimulus pair were further analyzed in details. The learning curves and their confidence intervals of individual rat in each session were estimated based on the state-space model of learning (Smith et al., 2004; Smith et al., 2007) (Figure 4). The learning states of each session were classified into acquisition phase or learned state (see Materials and Methods). As expected, the result revealed that the learning occurred at different speed among rats. Rat 344 and 389 reached the learned state on session 5 (Figure 4, upper two rows), and rat 395 and 396 reached the learned state on session 3 (Figure 4, bottom two rows). There were abrupt change in mean performance between acquisition phase and learned state at the

beginning of the session. These patterns of learning are in agreement with typical fashion of medial temporal lobe dependent learning (Eichenbaum et al., 2007).

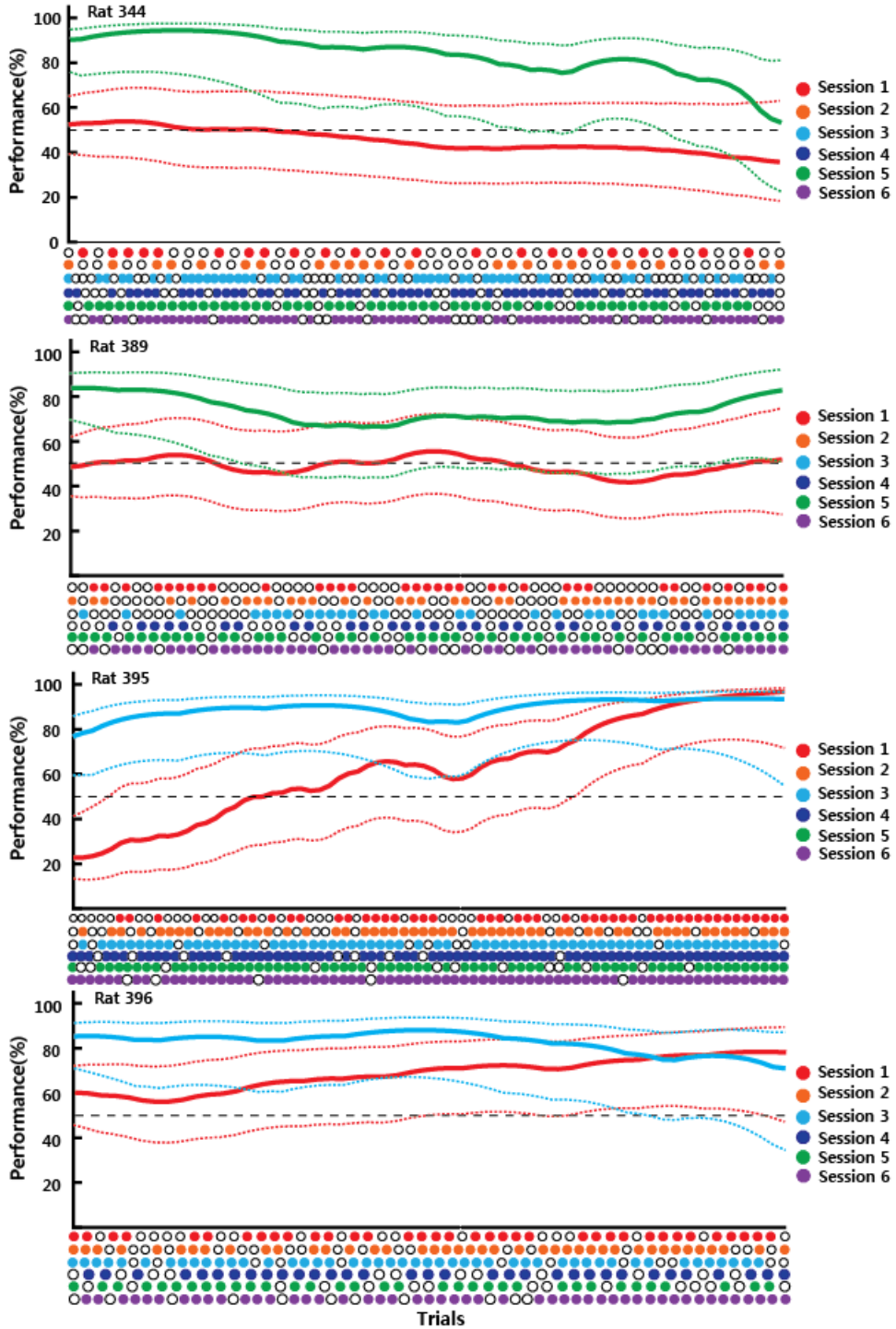

Figure 4. Individual Rat Performance for unfamiliar stimulus pair. Each graph shows Bayesian estimates of learning curves of individual rat across

the sessions. The mean learning curves are shown in solid lines, and dashed lines indicate 90% confidence intervals. Dark dashed line indicates chance level performance (50% correctness average). Under the performance graph of each rat, correct and incorrect trials are depicted as colored circles and open white circles, respectively. The behavioral performances of each session were classified into acquisition phase and learned state. The session was classified as acquisition phase if the lower confidence bound did not exceed the chance level performance at the beginning of the session, and the session was classified as learned state if the lower confidence bound exceeded the chance level performance. The learning curves of the first session and only the first learned states are shown in this figure for display purpose. Rat 344 and 389 reached the learned state on session 5, and rat 395 and 396 reached the learned state on session 3. Note the abrupt change in mean performance between acquisition phase and learned state at the beginning of the session.

3.2. Histology

The locations of recorded cells were identified by comparing the depth profile recorded during the data acquisition and the histological sections with tetrodes final tip positions (Figure 5). Total of 118 perirhinal cortex neurons and 61 postrhinal cortex neurons were recorded across the daily sessions (Table 1).

Table 1. The number of neurons recorded across days

Region	Day1	Day2	Day3	Day4	Day5	Day6	Total
PER	22	15	31	19	14	17	118
POR	9	7	8	19	10	8	61

Only the cells that met the unit-quality criteria are included.

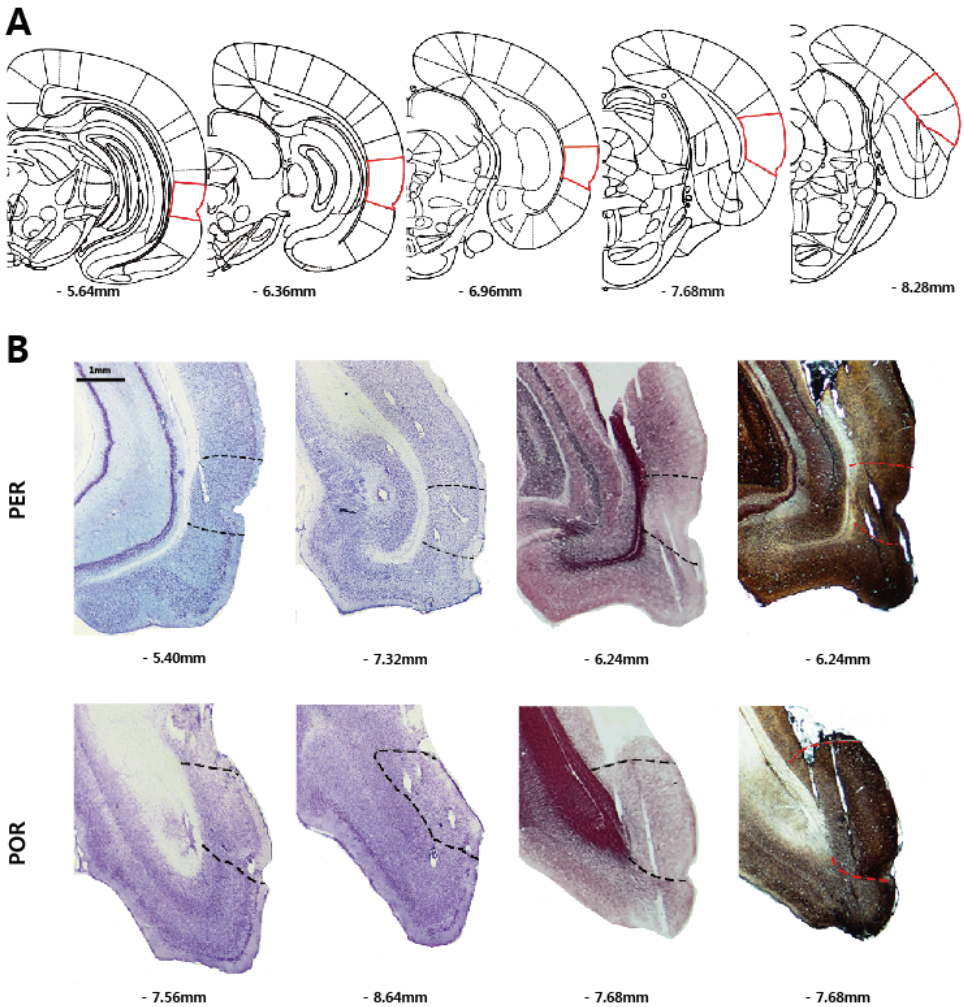

Figure 5. Histological verification of tetrode positions. **A.** schematic illustration of the tetrode positions (Paxino and Watson, 2007) targeting the perirhinal and postrhinal cortex. Regional boundaries of the perirhinal and postrhinal cortex are demarcated with solid red lines. The numbers at the bottom indicate the relative position away from the bregma. **B.** Representative histological sections with tetrode tracks. The perirhinal and postrhinal cortex was divided by the presence of angular bundle with CA1 pyramidal layers. Area posterior to caudal limits of the landmark classified as postrhinal cortex. The upper row shows sections of the perirhinal cortex and the bottom row shows those of the postrhinal cortex. First two columns show Nissl stained sections, third column shows myelin stained sections, and the fourth columns shows Timm's stained sections. Abbreviation- PER: perirhinal cortex, POR: postrhinal cortex.

3.3. Spiking properties of perirhinal and postrhinal cortex

The mean firing rate of single units in perirhinal and postrhinal cortex were 3.48 ± 0.31 Hz and 3.19 ± 0.34 Hz (mean ± SEM), respectively. The mean firing rates between two regions were not significantly different ($p = 0.55$, unpaired t-test). The cells were classified into three different types of firing pattern based on the autocorrelogram (see Materials and Methods) (Figure 6). Cells were also categorized into putative pyramidal neurons and interneurons based on spike width (see Materials and Methods) (Figure 7A). The overall composition of the firing patterns in perirhinal and postrhinal cortex were not different from each other (Figure 7B). For single units in the perirhinal cortex, 64.4% were regular spiking neurons, 14.5% were busting neurons and 21.1% were unclassified neurons. For single units in the postrhinal cortex, 62.3% were regular spiking neurons, 21.3% were busting neurons and 16.4% were unclassified neurons. The majority of neurons recorded both regions were putative pyramidal neurons. 93.2% of perirhinal cortex neurons and 88.5% of postrhinal cortex were categorized as putative pyramidal neurons. The proportion of cell types between two regions were not significantly different ($p= 0.305$, Chi square test) (Figure 7B). For the perirhinal cortex, the mean spike width of interneurons was 218.75 ±

8.069 μs (mean ± SEM), and that of the pyramidal neurons was 347.66 ± 3.59 μs (mean ± SEM). The mean firing rate of putative interneurons and pyramidal neurons were 4.48 ± 1.31 and 3.412 ± 0.32 (mean ± SEM), respectively. For the postrhinal cortex, the mean spike width of interneurons was 227.68 ± 5.76 μs (mean ± SEM), and that of the pyramidal neurons was 350.12 ± 7.17 μs (mean ± SEM). The mean firing rate of putative interneurons and pyramidal neurons were 2.45 ± 0.78 and 3.282 ± 0.37 (mean ± SEM), respectively. This result match with previous reports (Deshmukh et al., 2012; Ahn and Lee, 2015), and shows that putative interneuron in the perirhinal cortex did not exhibit high firing rate (absence of firing rate higher than 10 Hz). Similar to putative interneuron in perirhinal cortex, putative interneurons in postrhinal cortex also were in absence of high firing rate (Figure 7A).

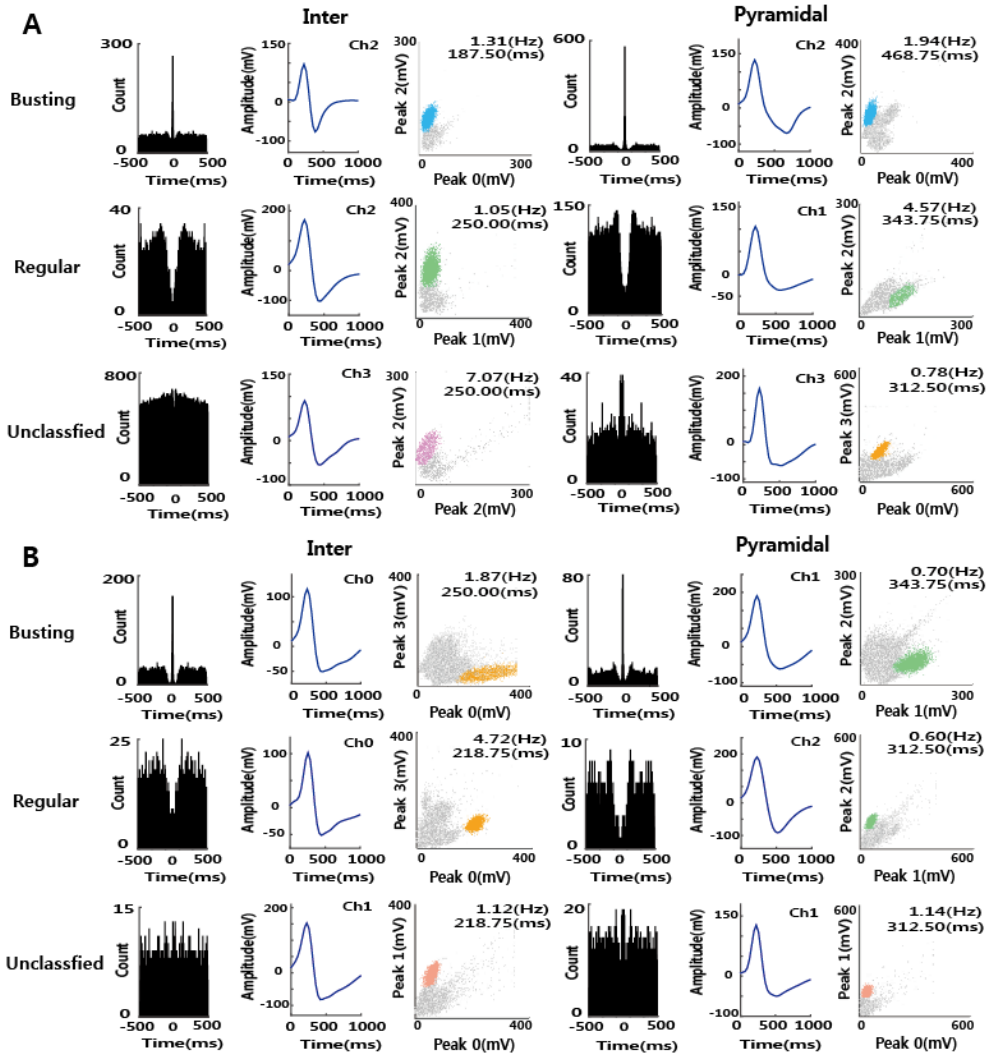

Figure 6. Cell classification I (firing pattern). **A.** Representative autocorrelograms (time window = ± 500 ms, bin size = 1 ms) drawn for putative interneurons (Inter, left) and pyramidal neurons (Pyramidal, right) in the perirhinal cortex. The firing pattern of the cells are categorized into busting, regular and unclassified neuron based on autocorrelograms. Each row shows representative autocorrelograms for busting, regular, unclassified neuron. First column shows the autocorrelograms. Second column shows average waveform of a neuron from a channel with the highest peak magnitude. Third column shows an isolated cell cluster by peak magnitudes. Mean firing rate and spike width are indicated at the top right corner of third column. **B.** Same as in **A**, but for postrhinal cortex units.

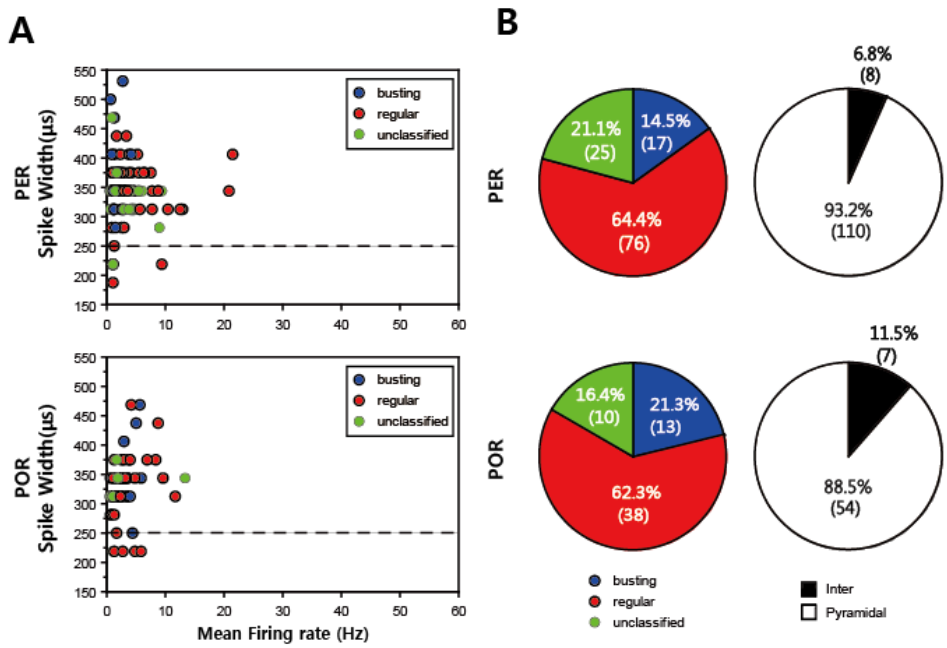

Figure 7. Cell classification II (cell type). **A.** Scattergram of spike width vs mean firing rate. The scatter plots show relationship between the average spike widths (peak-to-through) and the mean firing rate of single units from perirhinal and postrhinal cortex. The upper row shows the scattergram of perirhinal cortex neurons and the bottom row shows the scattergram of postrhinal cortex neurons. The horizontal dashed lines indicate the cutoff point of spike width (250 μs) that separated the putative interneurons and pyramidal neurons. **B.** pie charts showing the proportion of the cell types. Charts in upper row and bottom row show the percentage of perirhinal and postrhinal cortex units, respectively. Left column show percentage of busting, regular and unclassified neurons based on autocorrelograms, and the right column show percentage of putative interneurons and pyramidal neurons based on the spike width criterion. The number in the parentheses indicates the number of units.

3.4. Multiple repetition of familiar object suppressed the single unit activity in postrhinal cortex

For each cell, repetition sensitive slopes for unfamiliar and familiar stimulus pair were obtained (see Materials and Methods) (Figure 8-11).

19.5% (23 out of 118) and 17.8% (21 out of 118) of single units in perirhinal cortex had significant slope for unfamiliar stimulus pair, respectively. 24.6(15 out 61) and 22.9 %(14 out of 61) of single units in postrhinal cortex had significant slope for unfamiliar stimulus pair, respectively.

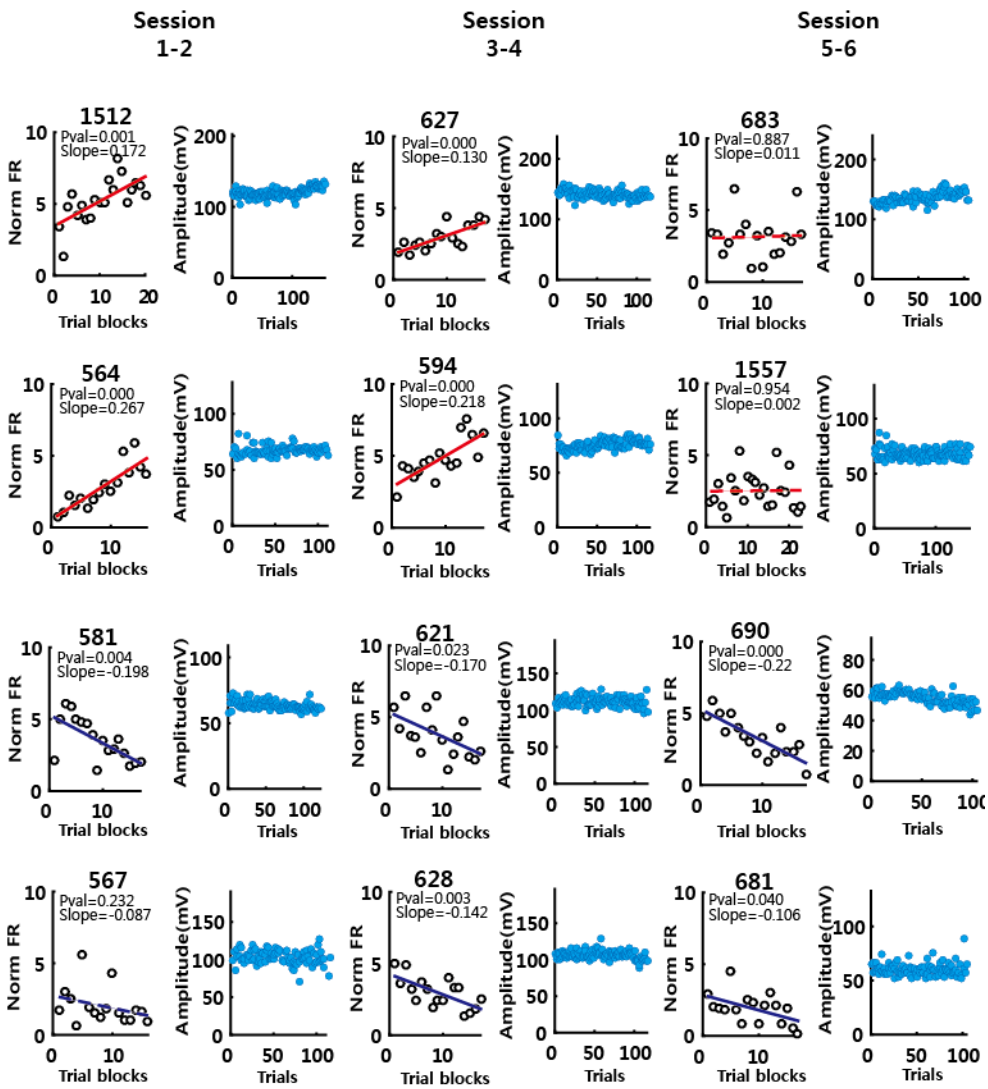

Figure 8. Repetition slope of PER single units (familiar stimulus). Examples of perirhinal cortex neurons responding to multiple repetition to unfamiliar stimulus pair in each session groups are shown. First column shows firing rate change across trial blocks. Each open circle indicates

normalized firing of a trial block, and solid lines show linear slopes that significantly fitted into the normalized firing rate across the trial blocks. Dashed line indicates slope that did not significantly fitted into the firing rate across the trials. Cell ID is displayed on the top of each plot. Slope and its p-value are shown below the cell ID. Upper two rows are example of cells with positive slope, and bottom two rows are example of cells with negative slope. The positive and negative slopes are indicated with red and dark blue lines, respectively. Second column shows mean peak amplitude of the single unit across the trials. Only cells with reliable amplitude were included in the analysis.

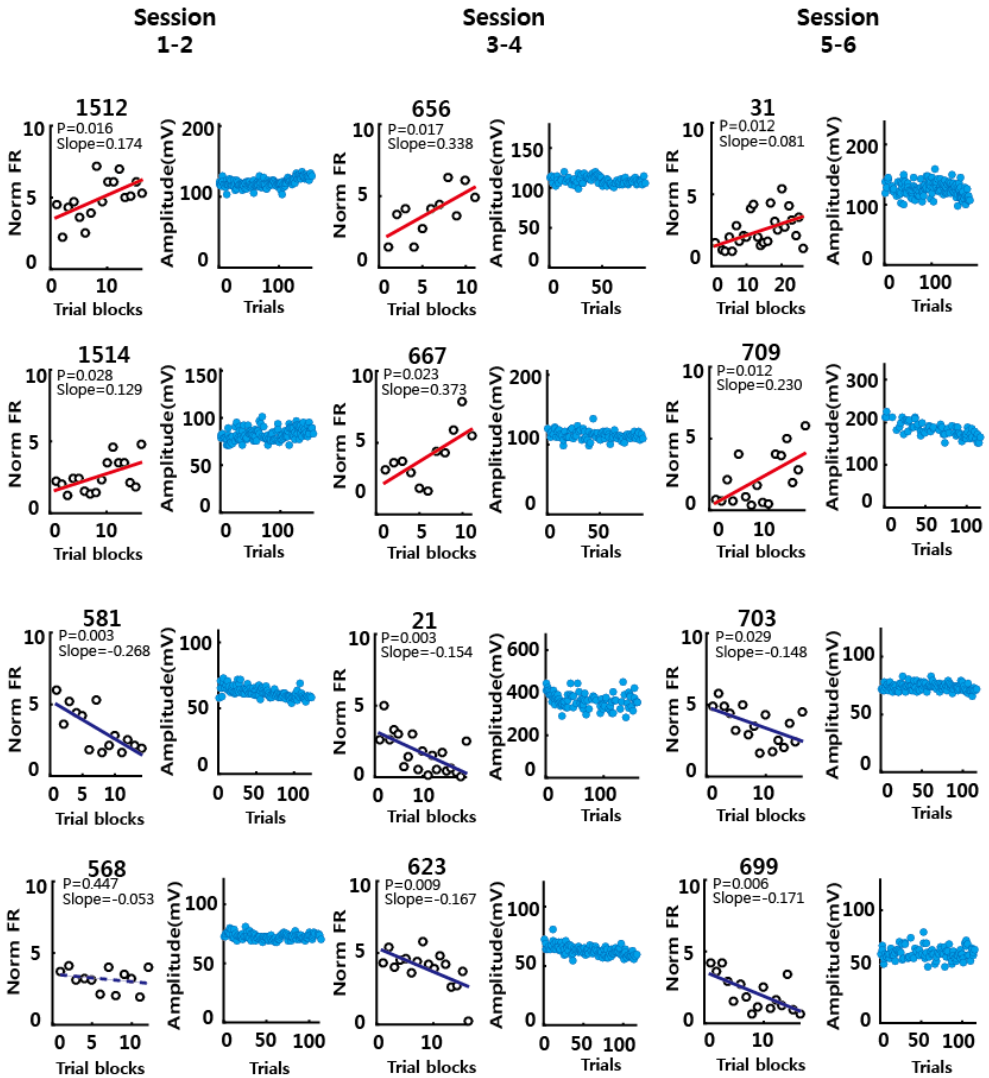

Figure 9. Repetition slope of PER single units (unfamiliar stimulus).

Examples of perirhinal cortex neurons responding to multiple repetition to familiar stimulus pair. Details are same as described in **Figure 8**.

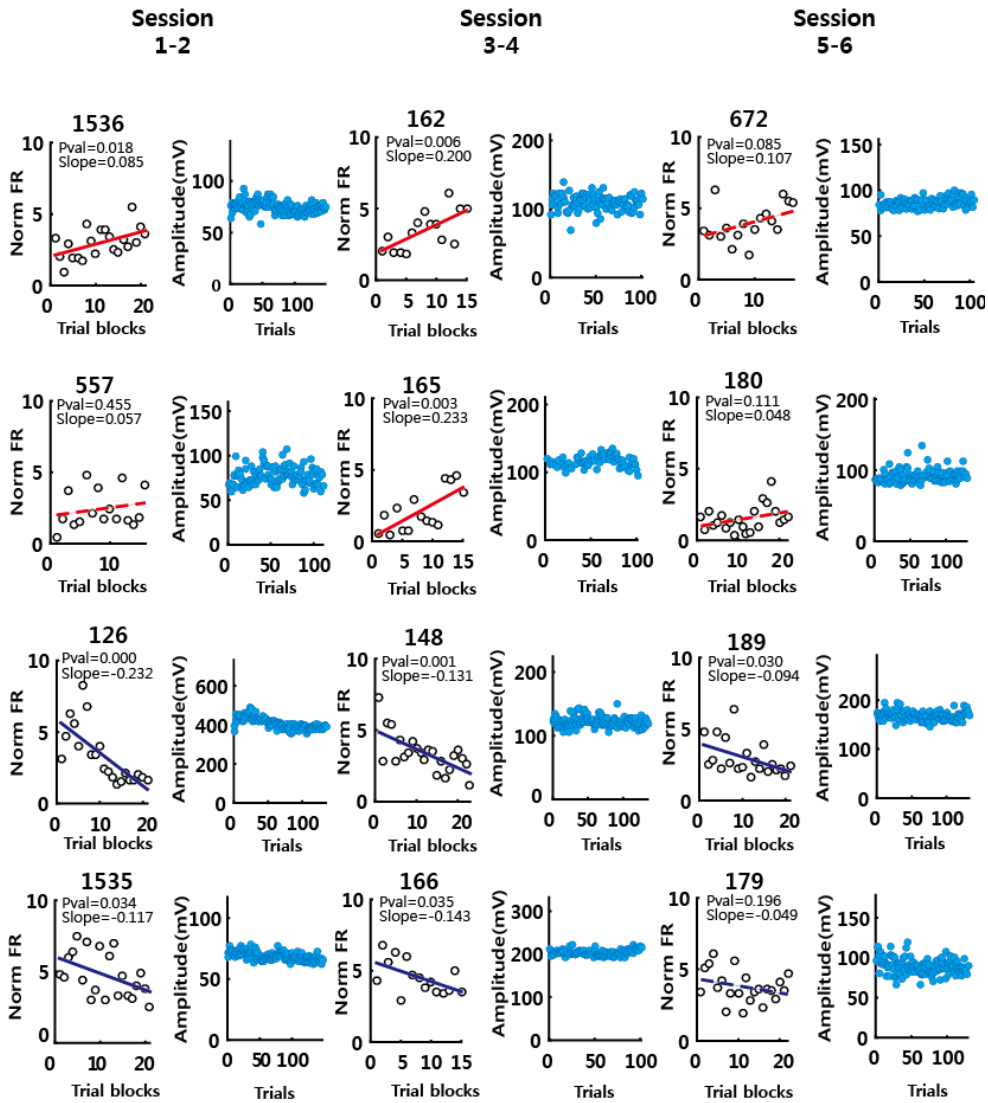

Figure 10. Repetition slope of POR single units (familiar stimulus). Examples of postrhinal cortex neurons responding to multiple repetition to unfamiliar stimulus pair. Details are same as described in **Figure 8**.

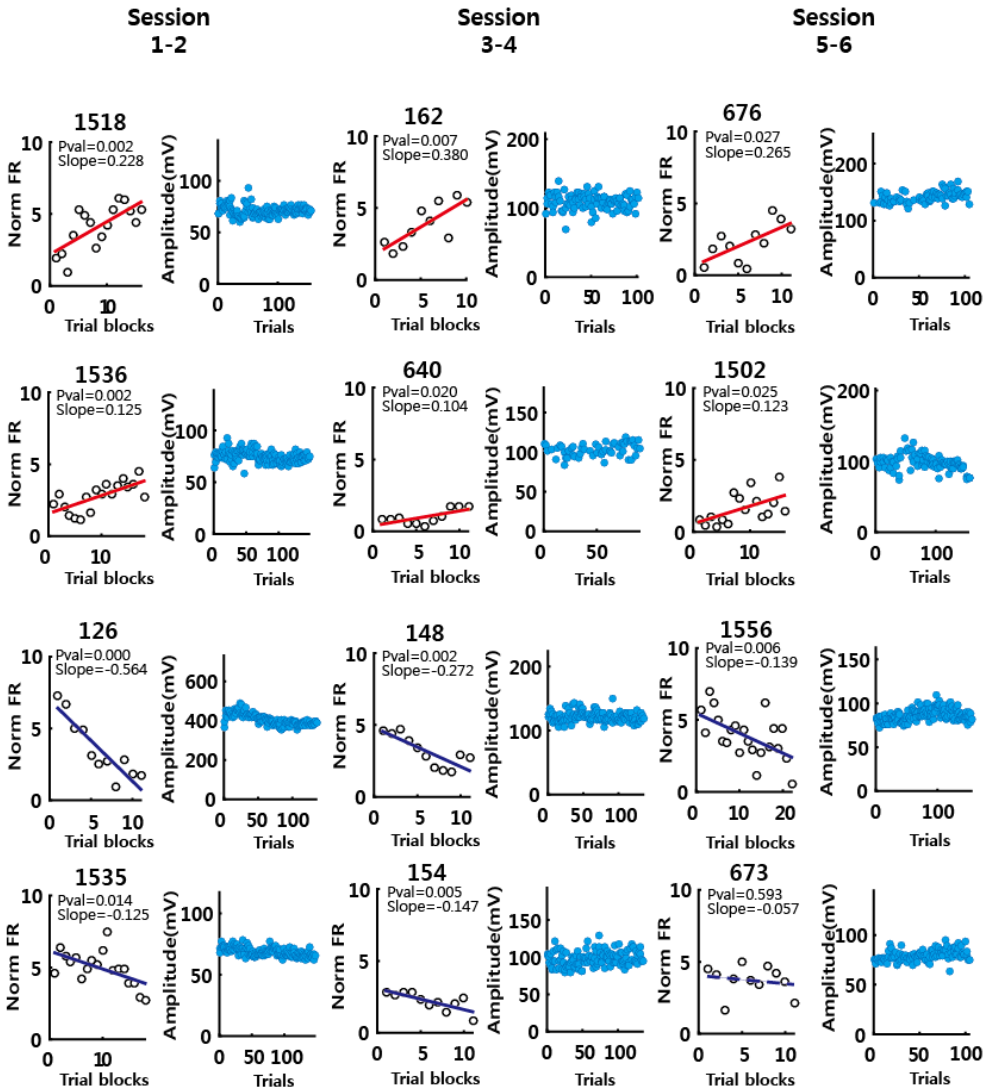

Figure 11. Repetition slope of POR single units (unfamiliar stimulus). Examples of postrhinal cortex neurons responding to multiple repetition to familiar stimulus pair. Details are same as described in **Figure 8**.

The cells with significant slopes were used in further analysis. Of the single units in perirhinal cortex, 50.9% and 49.1% of the slopes show positive and negative slope for unfamiliar stimulus pair, respectively. For familiar stimulus pair, 61.9% and 38.1% of the slopes show positive and

negative slope for unfamiliar stimulus pair, respectively (Figure 12A, left). The proportions of response change direction for unfamiliar and familiar stimulus pair were not significantly different (p=0.514, Chi square test). Of the single unis in postrhinal cortex, 53.3% and 46.7% of the slopes show positive and negative slope for unfamiliar stimulus pair, respectively. For familiar stimulus pair, 21.4% and 78.6% of the slopes show positive and negative slope for unfamiliar stimulus pair, respectively (Figure 12A, right). The proportion of negative slope in familiar stimulus pair was not significantly greater than those in unfamiliar stimulus pair, but showed strong trend (p=0.0546, Chi square test).

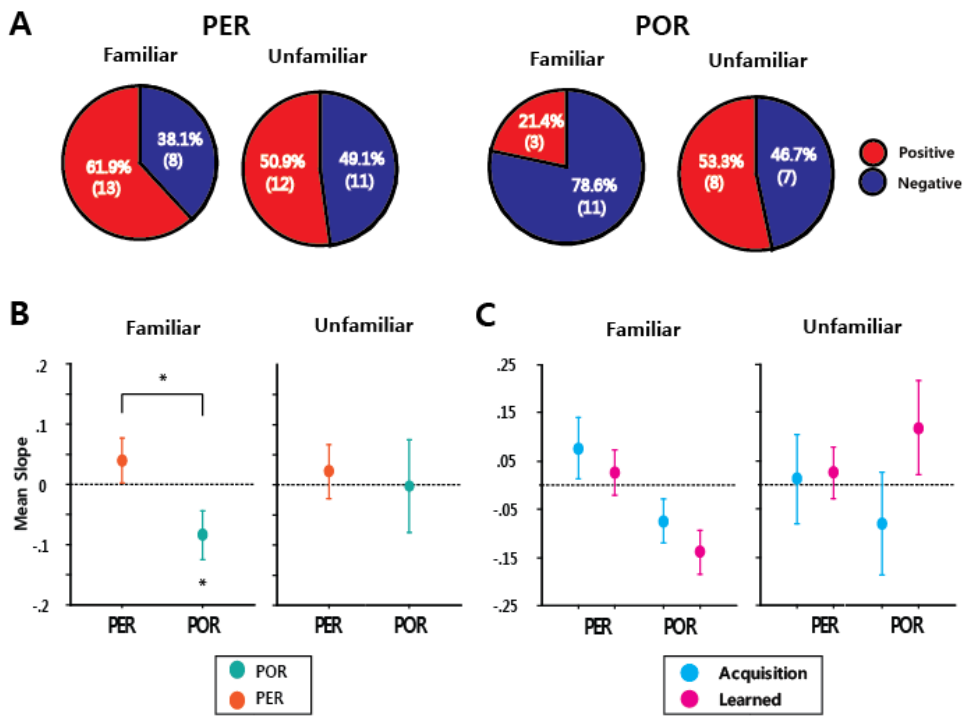

Figure 12. Repetition slope summary. **A.** Pie charts showing the proportion

of the response change direction. The charts show the percentage of cells that significantly changed their firing rate to multiple stimulus repetition over the experimental session. Approximately half of the cells in both perirhinal cortex and postrhinal cortex increased their response and half of the cells decreased their response to multiple stimulus repetition of unfamiliar objects. The proportion of response change direction of familiar objects in postrhinal cortex were not significantly different from those of unfamiliar objects, but show strong trend (p=0.0546, Chi square test). The proportion of response change direction for the unfamiliar stimulus pair between the two regions were not different, but the postrhinal cortex neurons show significantly greater proportion of negative slopes in familiar stimulus pair than those of perirhinal cortex neurons (p=0.007 Chi square test). **B**. Average slope between regions. The mean slope of perirhinal and postrhinal cortex neurons were compared. Significant difference was not found in unfamiliar pair, but the postrhinal cortex neurons showed significantly negative slope than those of perirhinal cortex neurons (p=0.0361, unpaired t-test) in familiar pair. The average slope for postrhinal cortex neurons to familiar stimulus pair was significantly smaller than 0 (p=0.030, one sample t-test, one tail). *p< 0.05. **C.** Interaction between behavioral performance and slope. Mean slopes of the perirhinal and postrhinal cortex neurons to familiar stimulus pair were not affected by behavioral state. Mean slope of the perirhinal cortex neurons to unfamiliar stimulus were not affected by behavioral state, but the postrhinal cortex neurons showed visibly separated mean slope between slope from acquisition phase and learned state. Nevertheless, no statistically significant difference were found.

When comparing the proportion of response change direction between the two regions, proportion of the unfamiliar stimulus pair were not different, but the Postrhinal cortex neurons show significantly greater proportion of negative slopes in familiar stimulus pair than those of perirhinal cortex neurons (p=0.007 Chi square test) (Figure 12A).

The overall average slope of postrhinal cortex neurons for familiar stimulus pair was significantly negative than those of perirhinal cortex neurons (p=0.0361, unpaired t-test), but the difference in was not found for

unfamiliar stimulus (Figure 12B). The overall average slopes of perirhinal cortex for both unfamiliar and familiar stimulus pair were not significantly different from 0. The average slope of postrhinal cortex neurons for unfamiliar stimulus pair was not significantly different from 0 ($p=0.4943$, one sample t-test, one tail), but the average slope for familiar stimulus pair was significantly smaller than 0 ($p=0.030$, one sample t-test, one tail) (Figure 12B). The mean slope was subdivide and compared based on the behavioral state. Both mean slopes of perirhinal and postrhinal cortex neurons to familiar stimulus pair were not affected by behavioral state, but the postrhinal cortex neurons showed visibly separated mean slope between slope from acquisition phase and learned state. However, this difference did not yield significant effect (Figure12 C). Taken together from the results above, the perirhinal cortex neurons do not change their neural response across multiple repetition of stimulus regardless of the stimulus types and learning state, but the postrhinal cortex neurons tend to decreased their neural response across multiple repetition of stimulus when the stimulus was highly familiar. Also, the response to unfamiliar stimulus in postrhinal cortex might be modulated by learning state, although statistically insignificant result suggests that it might just be a spook.

3.5. Single repetition of unfamiliar object lead to

decremental response change in the postrhinal cortex

The effect of single trial repetition was also investigated (see Materials and Methods) (Figure 13-15). The mean firing rates of individual cells to first presentation of each stimulus were compared against those of the second presentation (Figure 13). The perirhinal cortex neurons seemed to have equal distribution of decremental and incremental responses, while the postrhinal cortex seemed to have more decremental responses. To compare response change quantitatively, the neural response changes of each neuron were quantified by calculating the normalized firing rate difference (NFD) (see Materials and Methods). Then, the average NFDs were compared between regions and between stimulus types. The postrhinal cortex neurons shows greater decremental response than the perirhinal cortex neurons in overall ($p=0.003$, repeated measures- two way ANOVA) (Figure 14A). No main effect of stimulus type or effect of interaction was detected.

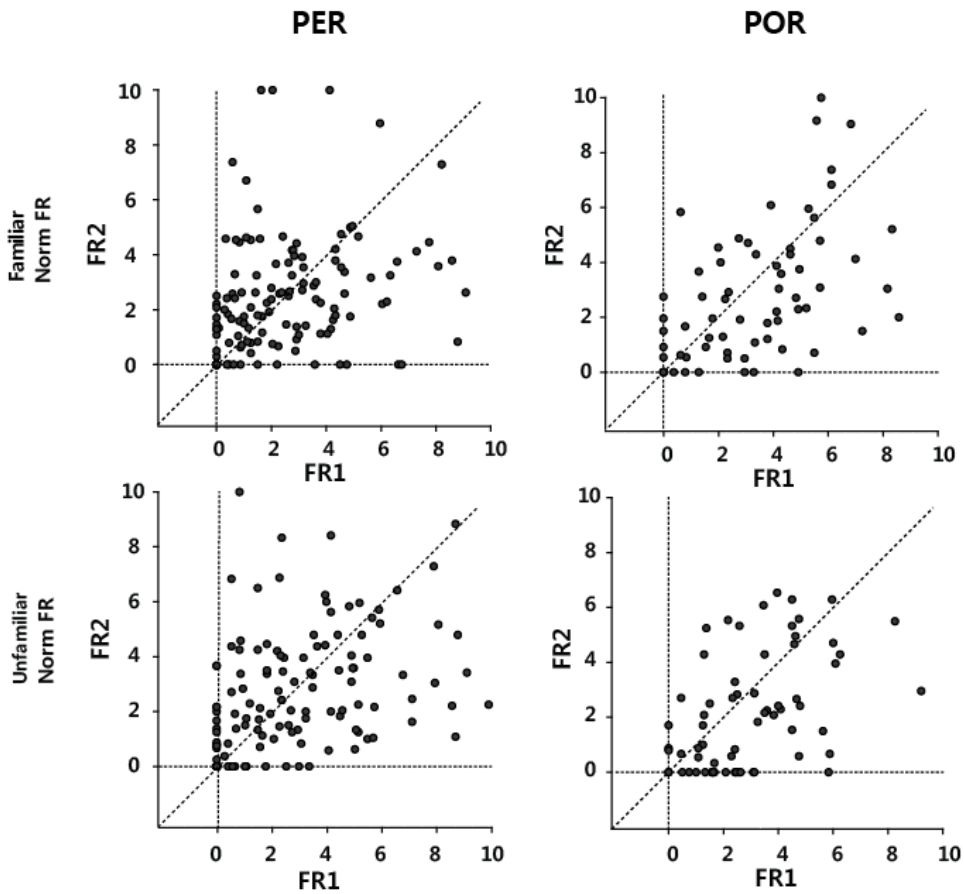

Figure 13. Response change between first and second presentation. Scatterplots showing relationship between firing rate in first presentation and second presentation of stimulus. Left column shows scatterplots for perirhinal cortex neurons, and right column shows scatterplots for postrhinal cortex neurons. Upper and bottom row show scatterplots for familiar and unfamiliar pair stimulus, respectively. Each circle is a neuron that has firing rate in first presentation and its corresponding firing rate in second presentation. A response of cell was classified as decremental response if the firing rate in first trial was higher than that of second trial. If firing rate in second trial was higher than that of first trial, a response was classified as incremental response. The perirhinal cortex neurons seemed to have equal distribution of decremental and incremental responses, while the postrhinal cortex seemed to have more decremental responses.

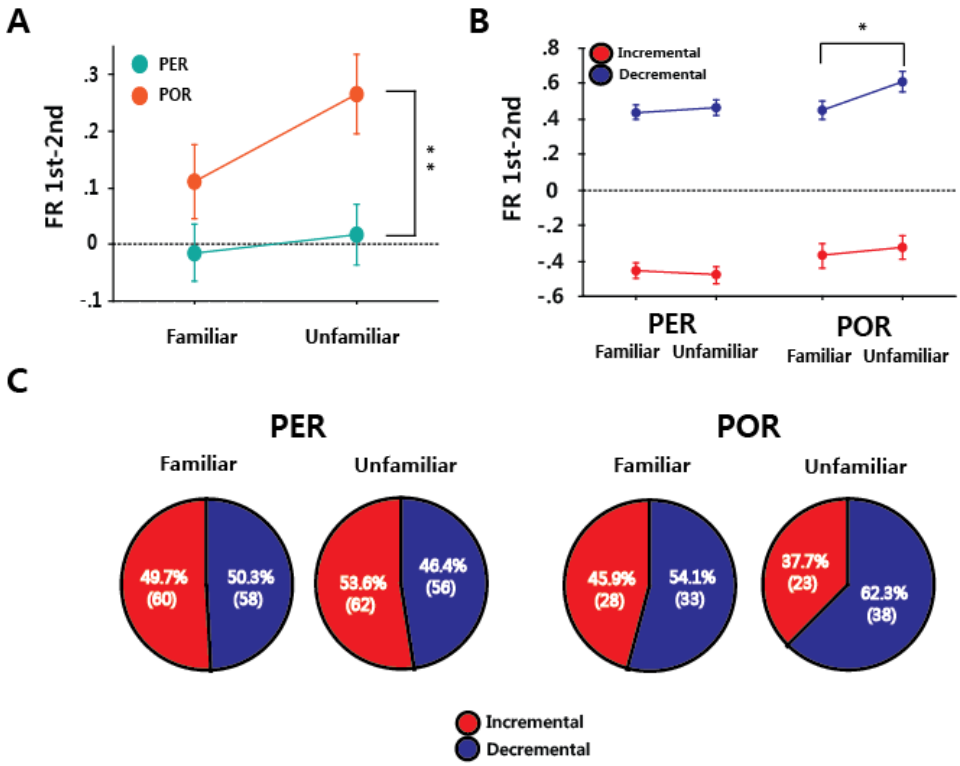

Figure 14. Single repetition effect. **A.** Mean firing rate differences between first and the second trial were compared among regions and stimulus type. The perirhinal cortex neurons shows significantly lower firing rate difference than those of the postrhinal cortex neurons ($p=0.003$, repeated measures- two way ANOVA). The firing rate difference to familiar and unfamiliar stimulus pair were not significantly different both in perirhinal and postrhinal cortex. Though, postrhinal cortex neurons shows seemingly different firing rate difference to familiar and unfamiliar stimulus pair. **$p< 0.01$. **B.** The firing rate difference of incremental, and decremental response were compared separately. Only the decremental response in POR showed significant difference between familiar and unfamiliar stimulus ($p= 0.038$, unpaired t-test). *$p< 0.05$. **C.** Proportion of Incremental and decremental responses. The response of postrhinal cortex neurons to unfamiliar stimulus showed larger portion of decremental response than that of other conditions.

The firing rate difference of incremental, and decremental response were compared separately (Figure 14B). A response of cell was classified

as decremental response if the firing rate in first trial was higher than that of second trial. If firing rate in second trial was higher than that of first trial, a response was classified as incremental response. Only the decremental response in POR showed significant difference between familiar and unfamiliar stimulus ($p= 0.038$, unpaired t-test). This result suggest that greater NFDs in postrhinal cortex to unfamiliar stimulus pair were due to increased decremental response change to unfamiliar stimulus in postrhinal cortex. The proportion of incremental and decremental responses were also compared between regions and stimulus types (Figure 14C). The proportion of decremental response to unfamiliar stimulus in the postrhinal cortex failed revealed significant difference against the proportion of decremental response to unfamiliar and familiar stimulus in the perirhinal cortex. Though, strong trends were found ($p= 0.0888$ and $p=0.0546$). This result possibly indicates the increased decremental response were not due to increased magnitude of individual neural responses, but due to increased number of cells showing the decremental response to unfamiliar stimulus.

Then, the neural responses to unfamiliar stimulus were further analyzed to investigate the effect of learning state on the neural activity in each region. Figure 15A shows Scatterplots showing relationship between firing rate in first presentation and second presentation of unfamiliar stimulus. Both the perirhinal and postrhinal cortex neurons seem to have larger

distribution of decremental cells during the learned state than during acquisition phase. To quantitatively test the difference, the mean NFDs were compared between the stimulus types and learning states in each regions (Figure 15B). The perirhinal cortex neurons revealed significant interaction effect of behavioral state and stimulus type ($p=0.014$, repeated measures- two way ANOVA). Similar effect of interaction trend was detected in the postrhinal cortex, but p-value was not significant ($p=0.068$, repeated measures- two way ANOVA). To summarize the results presented above, both the perirhinal and postrhinal cortex neurons responses did not show changed responses to single repetition of highly familiar stimulus, but neural responses of perirhinal and postrhinal cortex showed decremental response when they successfully recognized relatively unfamiliar stimulus and made appropriate response associated with the stimulus.

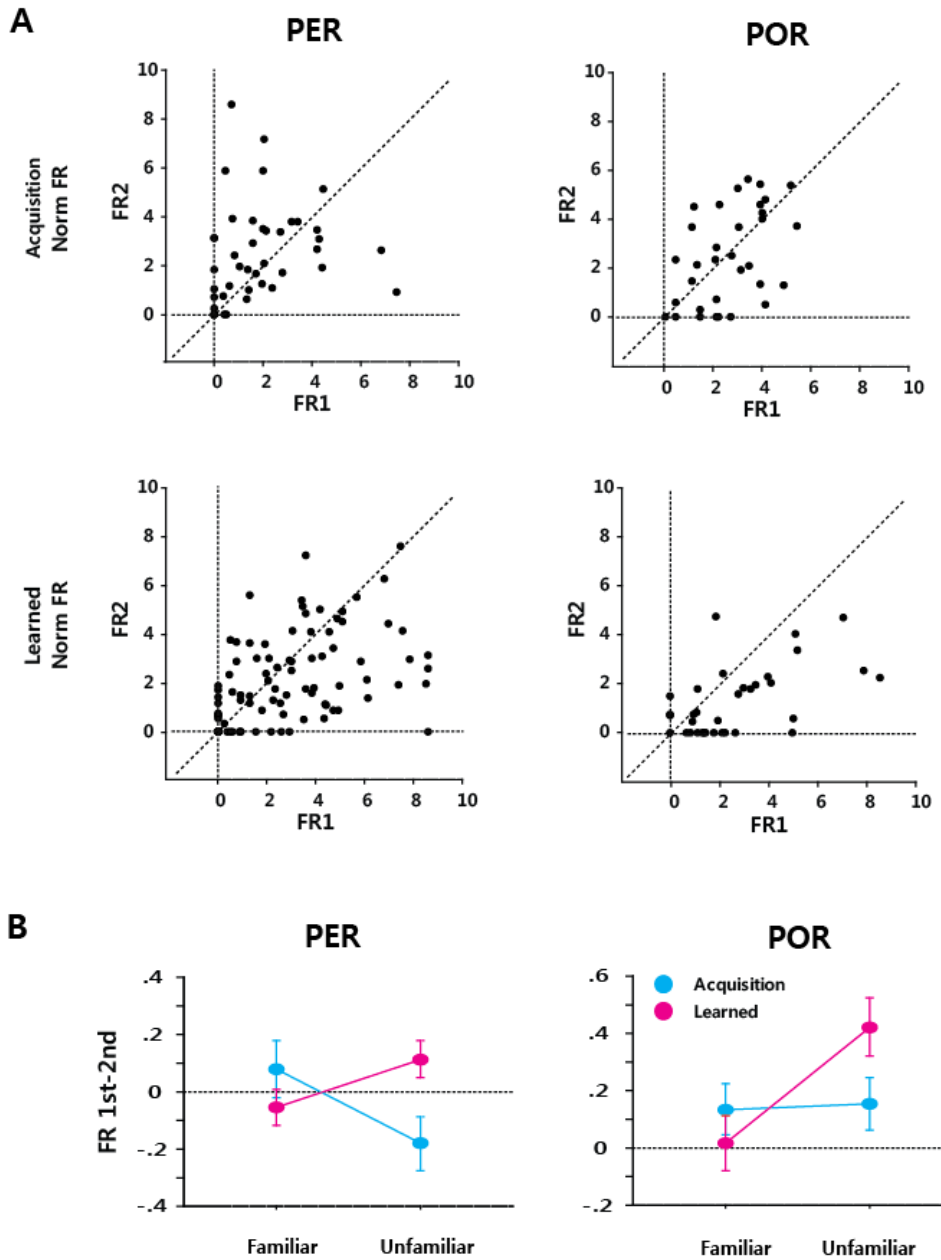

Figure 15. Interaction between behavioral performance and neural response change. **A.** Scatterplots showing relationship between firing rate in first presentation and second presentation of unfamiliar stimulus. Upper and bottom row show scatterplots for acquisition and learned state, respectively. The number of incremental response of neurons during learned state decreased in both perirhinal and postrhinal cortex. **B.** Mean firing rate differences were compared among behavioral state and stimulus type. The

perirhinal cortex neurons revealed significant interaction effect of behavioral state and stimulus type ($p=0.014$, repeated measures- two way ANOVA). Similar effect of interaction trend was detected in the postrhinal cortex, but p-value was not significant ($p=0.068$, repeated measures- two way ANOVA).

Chapter 4. Discussion

The current study examined the neural response change to stimulus repetition in the perirhinal and postrhinal cortex. The perirhinal and postrhinal cortex have been argued to be critical to recognition memory of objects and contextual information based on the behavioral studies (Mumby et al., 1994; Ennaceur et al. 1996; Winters et al., 2004; Winters and Bussey, 2005; Nemanic et al., 2004), and immediate early gene studies (Wan et al., 1999). However, there were dearth of electrophysiological studies to elucidate possible underlying mechanism under such memory process in rodents. A group of research has been hypothesized that the decremental response change in the perirhinal and its adjacent region were possible neural mechanism that could be used for recognition memory (Brown and Xiang, 1998). Although, few electrophysiological studies were conducted and found decremental response change to stimulus repetition (Zhu and Brown, 1995; Zhu et al., 1995), more recent studies failed to find such neuronal response change to stimulus repetition (Burke et al., 2012; Deshmukh et al., 2012). Contrary to prior concept that the perirhinal cortex neurons shows decremental response change when the novel stimulus were repeated, the result from current study show that the population of perirhinal cortex neurons did not decrease their neural activities when the unfamiliar stimuli

were repeated (Figure 12, 14, 15). This result seemed to be in line with relatively recent report from the perirhinal cortex electrophysiological studies that failed to find repetition sensitive activities in the perirhinal cortex (Burke et al., 2012; Deshmukh et al., 2012). However, decremental response changes in the perirhinal and postrhinal cortex were found when rats were able to perform successful associative recognition memory (Figure 15B).

The current study is the first experiment in rodents to report neural response change sensitivity to repetition of the stimulus in the postrhinal cortex. In addition, unlike previous studies in rodent electrophysiology (Zhu and Brown, 1995; Zhu et al., 1995), the current study directly measured the behavioral performance of the rats, thus able to investigate the role of learning state to neural activity of the perirhinal and the postrhinal cortex. The significant finding from the current study is that both perirhinal and postrhinal cortex show decremental responses change to single repetition only once the rats were able to perform successful associative recognition memory between unfamiliar stimulus and correct response (Figure 15B). The decremental responses to single repetition were not found when the stimulus was highly familiar, or rats failed to demonstrate reliable recognition memory of unfamiliar stimulus (Figure 15B). In other words, this finding is the first report to show decremental neural response changes in the perirhinal and postrhinal cortex, which are correlated with object-response associative

recognition memory in rodents.

Two types of repetition-related neural response changes were investigated in current study. The first one was the neural response changes to multiple repetition across the trial in a session (Figure 8-12). This type of repetition-related neural change was not previously explored in rodent literature. The effect of the multiple repetition can be interpreted as information of relative recency rather pure familiarity, since the stimuli were not completely novel to the animal compared to the each previous trial. This type of responses can be considered as subpart of familiarity signal, but not do necessarily act as a novelty detector that only respond highly to novel stimulus than familiar stimulus (Zhu and Brown, 1995; Zhu et al., 1995). Hence, the absence of decremental response to multiple repetition in the perirhinal cortex does not necessarily contradict with result from the previous single repetition experiments (Zhu and Brown, 1995; Zhu et al., 1995), and behavioral studies with spontaneous exploration paradigms (Mumby et al., 1994; Ennaceur et al. 1996; Winters et al., 2004; Winters and Bussey, 2005). One the other hand, the presence of decremental response to multiple repetition of familiar stimulus in the postrhinal cortex suggest that the postrhinal cortex have mnemonic capability to carry recency information across the multiple trials that spread over more than a hour. The smaller portion of such decremental response to unfamiliar stimulus (Figure 12A)

also in agreement with the possibility that the mnemonic function in such response since the smaller portion of such decremental response to unfamiliar stimulus indicate that the capability of recency information can be processed only when the stimulus is well learned.

The second type was the neural response changes to single repetition of the stimulus at the beginning of the sessions (Figure 13-15). This type of repetition-related neural change is somewhat similar to previously reported response change between first presentation and the subsequent presentation of same stimulus (Zhu and Brown, 1995; Zhu et al., 1995). When the neural response changed were investigated solely based on the stimulus types, the postrhinal cortex showed decremental response change, but the perirhinal cortex failed yield decremental response change to unfamiliar stimulus (Figure 14). But when the role of behavioral state accounted for neural response changes, the significant interaction between behavioral state and neural response changes were revealed (Figure 15B). The results suggest that both perirhinal and postrhinal cortex shows larger portion decremental responses to stimulus in population level when the rats were able to perform associative recognition memory.

The recognition memory can be defined at two different class. One is familiarity based recognition and the other is recollection based recognition memory (Eichenbaum et al., 2007). The damage to or inactivation of

perirhinal cortex yield impairment in both types of recognition memory, and those results suggest that the perirhinal cortex plays an important role in both class of recognition memory (Mumby et al., 1994; Ennaceur et al. 1996; Winters et al., 2004; Winters and Bussey, 2005; Ahn and Lee, 2015). While the previous electrophysiological studies mainly focused on spontaneous recognition that mostly rely on familiarity based recognition memory. The behavioral paradigm used in the current study required associate recognition memory, which is required recollection process for making correct response to stimulus. The main caveat in the previous electrophysiological studies was that the neural response cannot be analyzed based on behavioral performance of the animals. Particularly, the passive-viewing paradigm cannot assure whether the rat was actually engaged or not engaged in recognition memory process, since the reward was delivered in regular interval regardless of the rat's behavior (Zhu and Brown, 1995; Zhu et al., 1995). The OCRS task used in current study yield behavioral performance, thus the neural response cannot be analyzed based on behavioral performance of the animals. The result from current study is unique since it showed that the repetition signals were directly modulated by learning state of animals.

The reported neural response cannot be due to neuronal "fatigue or habituation-like behavior. The recorded cells experienced both familiar and unfamiliar type stimulus in a same session, and thus differential neural

response change to stimulus types could not be explained by simply cells being fatigued. In case of the single repetition related response change, the decremental magnitude is larger and much faster than commonly observed in classical habituation.

In conclusion, the current study demonstrated that the both perirhinal and postrhinal cortex neurons signal relative familiarity of unfamiliar stimulus by decremental neural response change to repeated stimulus once the rat was able to perform successful associative recognition memory. Both perirhinal and postrhinal cortex did not changed their neural response if the stimuli were highly familiar. The finding suggest that perirhinal and postrhinal cortex do not show decremental response change to all novel stimulus, but only show decremental response change to relatively unfamiliar stimulus when the recognition memory is acquired.

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국문초록

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비주위 및 후비강 피질은 인식기억에 중요한 역할을 한다고 제안되어 왔습니다. 인식 기억을 위한 신경적 메커니즘 후보로 반복 억제라고 불리는 현상이 있는데, 이는 자극이 반복 될 때 신경 세포의 반응이 감소하는 것을 의미합니다. 원숭이 연구를 통해 자극의 친숙성에 따라 변하는 비주위 피질 신경세포의 비율이 발견되었습니다. 설치류에 관한 연구는 거의 없었으며, 쥐를 대상으로 한 기존의 생리학적 연구 결과들은 일치하지 않았습니다. 이러한 생리학적 실험의 부족한 점을 해소 하기 위해 실험을 진행하였습니다. 쥐가 물체자극 신호에 의한 반응 선택 작업을 수행하는 동안 비주위 및 후비강 피질내 단일 신경 세포들의 활동을 동시에 기록하였습니다. 친숙하고 익숙하지 않은 자극끼리의 신경 반응을 각 뇌 지역에서 비교했습니다. 후비강 피질 신경세포는 친숙한 자극이 실험 세션동안 여러 번 반복되었을 때 신경반응의 감소를 보이는 신경세포가 많았으며 (79%), 익숙하지 않은 자극이 제시될 때 신경반응이 감소하는 것을 발견하였습니다. 이에 반해, 비주위 피질에서 이와 같은 반응 변화는 발견되지 않았습니다. 동물의 학습 상태가 신경 반응 변화에 영향을 미치는 정도를 보면, 비주위 및 후비강 피질은 기억획득 단계보다 학습된 상태에서 덜 익숙한 자극에 대해 더 큰 신경 감소 반응을 보였습니다. 이 결과는 비주위 및 후비강 피질 모두 쥐가 성공적으로 인식기억을 획득한 후

낯선 자극에 대한 상대적인 친숙성 정보를 처리하지만, 매우 친숙한 자극에 대해서는 친숙성 정보를 처리 하지 않는다는 것을 시사하고 있습니다. 이 연구 결과는 설치류의 반응 연관 인식기억에 따라서 비주위 및 후비강 피질의 신경 반응의 감소를 보여주는 최초의 보고입니다.

주요어: 사물 인식, 연합 인식 기억, 비주위 피질, 후비강 피질, 친숙성
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