Olfactory Oscillations In Responses To Sociability Test In Female Mice

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Abstract

Social behaviors can be defined as any modality of communication and/or interaction between two conspecifics of a given species. The social behaviors displayed in an inappropriate way can have detrimental effects. Impaired sociability had also associated with various kinds of neuropsychiatric disorders including depression, anxiety, or schizophrenia. Many excellent models of mouse's social behaviors are well-established. However, most studies have been conducted in male mice due to the fluctuating hormone levels in female mice. Since estrogen is the primary female sex hormone that plays a role in social behaviors, the major aim of this study was to characterize olfactory oscillations in response to sociability cues in female mice. Female Swiss albino ICR mice implanted with the intracranial electrodes for local field potential (LFP) recording were used. The LFP signals from the neural network associated with social behaviors, the olfactory bulb (OB), were simultaneously recorded during performed sociability test compared with a baseline and novel object exploration (habituation session). The results showed that normal female mice significantly increased time spent exploring a stimulus mouse, which indicated the social target responses. The analysis of the LFP olfactory signals also revealed the changes of neural activity within specific frequency ranges during social exploration, decreasing of high beta (19-30 Hz) and increasing of high gamma (61-100 Hz). These findings implied the specific response of the olfactory bulb in the female mice that may indicate the encoding of social exploration.

***Keywords*:** Sociability, Olfactory bulb, Local field Potential, Female, Social brain circuit

1. Introduction

Social behaviors can be defined as any modality of communication and/or interaction between two individuals of the same species (conspecifics) and have persisted throughout evolutionary history due to their contributions toward increasing survival and reproductive fitness. Inappropriate displays of social behaviors can have detrimental effects on both the individuals and a social community (Okuyama, 2018). In most mammalian including humans, the social organization depends on the ability to recognize and discriminate between individual conspecifics. In humans, impaired social behavior had associated with various neuropsychiatric disorders such as autism, schizophrenia, depression, or anxiety disorders (Cheaha et al., 2015; Pepper et al., 2018; Wilson & Koenig, 2014). Social recognition is used as a generic term for both the ability of a subject to categorize conspecifics into different classes, such as sex, genetic relatedness, and familiarity, as well as for the ability to recall the learned distinctive identity of a specific individual based on a previous encounter (de la Zerda et al., 2020). In general, rodents tend to investigate novel conspecifics more persistently than familiar ones (Gheusi et al., 1994).

Given the complexity of social behavior and/or recognition, specific brain regions or neural circuits process social information and make social behavior processing remained unclear. Various brain circuits play a major role in the processing of social behavior, namely, the amygdala, hippocampus, and nucleus accumbens (Ernst & Fudge, 2009). Social-related behavior in the rodent is mediated mainly by chemical cues known as a pheromone, perceived via the main olfactory system and accessory olfactory system. Therefore, the olfactory bulb is mainly known as the first relay center in the olfactory neural pathway displayed by the olfactory cue input for social interaction in the rodent (Sullivan et al., 2015). A recent study of social brain circuits has shown the connectivity of social information flows within an olfactory-related network, which includes the hippocampus, amygdala, and medial prefrontal cortex (Okuyama, 2018).

The electrophysiological technique is the most suitable tool to examine the neural mechanism underlying cognitive processing including social recognition. Local field potential (LFP) recorded from the interconnected social-related neural circuits have been investigated for their relationship with social cognitive

function (Bosman et al., 2014). Two major oscillatory rhythms in the olfactory bulb, one of the main social-related brain region; gamma band (~60-90 Hz) and the beta (15-40 Hz), have been demonstrated in association with odors processing, attention, perception, and cognition (Kopell et al., 2000; Martin & Ravel, 2014). Gamma oscillations were found during an animal's exploration activity (Rojas-Líbano et al., 2018). Moreover, beta oscillations have also been used as a tool to identify neurobehavioral dysfunctions (Wesson et al., 2011). Therefore, the gamma and beta activities in the olfactory bulb might also be associated with social exploration. On the other hand, the oscillatory patterns of the social neural circuit have also been linked to the symptomatology of some neuropsychiatric disorders involved in social deficit (Herrmann & Demiralp, 2005; Uhlhaas & Singer, 2010).

Most preclinical studies avoid using female animals due to the females' fluctuating hormone levels. Although women are more likely to be diagnosed with psychiatric disorders, including anxiety or depression (Remes et al., 2016), researchers often use only male animals. Moreover, many social situations can provoke anxiety, and women have been reported with more social anxiety than men (Norberg et al., 2010). However, few studies have examined how gender affects social recognition. Most social behavior studies in animals have also been conducted mostly using male mice. To understand the neural mechanism underlying social recognition in female mice, the olfactory oscillatory pattern were analyzed while the animal explores the social target.

2. Objectives

This study aimed to identify and characterize the neural oscillatory patterns related to social recognition in normal female mice by using the LFP signal from the olfactory bulb, the main social-associated brain area in rodents.

3. Materials and Methods

3.1 Animals and surgery

Female Swiss Albino ICR mice (10-12 weeks old, n=8) were purchased from Nomura Siam International Co., Ltd. and kept in the animal houses at the Prince of Songkla University. All mice were placed separately in laboratory animal houses at 23 ± 2°C with 55 ± 10% relative humidity and 12 hours light/dark cycle with the lights off at 7 PM, based on the Guidelines of the International Committee on Laboratory Animals. The animals were fed irradiation-sterilized pellet feed (No. CP082, Perfect Companion Group Co., Ltd., Bangkok, Thailand) and allowed access to distilled water ad libitum and acclimated to laboratory conditions for 7 days before the experiment. All procedures were performed following the guidelines outlined in the European Science Foundation (Use of Animals in Research, 2001) and the International Committee on Laboratory Animal Science, ICLAS (2004). The experimental protocols were approved and guided by the Animals Ethical Committee of Prince of Songkla University (MOE 0521.11/230). All efforts were made to minimize animals' suffering and to reduce the number of animals used.

Prior to the experimental day, all animals underwent electrode implantation for the LFP signal recording. The animals were anesthetized by intraperitoneal pre-injection of 16 mg/kg xylazine (Xylavet, Thai Maji Pharmaceutical co., Ltd., Thailand), followed by 50 mg/kg Zoletil® (Virbac, Thailand Co. Ltd.). Then, the animal's head was fixed within the stereotaxic frame through the earpieces. The scalp was shaved and swabbed with a povidone-iodine solution. Local analgesic, lidocaine (Locana, L.B.S. Laboratory Ltd., Part., Thailand) was applied to the exposed tissue of the head. An incision was made at the midline to expose the skull. The silver wire electrodes (diameter = 203.2μm; DC resistance = 8.7 Ω, A.M. system Inc., USA) was stereotaxically positioned on the left side of the olfactory bulb (OB) (AP: +4.5 mm; ML; 1 mm; DV; 1.5 mm) according to mouse brain atlas (Franklin and Paxinos, 1998). The reference and ground electrodes will be placed at the midline, overlying the cerebellum (Midline, AP: -6.5, DV: 2). All electrode wires were inserted into a female connector and fixed to the skull by dental cement. After surgery, the animals were administered antibiotic ampicillin (General Drug House Co., Ltd., Thailand) intramuscularly (100 mg/kg) once a day for three days to prevent infection and allowed them to recover for at least 7-14 days before the study.

3.2 Olfactory LFP signals recording and analysis

The olfactory LFP signal from the recording electrodes was amplified, analog filtered (0.3-1000 Hz) by PowerLab 16/35 system (AD Instruments, Castle Hill. NSW, Australia) with 16-bit A/D and displayed on a PC through the LabChart 7 pro software. The data were digitized at 2 kHz, acquired using LabChart 7 pro software, and stored for offline analysis. 50 Hz notch and main filter were applied to remove the noise from power line artifacts. The spectral power of the LFP oscillations in each region was analyzed using Brainstorm software (Tadel et al., 2011). Spectral power from each segment was averaged within the following frequency bands: slow delta (0.5–4 Hz), theta (5–8 Hz), alpha (9–12 Hz), low beta (13–18 Hz), high beta (19–30 Hz), low gamma (31–45 Hz), and high gamma (60–100 Hz). To compare across different groups, the power values for each animal in a group were normalized to the sum of total power values for that group and are referred to as "percentage total power."

3.3 Precedure of sociability test

Both LFP signals and behaviors were recorded simultaneously while the animals performed the baseline, habituation, and sociability test sessions as shown in Figure 1A. The sociability test was modified from a previous three-chamber social test study (Lee et al., 2018). The animals were acclimatized for 5 minutes per day for two consecutive days in the Plexiglas chamber (25 x 45 x 20 cm). On the testing day, animal behaviors and LFP signals were recorded for 5 minutes freely in the empty chamber arena as initial baseline activities, followed by 5 minutes of habituation and sociability sessions. All animals were brought back to their home cage for resting at a 20-minute interval between each session. For the habituation session, the mouse was reintroduced to the arena and allowed to freely explore the two hole-drilled cylinder cups placed at two sides of the wall in the opposite position. Since mice prefer to explore novel objects, this habituation session, which is primarily aimed to examine side preference between the two cups, can also be used to examine the LFP associated with novel object exploration. During the sociability session, an individual tested mouse was placed in the middle between the two cups, in which one cup contained the sex/age-matched stranger stimulus mouse. Animal behaviors and movement were recorded by using a video camera mounted on the top of the recording apparatus. Animal position, tracking, and time spent exploring each cup were semi-automatically analyzed by the OptiMouse program (Ben-Shaul, 2017). Locomotor activities including total distance travel (cm) and mean speed (m/s) were extracted. Simultaneously, side preference during both habituation and sociability tests were analyzed from time spent exploring either empty cups or a cup containing a novel stranger mouse.

3.4 Statistical analysis

All data were averaged and expressed as a mean ± S.E.M. The experiment designed in this study was the repeat data collection from the same set of animals. Therefore, the total time travel, mean speed, and LFP signals were analyzed using repeated measure one-way ANOVA. Moreover, the two-way repeat measure ANOVA was used to analyze the impact of the social target on the time spent in the zone study. Differences were considered statistically significant at a p-value < 0.05

4. Results and Discussion

4.1 Representative raw and spectrogram obtained from olfactory LFP signal

The Olfactory LFP signal recorded while the animal performed the baseline, habituation, and sociability test sessions were displayed as raw LFP tracings and spectrograms as shown in Figure 1. Visual inspection of raw tracings showed a slight increase of slow-wave and superimposed gamma wave during the habituation and sociability test sessions (Figure 1B). Interestingly, the spectrograms revealed an obvious increase of high gamma frequency power especially during the sociability test, which indicated an association of high gamma power and olfactory signal processing during the sociability recognition.

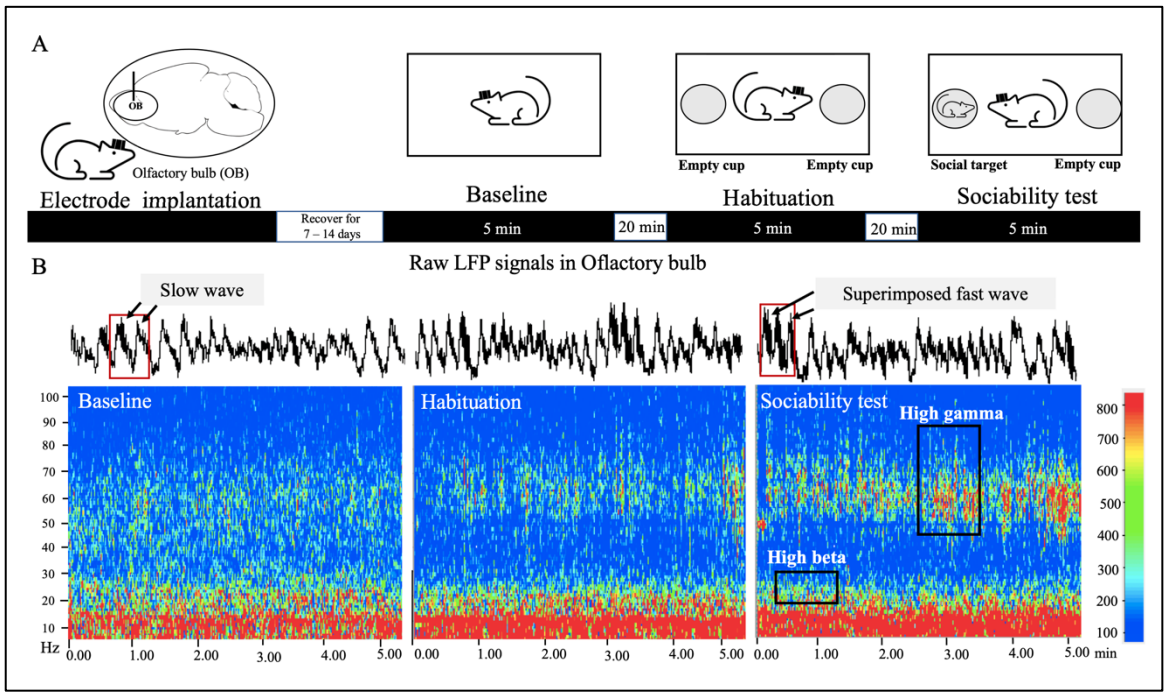

Figure 1 The schematic of experimental paradigm and raw olfactory LFP signal. (A) An overview of the experimental procedure. After recovery from electrode implantation, the animals have exposed to 3 days of habituation in the chamber, on the testing day. Animal behaviors and LFP signals were recorded for 5 minutes freely in the empty chamber arena as initial baseline activities, followed by 5 minutes of habituation and sociability sessions. (B) Raw olfactory LFP tracing and spectrogram of the representative mouse during the baseline activities, habituation, and sociability sessions. The color code of the spectrogram indicated the power of the signal, which red tone color represents high power while blue tone color represents low power.

4.2 The locomotor activities and side preference analysis

The locomotor activities including total distance and mean speed during animals performed the baseline, habituation, and sociability test sessions were analyzed using repeated one-way measure ANOVA analysis. The authors found that both total distance traveled [$F(2, 14) = 5.120$, $p = 0.045$] and the mean speed [$F(2, 14) = 5.826$, $p = 0.001$] were significantly decreased during the habituation and sociability tests. Significant differences were observed only between the baseline and the sociability test.

Animal position and locomotion were tracked and displayed as heat map and tracking line in Figure 2C and 2D. Eventually, the distribution of heat map color and tracking line of animal locomotion was seen while the animal performed the habituation session since both sides of the wall contained empty cups (zone 1 and zone 2) (Figure 2C). During the sociability test session, a cup containing a novel stranger mouse was placed at one side of the wall (zone 1), and the opposite side had an empty cup (zone 2). The heat map and tracking line in Figure 2D indicated that the animal frequently explored zone 1, which is the sociability zone, rather than zone 2, which had an empty cup. In addition, the time spent in both zone 1 and zone 2 were analyzed and plotted as a box plot for statistical comparison. The paired sample T-Test showed no significant difference between both zones during the habituation session (Figure 2C), while a significantly increased time spent in zone 1, which is a sociability zone, compared with zone 2 (empty cup) was observed during the sociability test [$t(7) = -3.942$, $p = 0.01$] (Figure 2D).

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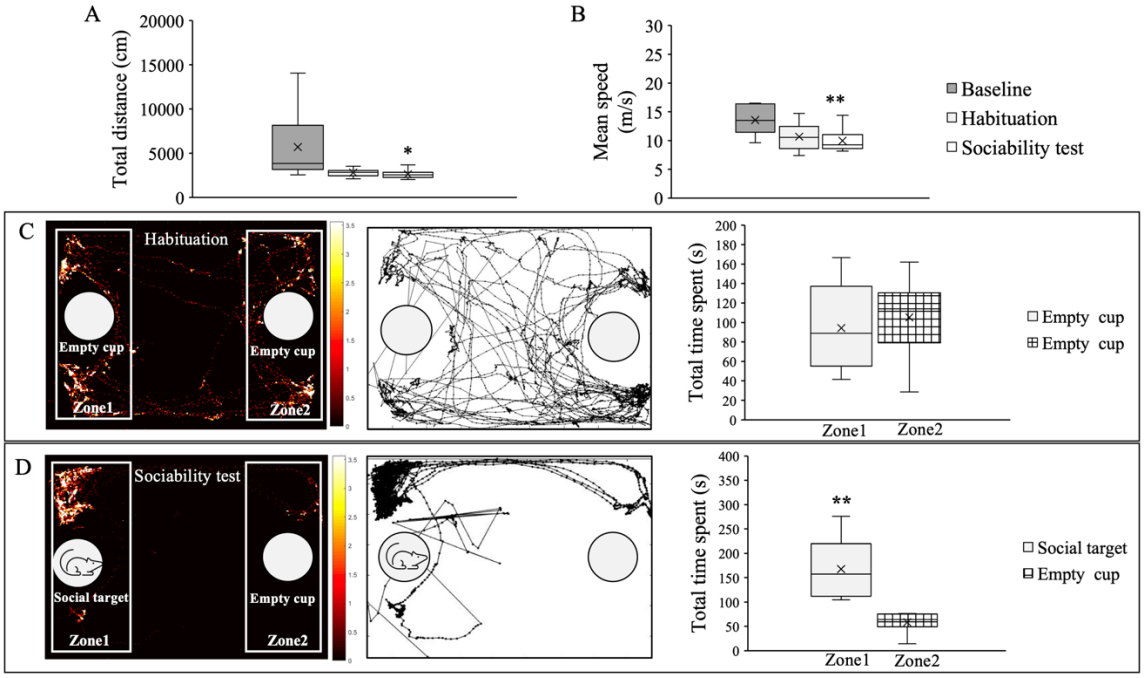

Figure 2 The locomotor activities and side preference analysis. (A) The total distance traveled and (B) the mean locomotor speeds analysis while the animal performed a behavioral test session. Side preference analysis of during habituation test (C) and sociability test (D). The heat map and a tracking line in the left and middle panels showed different patterns of animal locomotion. The total time spent in zones during both the habituation session and sociability test were averaged and showed as a boxplot in the right panel. The total distance and mean speed data were compared with the baseline session using repeated measure one-way ANOVA while differences between zone 1 and zone 2 were compared using paired sample t-test. * and ** indicate significant differences at $p<0.05$ and 0.01, respectively.

4.2 LFP olfactory signals during the sociability

To further investigate the olfactory signal processing, raw olfactory LFP signals were transformed into the frequency domain and expressed as a percentage of the total power as shown in Figure 3. The results in Figure 3A revealed distinct patterns of the 3 conditions; the baseline and the habituation and sociability tests, particularly the high beta (19-30 Hz) and high gamma (61-100 Hz) frequency ranges. Therefore, the spectral power of both frequency ranges was averaged and displayed as a boxplot (Figure 3B and C) for statistical analysis. The repeated measure one-way ANOVA analysis revealed a significant difference of both high beta [$F(2, 190) = 60.677$, $p = 0.01$] and high gamma [$F(2, 638) = 60.677$, $p = 0.01$].

Pairwise comparison showed a significant difference between particular pairs of the experimental sessions. The habituation and sociability tests significantly decreased the high beta power (Figure 3B) while the high gamma (figure 3C) was significantly increased in comparison to that of the baseline. In addition, both high beta and gamma were significantly different compared between the habituation and sociability test sessions.

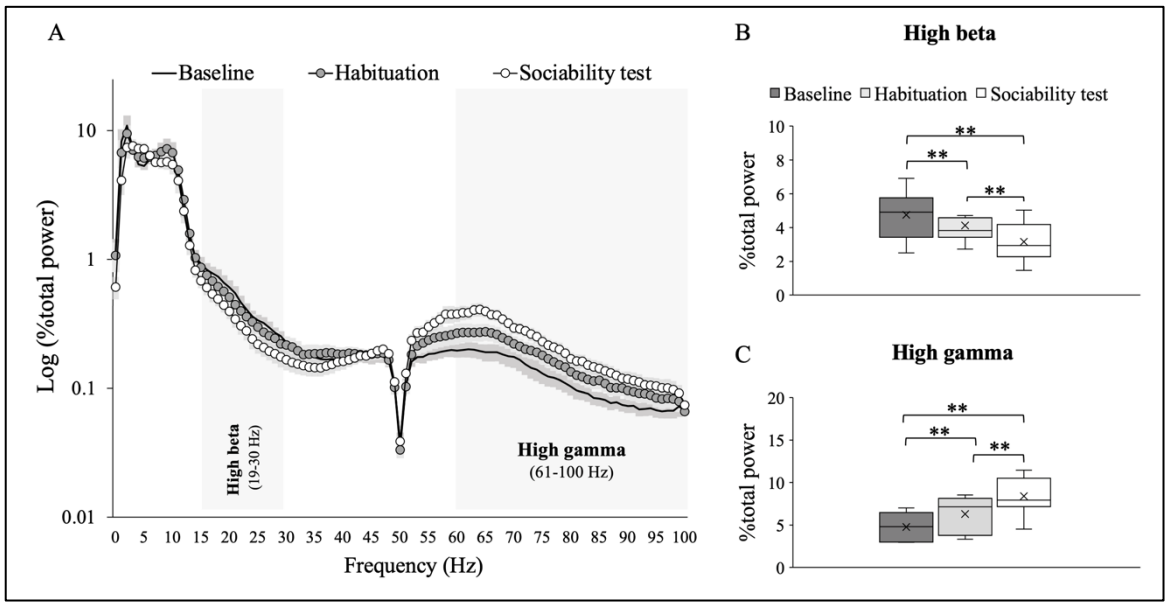

Figure 3 Frequency spectral analysis. (A) The LFP olfactory power spectrums are expressed as a percentage of the total power in the frequency domain during the baseline and the habituation and sociability test sessions. Compared with the baseline, the power within the high beta (19-30 Hz) frequency range decreased during both habitation and sociability test sessions while the high gamma (61-100 Hz) frequency range increased during the habitation and sociability test sessions. The power within the high beta and high gamma were averaged and expressed as a boxplot in (B) and (C), respectively. The data were analyzed using repeated measure one-way ANOVA. ** indicates significant differences at $p<0.01$.

4.3 Discussion

This study was the first study that reported changes in the olfactory bulb signal processing in socially experienced female mice. The sociability test has been used as a standard behavioral tool to investigate the specific aspects of social behaviors such as social interactions, social recognition, and social communication using olfactory and visual cues or vocalization (Berton et al., 2006; McFarlane et al., 2008). Using a modified three-chamber sociability test, our finding demonstrated that the female mice also displayed an increase in time spent exploring social targets, which indicated that mice both male and female prefer to explore a social target rather than a non-social target. According to previous social behavior studies, social recognition tests in rodents depend on the animals' intrinsic motivation to investigate other individuals, particularly the rodents that commonly investigate novel unfamiliar objects as well as a stranger conspecific (Carr et al., 1976). The consistent finding had also been reported in the previous study which indicated that the females also increase time interaction with a social target in conjunction with the male mice (Moy et al., 2004). Therefore, our finding confirmed that the female mice also show an increase in the time spent exploring social stimuli during the sociability test.

In rodents, the olfactory bulb is the important brain region that plays a major role in the olfactory processing associated with social behaviors (Chen & Hong, 2018). However, few studies investigated the signal processing of social-related brain circuits, especially in female mice. In general, the frequency analysis of the LFP signals, including the olfactory bulb signal, provides changes in neural oscillatory patterns, which indicate important information of neural activity associated with the recognition tasks. These oscillatory brain activity commonly categorized into the theta (3–12 Hz), beta (12–30 Hz), and gamma (30–80 Hz) frequency bands. These frequency bands are associated with various cognitive functions in different brain regions, such as speech and social communication (Uhlhaas & Singer, 2006). A previous study that examined neural processing in the olfactory bulb found that the two main olfactory oscillatory patterns, beta and gamma bands are closely related to odor processing, attention, perception, and cognition (Olufsen et al., 2003).

Our present study demonstrated significant changes in the olfactory LFP oscillations in socially experienced female mice. Following the sociability test, the animals showed a decrease in the high beta power (19-30 Hz) and an increase in the high gamma power (61-100 Hz) while fewer effects were seen during a non-social exploration (baseline activity). These results are consistent with a previous study in male mice that demonstrated an increase in fast gamma power following social investigation and odor stimulation (Almeida-Santos et al., 2019). While gamma rhythm is more related to local intra-structure processing, the concept of beta rhythm is an organizing of long-range communication between brain circuits. Therefore, the presence of these two rhythms in the olfactory system is more likely to retain distinct network properties and processing in particular social-related processing (Cannon et al., 2014; Kopell et al., 2000). Our finding may confirm that the presence of the high gamma indicates the association between the local olfactory bulb processing during the social exploration, while the presence of the beta may indicate the interrelatedness of the olfactory with other social-related brains.

The main purpose of the habituation session by exploring a novel object (empty cups) is to confirm whether the changes in the olfactory bulb signal are associated with a social stimulus. The researchers also found a subtle decrease in the high beta power (19-30 Hz) and an increase in the high gamma power (61-100 Hz) in comparison to the baseline activity. However, the changes in the high beta and high gamma power during the sociability were more pronounce and significantly different compared with the habituation session. Regarding locomotor activities, there was no significant difference in both averaged total distance and mean speed between the habituation and the sociability test sessions, which indicated that the animals spent more time observed novel objects similar as well as novel social stimuli. Therefore, significant differences in the olfactory high beta and gamma power between both groups suggested that the social stimulus may strongly induce changes in the activity of the olfactory bulb rather than the object exploration.

The findings from this study implied the specific response of the olfactory bulb in female mice specifical decrements of the high beta (19-30 Hz) and increments of the high gamma (61-100 Hz) power in association with the social stimulus. Since most previous studies investigated the social relayed olfactory processing only in male animals, our study, therefore, examined female mice, which may help to further characterize and understand the underlying mechanism of neural oscillatory patterns related to social exploration in the normal female mice.

5. Conclusion

In summary, the present data demonstrate the effect of social exploration of normal female mice on the social-related brain region; the olfactory bulb. The reduction of the beta power and the enhancement of the gamma power in the olfactory bulb associated with the response to the social stimulus rather than novel object exploration. Specific response of the olfactory bulb signal may indicate the encoding of social exploration. This finding also helps to understand the underlying mechanism of social-related processing of the olfactory LFP, which is the major brain target involved with the social behavior in rodents. Since the major process of brain function is complex and relies on the connectivity between various brain areas, future study needs to be focused on the interconnected social brain circuit associated with social exploration.

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