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Research Article

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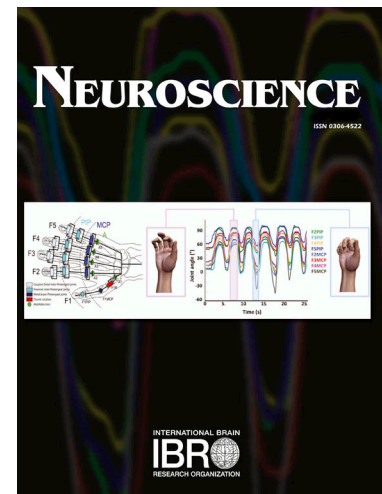
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Enhanced discriminative abilities of auditory cortex neurons for pup calls despite reduced evoked responses in C57BL/6 mother mice.

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Abbreviations list

ABR: Auditory Brainstem Response

ACx: Auditory Cortex

AP: Action Potential

BF: Best Frequency

MI: Mutual Information

NC: Noise Correlations

PPN: Putative Pyramidal Neuron

SNR: Signal-to-Noise Ratio

SSNC: Stimulus-Specific Noise Correlations

STRF: Spectro-Temporal Receptive Field

USV: Ultrasonic Vocalizations

Abstract

A fundamental task for the auditory system is to process communication sounds according to their behavioral significance. In many mammalian species, pup calls became more significant for mothers than other conspecific and heterospecific communication sounds. To study the cortical consequences of motherhood on the processing of communication sounds, we recorded neuronal responses in the primary auditory cortex of virgin and mother C57BL/6 mice which had similar ABR thresholds. In mothers, the evoked firing rate in response to pure tones was decreased and the frequency receptive fields were narrower. The responses to pup and adult calls were also reduced but the amount of mutual information (MI) per spike about the pup call's identity was increased in mother mice. The response latency to pup and adult calls was significantly shorter in mothers. Despite similarly decreased responses to guinea pig whistles, the response latency, and the MI per spike did not differ between virgins and mothers for these heterospecific vocalizations. Noise correlations between cortical recordings were decreased in mothers, suggesting that the firing rate of distant neurons was more independent from each other. Together, these results indicate that in the most commonly used mouse strain for behavioral studies, the discrimination of pup calls by auditory cortex neurons is more efficient during motherhood.

Keywords :

Communication sounds – Cortical discrimination – Mutual information – Noise correlations – Auditory Brainstem Response (ABR) – Motherhood.

Highlights

- ABR thresholds were similar in mother vs. in virgin mice but latencies were shorter
- Evoked cortical responses were decreased in mothers compared to virgins
- Cortical response latencies were shorter in mothers than in virgins
- The MI per spike was higher in mothers than in virgins only for pup calls
- The noise correlations were lower in mothers than in virgins for all stimuli

Introduction

Acoustic communication is crucial for social interactions, and many animal models have been proposed to understand how the behavioral significance of communication sounds impacts their processing by central auditory neurons. The mouse ultrasound communication provides such an opportunity. When isolated from the nest, mouse pups emit bouts of ultrasonic calls ($> 25\text{kHz}$, Noirot 1966; Sewell 1968), which act as a trigger to elicit the search and retrieval by the mother mice (Sewell 1970; Haack et al. 1983). It has been shown that some call parameters, like ultrasonic bandwidth and duration, are perceived in a categorical fashion by mothers (Ehret and Haack, 1981, 1982; Ehret, 1992). In two-alternative choice experiments, mothers preferentially approach pup-like ultrasounds compared with a neutral non-communicative sound; while pup-naïve, virgin females do not (Ehret et al. 1987). This suggests that pup calls do not trigger a selective caring behavior in virgin females, while they do in mothers (Ehret, 2005).

Initially, many studies that have investigated the neural bases of pup call detection and discrimination have used the CBA/CaJ mouse strain which is known to have good hearing and show moderate age-related hearing loss until almost 2 years old (Willott, 1986; Willot et al. 1991; Walton et al. 1998). Using this strain as model, several important findings have been reported. First, although cortical neurons recorded in mothers (11-18 weeks old) do not fire more at pup call presentation, their responses peaked earlier with a shorter response duration (Liu and Schreiner 2007). More importantly, the responses of neurons in mothers convey more information for detecting and discriminating pup calls, especially during the very first ms of the response (Liu and Schreiner 2007). Subsequent studies have indicated the lack of firing rate difference between the responses to pup calls and adult calls in mother mice (14-24 weeks old), and pointed out that only putative pyramidal neurons (PPNs) in mother mice (but not in non-maternal mice) showed a larger Signal-to-Noise Ratio (SNR) for pup calls compared to adult calls. In these PPNs, the discrimination between pup calls and adult calls was better than between adult call themselves (Shepard et al. 2015). Last, a multiunit study revealed that animals (11-17 weeks old) with more maternal experience show enhanced suppression of responses to ultrasound stimuli in low frequency tuned cortical areas (Shepard et al. 2016).

The results seem different in mice strains having a limited cortical representation of ultrasounds such as the C57BL/6 mouse, which is the most widely used in behavioral studies. For example, this mouse strain was widely used when testing performance in spatial learning tasks (review in Rossi-Arnaud and Ammassari-Teule 1998), in olfactory learning (Restivo et al. 2006), in object recognition tasks (Fahlström et al. 2011), and also in tasks involving auditory stimuli (André et al. Gould 2012; Behrens and Klump, 2016; Pollack et al. 2018) and social interactions (Chabout et al. 2013; Faure et al. 2017; Ey et al. 2012; Carola et al. 2008). Furthermore, this strain became the most widely used in studies aiming at targeting specific cell types by Cre-dependent reporters. In this mouse strain, there was no difference in firing rate between lactating mothers (10-12 weeks old) and naïve virgins both for pyramidal cells and for parvalbumin positive cells (Cohen and Mizrahi 2015), a finding that has been replicated in NMRI mice (Rothschild et al. 2013). There was also very few cells responding to pup calls: 0/77 cells in naïve virgins and 3/70 in lactating mothers (Cohen and Mizrahi 2015). However, a recent study performed in C57BL/6 mice (8-10 weeks old), using a new reporter mouse strain to target specifically neurons activated by natural sounds, has shown a transient recruitment of neurons responsive to ultrasonic vocalizations (USV) (Tasaka et al. 2018). Interestingly, note that in this study, the vast majority of the responding neurons have Best Frequency (BF) <20kHz.

In the present study, we aimed at determining whether the differences in neuronal response parameters between virgins and mothers described in CBA/CaJ mice can also be found in C57BL/6 mice. To answer this question, we provided here exhaustive quantifications by (i) analyzing the auditory brainstem responses in terms of threshold, amplitude and latency, and (ii) using a large database to compare responses of auditory cortex neurons to pure tones, conspecific (pup and adult calls) and heterospecific vocalizations (as control stimuli) between these two groups of C57BL/6 mice. Our main findings were that at the brainstem level, thresholds were similar with shorter latencies in response to pure tones in mothers; whereas at the cortical level, the responses to all auditory stimuli were decreased with shorter latencies in mothers except for the heterospecific vocalizations. In addition, the mutual information per action potential was significantly higher, for the pup calls only, in mother mice.

Methods

Subjects and audiogram

These experiments were performed under the national license A-91-557 (project 2017-31, authorization 05202.02) and using the procedures N° 32-2011 and 34-2012 validated by the Ethic committee N°59 (CEEA Paris Centre et Sud). All surgical procedures were performed in accordance with the guidelines established by the European Communities Council Directive (2010/63/EU Council Directive Decree).

Data are from 15 virgin and 15 mother C57BL/6 background mice (9 to 24 weeks old) weighting from 21 to 40g (virgin median 25g; mother median 33g). They came from our own colony housed in a humidity (50-55%) and temperature (22-24°C)-controlled facility on a 12h/12h light/dark cycle (light on at 7:30 A.M.) with free access to food and water. The day of the experiment, the animal's pure-tone audiogram was determined by testing auditory brainstem responses (ABR) under Ketamine/Xylazine anesthesia as previously described (Chaussonot et al. 2015, Martucci et al. 2019). A software (RTLab, Echodia, Clermont-Ferrand, France) allowed averaging 500 responses during the presentation of five pure-tone frequencies (between 4 and 32 kHz) delivered by a speaker (Knowles Electronics) placed in the animal right ear. The auditory threshold for each frequency was the lowest intensity where a small ABR wave can still be detected (usually waves II and III). For each frequency, the threshold was determined by gradually decreasing the sound intensity (from 80 dB down to -10 dB SPL). For their age (2-5months), all the animals used in this study had normal pure-tone audiograms for the C7BL/6 genetic background (Chaussonot et al. 2015). During off-line analyses, the amplitudes and latencies of the five ABR waves were quantified at 70dB SPL for both groups.

Recording procedures

Cortical extracellular recordings were obtained from arrays of 16 tungsten electrodes (\varnothing : 33 μ m, <1 M Ω) composed of two rows of 8 electrodes separated by 1000 μ m (350 μ m between electrodes of the same row). A silver wire, used as ground, was inserted between the temporal bone and the dura matter on the contralateral side. A large craniotomy was performed based on stereotaxic coordinates (Anteriority: 0 to -5 mm from Bregma; Laterality: -1 to -7 mm from Bregma) then the location of the left primary auditory cortex was estimated from the pattern of vasculature reported in previous

studies (Hackett et al. 2011, Willott and Aitkins 1993; Barkat et al. 2011; Joachimsthaler et al. 2014).

The raw signal was amplified 10,000 times (TDT Medusa). It was then processed by an RX5 multichannel data acquisition system (TDT). The signal collected from each electrode was filtered (610-10000 Hz) to extract multi-unit activity (MUA). The trigger level was set for each electrode to select the largest action potentials from the signal. On-line and off-line examination of the action potential waveforms indicates that the MUA collected here was made of 2-6 shapes of action potentials generated by neurons at close vicinity of the electrode.

Acoustic stimuli

Acoustic stimuli were generated using MATLAB, transferred to a RP2.1-based sound delivery system (TDT, sampling rate 195 kHz) and sent to an electrostatic speaker driver (ED1) and electrostatic speaker (EC1, Tucker Davis Technologies, Alachua, FL). The polyethylene tube at the output of the speaker was inserted in the mouse's right ear. Calibration of the speaker was made using pure tones recorded by a Bruel & Kjaer microphone 4138 coupled to a preamplifier B&K 2670 and a digital recorder (Marantz) on the Avisoft software.

Spectro-temporal receptive fields (STRFs) were first determined using 129 pure-tones frequencies scaled with a gamma function presented at 75 dB SPL covering more than 5 octaves (2 to 80 kHz). Each frequency was repeated 20 times at a rate of 4Hz in pseudorandom order. The duration of these tones over half-peak amplitude was 15 ms and the total duration of the tone was 50 ms, so there was no overlap between tones.

We played a set of 18 pup and 18 adult mice calls extracted from a large library of pup and adult calls initially described by Liu and colleagues (2003). These calls were already used in several electrophysiological studies performed on CBA/CaJ mice (Liu and Schreiner 2007; Lin and Liu 2010; Shepard et al. 2015). Both the pup and adult calls were 12-65 ms in duration and were in the 60-80kHz range (see figure 9 in Liu et al. 2003). They differ in terms of their degree of frequency modulation at onset and in terms of their rise-fall time. We also used a set of heterospecific vocalizations consisting in four guinea pig whistles. The maximal energy of these four whistles was in the same frequency range (typically between 4 and 26 kHz), they only displayed slight differences

in their spectrograms, but their temporal envelopes clearly differed as shown by their waveforms (see figure 1 from Aushana et al. 2018). These stimuli have been used in previous electrophysiological studies (Aushana et al. 2018; Souffi et al. 2020).

Experimental protocol

All data were collected under Ketamine/Xylazine anesthesia (initial dose: 150 mg/kg and 5 mg/kg, supplemented every hour by 20mg/kg of the mixture). After inserting the array in the cortex, a 10-minutes recovering time lapse was allowed for the cortex to return to its initial shape, then the array was slowly lowered. Quantifications of spectro-temporal receptive fields (STRFs) were used to assess the quality of our recordings and to adjust electrodes' depth. We looked for the inversion of the local field potential polarity (as in Christianson et al. 2011) and recorded at depths between 400-600 μm below pia, which corresponds to layers III and IV according to Anderson et al. (2009).

When a clear frequency tuning was obtained for at least 4 of the 16 electrodes, the stability of the tuning was assessed: we required that the recorded neurons displayed at least three successive similar STRFs (each lasting 240s) before starting the protocol. The similarity was based on the BF value, as well as the breadth of tuning and the duration of the response. When the stability was satisfactory, the protocol was started by presenting the acoustic stimuli in the following order: First pure tones at 75dB, then the pup and adult calls at 85dB, then the 4 whistles at 75 dB SPL. Each vocalization was repeated 20 times with an inter-stimulus interval of 500ms. Presentation of this entire stimulus set lasted 25 minutes. The protocol was re-started after moving the electrode arrays on the cortical map. Two to six positions of the electrode array were set in such a way that the two rows of eight electrodes sample neurons from the more dorsal to the more ventral portion of AI/AAF. At the end of recording session, the animal was euthanatized with an overdose of Exagon (Pentobarbital, 200mg/kg).

Data analysis

Quantification of responses to pure tones

The STRFs derived from MUA were obtained by constructing post-stimulus time histograms for each frequency with 1 ms time bins. The firing rate evoked by each frequency was quantified by summing all the action potentials from the tone onset up to

50 ms after this onset. Thus, STRFs are matrices of 100 bins in abscissa (time) multiplied by 129 bins in ordinate (frequency).

Peaks of significant response were automatically identified using the following procedure: A significant peak in the STRF was defined as a contour of firing rate above the average level of the spontaneous activity (estimated from the ten first milliseconds after tone onset) plus six times the standard deviation (SD) of the spontaneous activity. For each STRF, the Best Frequency (BF) was defined as the frequency at which the highest firing rate was recorded.

Quantification of responses evoked by vocalizations

The responses to vocalizations were quantified using four parameters: (i) the firing rate of the evoked response, which corresponds to the total number of action potentials occurring during the presentation of the stimulus minus spontaneous activity; (ii) the latency and (iii) the duration of the response and, (iv) the spike-timing reliability coefficient (CorrCoef), which quantifies the trial-to-trial temporal reliability of the response. This index was computed for each vocalization: it corresponds to the normalized covariance between each pair of spike trains recorded at presentation of this vocalization and was calculated as follows:

$$CorrCoef = \frac{1}{N(N-1)} \sum_{i=1}^{N-1} \sum_{j=i+1}^N \frac{\sigma_{x_i x_j}}{\sigma_{x_i} \sigma_{x_j}}$$

where N is the number of trials and $\sigma_{x_i x_j}$ is the normalized covariance at zero lag between spike trains x_i and x_j where i and j are the trial numbers. Spike trains x_i and x_j were convolved with a 10-ms width Gaussian window. Based upon computer simulations, we have previously shown that this CorrCoef index is not a function of the neurons' firing rate (Gaucher et al. 2013). We computed the CorrCoef index with a Gaussian window of 10 ms because this value was found to be optimal for describing the neurons' trial-to-trial precision of responses to communication sounds in previous cortical studies (Aushana et al. 2018, Gaucher et al. 2013, 2015; Huetz et al. 2009).

Quantification of mutual information from the responses to vocalizations

The method developed by Schnupp et al. (2006) was used to quantify the amount of information (Shannon 1948) contained in the responses to vocalizations obtained with natural vocoded and noise stimuli. This method allows quantifying how well the vocalization's identity can be inferred from neuronal responses. Here, "neuronal responses" refer to the spike trains obtained from a small group of neurons below one electrode (for the computation of the individual Mutual Information, MI). Neuronal responses were represented using different time scales ranging from 65ms (duration of the longest vocalization) to a 1-ms precision (precise temporal patterns), which allows analyzing how much the spike timing contributes to the information. As this method is exhaustively described in Schnupp et al. (2006) and in Gaucher et al. (2013a), we only present below the main principles.

The method relies on a pattern-recognition algorithm that is designed to "guess which stimulus evoked a particular response pattern" by going through the following steps: From all the responses of a cortical site to the different stimuli, a single response (test pattern) is extracted and represented as a post-stimulus time histogram with a given bin size (different sizes were considered as discussed further below). Next, a mean response pattern is computed from the remaining responses (training set) for each stimulus class. The test pattern is then assigned to the stimulus class of the closest mean response pattern. This operation is repeated for all the responses, generating a confusion matrix where each response is assigned to a given stimulus class. From this confusion matrix, the Mutual Information (MI) is given by Shannon's formula:

$$MI = \sum_{x,y} p(x,y) \times \log_2 \left(\frac{p(x,y)}{p(x) \times p(y)} \right)$$

where x and y are the rows and columns of the confusion matrix, or in other words, the values taken by the random variables "presented stimulus class" and "assigned stimulus class".

In our case, we used responses to the 18 pup and 18 adult male calls and selected the responses occurring during the 65ms after stimulus onset (i.e. the maximal duration of the calls). In a scenario where the responses did not carry information, the assignments of each response to a mean response pattern was equivalent to chance level (here 0.055 because we used 18 different stimuli and each stimulus was presented the same number

of times) and the MI would be close to zero. In the opposite case, when responses are very different between stimulus classes and very similar within a stimulus class, the confusion matrix would be diagonal, and the mutual information would tend to $\log_2(18) = 4.17$ bits. At the cortical level, several studies have reported that an optimal bin size for obtaining a maximal value of MI was on average 8ms (Schnupp et al. 2006; Gaucher et al. 2013; Gaucher and Edeline 2015; Souffi et al. 2020). Here, because the natural stimuli were very short (12-65ms), when we computed the MI for temporal precision ranging from 1-64ms, the maximal amount of MI was obtained for a temporal precision of 4ms. This value was therefore used for all the subsequent analyses.

The MI estimates are subject to non-negligible positive sampling biases. Therefore, as in Schnupp et al. (2006), we estimated the expected size of this bias by calculating MI values for “shuffled” data, in which the response patterns were randomly reassigned to stimulus classes. The shuffling was repeated 100 times, resulting in 100 MI estimates of the bias (MI_{bias}). These MI_{bias} estimates were then used as estimators for the computation of the statistical significance of the MI estimate for the real (unshuffled) datasets: the real estimate was considered as significant if its value was statistically different (at the p value <0.05) from the distribution of MI_{bias} shuffled estimates.

Quantification of Noise Correlations

One basic measure for network dynamics is pairwise noise correlations (NC; review in Averbeck and Lee 2004; Averberck et al. 2006). NC measure the tendency of two neurons (or groups of neurons) to respond simultaneously above and below their respective mean firing rate. The co-fluctuation of their firing rate on a trial-by-trial basis is usually viewed as an indication that the two neurons display functional connectivity (i.e. these two neurons belong to the same neural assembly as defined by Aertsen et al. 1989; Aertsen and Gerstein, 1991).

Here, we compute NC based upon the responses to the set of 18 pup calls and 18 adult calls. This analysis was performed on pairs of recordings when at least two out of 16 simultaneous recordings showed significant responses to at least one vocalization.

The technique used to calculate the NC was identical to the one used in a previous study comparing virgin and mother mice (Rothschild et al. 2013). We first subtracted the mean response of each recording to each stimulus from all the single-trial responses of this recording to that stimulus. This resulted in a vector of fluctuations around the mean

responses to the different stimuli. The correlation coefficients between pairs of such vectors were used as estimates of the NC between the two recordings.

Statistics

To compare the mean amplitude and latency of the five ABR waves between the two groups, a two-way ANOVA (fixed effect) was performed for each sound (click, pure tones at 8 and 16 kHz). Post-hoc comparisons were performed with Fisher LSD tests. The tests were corrected for multiple comparisons using Bonferroni corrections and were considered as significant if their p value was below 0.05.

We first tested whether we had normal distributions and equal variances in our sampled distributions for each parameters extracted from neuronal responses. In all cases, the distributions were normal allowing performing parametric tests (unpaired t-tests). When all data were compared between the two groups, Student t-tests were used, but Welch t-tests were used in some cases where the variances were not equal. To compare the mean firing rate and latency of cortical responses to pup and adult calls between the two groups, a n-way ANOVA (fixed effect; with stimulus type and groups as factors) was performed for the responses to pup calls and adult calls separately. The difference between the BF distributions was tested with Chi-Squares, and the differences in the cumulative percentage of neurons responding to 1-18 vocalizations were tested with Kolmogorov-Smirnov test. To compare the noise correlations of each stimulus from independent pairs of neurons, a one-way ANOVA test (fixed effect) was performed for each group.

In the figures, the distributions of all data are presented using violin plots, with the median indicated by a white dot and the mean by a red bar. In all figures displaying group data, we indicated by * a p value <0.05, by ** a p value <0.01 and by *** a p value <0.001.

Here, neuronal data were collected over time by placing a 16-electrodes array at different locations on the cortical tonotopic map. Two to six positions of the electrode array were used for each animal, resulting in 31 positions for the virgins and 68 positions for mother mice. Cluster analysis was also performed by taking the position of the electrode array as cluster. When comparing the effects obtained for the 31 positions of the virgins with the 68 positions in the mothers, all the significant effects reported in the present study still hold.

Results

The data presented here are from 9-24 weeks old virgins and lactating mother females (virgins median = 10 weeks; mothers median = 13 weeks). The day of the experiment, the mothers were lactating with at least 4 pups aged of 9-10 days old.

We collected a database of 154 recordings from virgin females (n=15) and of 407 recordings from lactating mothers (n=15), obtained with about twice more positions of the electrode array in mothers. To be included in the following analyses each recording has to meet two criteria. First, it had to present a significant receptive field (with tone-evoked responses 6 SD above spontaneous activity) when tested with pure tones presented at 75dB. Second, it had to present a significant response at least to one pup or adult call (at least 7 responses over 20 repetitions), i.e. an increase in firing rate above spontaneous activity (using Kruskal-Wallis test, $p < 0.05$).

Shorter latencies of the ABR waves in mothers compared to virgins

Before starting the cortical recordings, the ABR audiogram was systematically tested (see example Fig 1B) and we excluded partially deaf animals with click threshold \geq to 70dB SPL (3 animals were excluded: virgins n=2, mothers n=1).

For all the tested frequencies, the mean ABR threshold did not differ between virgin and mother mice (Figure 1A; unpaired t-tests, all p-values > 0.05). We quantified the mean latency and the mean amplitude of the ABR waves in virgins and in mothers for click (as in Miranda et al. 2014) and for 8 and 16kHz as it was shown to be the frequency range showing the lower thresholds in many mice strains (Zheng et al. 1999). Figure 1 shows the mean amplitude (Fig 1C) and mean latency (Fig 1D) for the five ABR waves. A two-way ANOVA compared the amplitude of the five ABR waves in mothers and in virgins. For the click and for 8kHz sound, there was a significant group-effect ($F_{1,14}=14.89$ and $F_{1,14}=10.33$, $p < 0.001$) and a tendency for a group effect at 16kHz ($F_{1,14}=3.15$, $p=0.07$). The wave-effect was systematically significant (all p values < 0.00001) and there was no interaction between groups and waves (lower p-value: $p=0.0855$ for 16kHz). Post-hoc analyses revealed that the amplitudes of wave IV at the click, 8 and 16kHz were higher in mothers than in virgins (Fig 1C, unpaired t-tests $p < 0.05$) and this was also the case for the wave III at 8kHz (unpaired t-tests $p < 0.05$).

Remarkably, the latencies of all the waves were significantly and systematically shorter in mothers compared to virgins. A two-way ANOVA confirmed that the latencies of the five ABR waves were shorter in mothers and in virgins. There was a significant group-effect (click: $F_{1,14}=53.63$, 8 kHz: $F_{1,14}=141.25$ and 16kHz $F_{1,14}=165.89$, all p -value < 0.00001), a wave-effect (all p -values < 0.00001) and an interaction between groups and waves (click and 8kHz $p<0.0001$, at 16kHz: $p=0.08$). Post-hoc analyses revealed that, for waves II to V, the latencies of responses to click and tones were shorter in mothers than in virgins (Fig 1D, all unpaired t -tests $p<0.05$).

In conclusion, the ABR threshold did not differ between the two groups but the amplitude of waves IV and III, which mostly reflect the neuronal activity of the superior olivary complex and inferior colliculus, was significantly larger. Except for wave I, the latency of the ABR waves was shorter in mother than in virgins.

Smaller receptive fields in the primary auditory cortex (A1) of lactating mothers

Typical examples of STRFs obtained at 75dB are displayed in Figure 2A. Similar to what has been previously reported in C57BL/6 mice (e.g., see Hackett et al. 2011), the BF values were between 2.5 kHz and 24 kHz, and none of the recordings obtained in our mice showed BFs between 24 kHz and 80 kHz, confirming the lack of high frequency representation at the cortical level in the C57BL/6 mouse. The two BF distributions did not significantly differ between lactating mothers and virgins ($\chi^2= 4.94$, $p=0.17$; Figure 2B).

Figure 2C displays the main parameters derived from the STRF quantifications, i.e., the evoked firing rate (the total number of action potentials falling in the significant contours of the STRFs), the total bandwidth (in octave), the response latency (in ms) at the best frequency and the responses duration (in ms). As shown on figure 2C, all these parameters were significantly lower in the lactating mother than in the virgin mice (unpaired t -tests; all p values $p<0.01$). This indicates that, in lactating mothers, auditory cortex (ACx) neurons emitted fewer action potentials (AP) at pure tone presentations, and that the temporal and spectral extents of the receptive fields were smaller. However, the evoked responses occurred at slightly shorter latency after tone onset.

Attenuation of the responses strength to pups and adult calls in lactating mothers

The typical example of cortical responses to pup calls, adult calls, and guinea pig whistle (repeated over 20 trials) presented on figure 3 illustrates that both spontaneous and evoked activities were lower in mothers (bottom) compared to virgins (top).

Figure 4 presents the parameters quantified from the responses to pup and adult calls. We first quantified the responses strength average across the eighteen pup calls and the eighteen male adult calls. Evoked activity was quantified over a 65 ms window starting at vocalizations onset; spontaneous activity was quantified over the 100 ms preceding each vocalization. As shown in figure 4A, both spontaneous and evoked activities were significantly lower (unpaired t-tests; p values $p < 0.001$) in lactating mothers compared to virgins. The number of spikes per trial was also significantly lower (unpaired t-tests; p values $p < 0.001$) in lactating mothers compared to virgins. As for the responses to pure tones, there was a small, but significant, reduction in mean latency to the USV calls for neurons recorded in lactating mothers compared to virgins (unpaired t-tests; p value $p < 0.05$), but neither the response duration nor the response trial-to-trial reliability (Corrcoef index) were changed in the lactating mothers compared with the virgins (data not shown, unpaired t-tests; p values > 0.20 in the two cases).

Figures 4B and 4C show that the reduction in firing rate (Fig 4B) and in response latency (Fig 4C) were systematically present for each of the 18 pup and adult calls.

For the evoked responses to pup calls, a n-way ANOVA revealed a significant group-effect ($F_{1,5268}=338$, $p < 0.0001$), a stimuli vocalizations-effect ($F_{17,5268}=4.4$ $p < 0.0001$ for pup calls), and no interaction between groups and vocalizations ($F_{17,5268}=0.58$, $p=0.9$). The same was true for the evoked response to adult calls (group-effect: $F_{1,5269}=250$, $p < 0.0001$, vocalization-effect: $F_{17,5269}=2.9$ $p < 0.0001$, and no interaction between groups and vocalizations $F_{17,5269}=0.7$, $p=1$).

Similar effects were found for the response latencies (Fig 4C): for the response to pup calls there was a significant group-effect ($F_{1,5268}=53.9$ $p < 0.001$), a vocalizations-effect ($F_{17,5268}=51.54$ $p < 0.0001$), and no interaction between groups and vocalizations ($F_{17,5268}=1.29$, $p=0.1$). For the responses to adult calls there was a significant group-effect ($F_{1,5269}=40.5$ $p < 0.001$), a vocalizations-effect ($F_{17,5269}=134.9$ $p < 0.0001$), and no interaction between groups and vocalizations ($F_{17,5269}=0.63$, $p=0.8$). Furthermore, when we compared the mean latency for each vocalization, there were more significant differences in response latencies between virgins and lactating mothers for pup calls (5

calls with unpaired t-tests $p < 0.05$) compared to adult calls (4 calls, with unpaired t-tests $p < 0.05$), indicating that the shorter response latency in mothers is more common when pup calls are presented compared to adult calls.

Interestingly, the difference between the mean latency to all pup calls (gray and blue dashed lines in Fig 4C) and the latency to each pup call was larger in mothers than in virgins (2.72 ms vs. 2.38 ms) whereas it was not the case for the adult calls (3.98 ms vs. 3.92 ms).

One potential consequence of the decrease in response strength is that auditory cortex neurons might respond to fewer calls in mother mice than in virgin mice. Therefore, we quantified the number of pup and adult vocalizations eliciting a significant neuronal response in mothers and virgins. We systematically tested whether there was a significant increase in firing rate (above spontaneous activity, $p < 0.05$) for each of the 36 calls (the eighteen pup and the eighteen adult calls). Figure 5 shows the cumulative distributions of response to the pup calls and adult calls in the two groups of females. There were slightly more recordings responding from 4 to 12 pup (Figure 5A) and adult calls (Figure 5B) in virgins compared to mothers, but this effect was not significant (Kolmogorov-Smirnov tests: $p = 0.46$ for pup calls and $p = 0.11$ for adult calls).

Neurons in lactating mothers convey more information per spike compared to virgins

We quantified the mutual information (MI) between the set of stimuli and the auditory cortex responses: MI was quantified based upon temporal patterns with a 4ms time precision (see Methods). There was no significant difference between the mean value of MI obtained for the two groups of females (0.92 for pup calls and 1.00 for adult calls in virgins vs. 0.93 for pup calls and 0.97 for adult calls in mothers; unpaired t-tests; $p > 0.18$; data not shown). However, as the number of evoked spikes was lower in the lactating females, the value of mutual information per spike (MI/spike) was higher in lactating mothers compared to virgins (unpaired t-tests; p value $p < 0.001$). Interestingly, this was the case for the MI/spike computed from the responses to pup calls but not for the MI/spike computed on the responses to adult calls (Fig6A).

Potentially, we could envision that the larger the number of pup calls triggering cortical responses, the higher the MI/spike. Therefore, we looked for relationships between the

MI/spike value and the number of vocalizations to which the neurons responded (Fig 6B) both for the adult calls and the pup calls. In virgin mice, both with the pup and the adult calls, a linear regression did not indicate significant correlation ($p > 0.20$) between the MI/spike value and the number of calls eliciting a response ($R = 0.12$ for pup calls and $R = 0.11$ for adult calls). In contrast, in mother mice the neurons having the highest values of MI/spike tended to respond to fewer vocalizations ($R = 0.38$ for pup calls and $R = 0.35$ for adult calls), and this negative correlation was significant ($p < 0.001$).

Responses to heterospecific vocalizations

Do the physiological changes occurring during motherhood only impact the responses to conspecific vocalization or in contrast also impact the responses to heterospecific vocalizations? To address this question, we analyzed the responses to guinea pig vocalizations in virgins and mothers.

The typical example of response to guinea pig vocalizations presented on figure 3 shows that cortical neurons mostly responded by onset responses to the four whistles with often an additional peak. Figure 7 presents the parameters quantifying the responses to these heterospecific vocalizations. The responses strength (averaged across the four whistles) was quantified over a 300 ms window starting at the onset of the vocalizations, and spontaneous activity was quantified over the 100 ms preceding each vocalization. Both spontaneous and evoked activities were significantly decreased (unpaired t-tests; p values $p < 0.001$) in lactating mother compared to virgins (fig 7A), as well as the number of spikes per trial (unpaired t-tests; p values $p < 0.001$). However, other response parameters were not altered. The latency did not significantly differ in mother and in virgins (fig 7B, unpaired t-tests; p value $p > 0.05$). Finally, the mutual information per spike was not different between mothers and virgins (Fig 7C, unpaired t-tests; p value $p > 0.3$).

Thus, the decrease in evoked responses was also observed in mothers compared to virgins, but the other parameters such as the latency and the MI/spike were not modified when presenting heterospecific vocalizations.

Co-variations between pairs of recordings in responses to calls decrease for mother mice

To assess the network dynamics in virgins and in lactating mothers, noise correlations (NC) were analyzed by computing trial-to-trial co-fluctuations in firing rate between pairs of recordings in response to the set of pup calls and the set of adult calls. When computed exactly with the same method (and under the same anesthetic agent) as Rothschild et al. (2013), the distribution of NC values was shifted toward lower values in mother mice compared to virgin mice both for the pup calls (Fig 8A1) and for the adult calls (Fig 8B1). The mean values of NC were significantly lower in mothers than in virgins both for the pup calls (0.19 vs. 0.28 unpaired- t-test, $p < 0.001$) and for the adult calls (0.19 vs. 0.27; unpaired- t-test, $p < 0.001$). Computing the stimulus-specific NC (as in Rothschild et al. 2013) led to similar results (Fig 8A2 and 8B2). For both mothers and virgins, stimulus-specific NC varied significantly with stimulus identity (pup calls: ANOVA for virgins $F_{17,551}=4.76$, $p < 0.001$, and for mothers $F_{17,1469}=11.96$, $p < 0.001$; adult calls: ANOVA for virgins $F_{17,499}=11.81$, $p < 0.001$, and for mothers $F_{17,1439}=18.12$, $p < 0.001$). In addition, the mean values of NC (across all calls) were lower in mother mice compared to the mean value in virgin mice (in mothers: 0.20 for pup and adult calls, versus in virgins: 0.29 for pup and adult calls; unpaired t-test, $p < 0.05$ in both cases).

We confirmed that NC (Fig 8C1) and stimulus-specific NC (Fig 8C2) were decreased whatever the stimulus presented, by quantifying the NC from the responses to the guinea pig whistles: both when computed on a similar time window as the mouse calls (70ms) or on the whole whistle duration (280ms), the NC obtained in mothers were systematically lower compared to virgins (over a duration of 70ms: 0.28 vs. 0.20 $p < 0.01$; over a duration of 80ms: 0.40 vs. 0.23, $p < 0.01$). Together, these analyses suggest that, on average, in mother mice two cortical recordings showed less trial-to-trial co-fluctuations in their firing rate than two cortical recordings obtained in virgin mice. This might be an indication that the cortical network dynamics is less synchronized in mother than in virgin mice.

Discussion

We show here in the most commonly used mouse strain for behavioral studies and studies involving genetic constructions, the C57BL/6 mouse, that the processing of acoustic information by auditory cortex neurons is modified from the virgin to the mother physiological state. In mother mice, the cortical frequency receptive fields were narrower and the responses to pure tones were decreased. This contrasts with the fact that the amplitude of the ABR waves IV and V were larger in mothers compared to virgins. The cortical responses to pup and adult calls were also reduced but, strikingly, the amount of information per emitted action potential (MI/spike) about the pup call's identity was increased in mother mice. The response latencies to pure tones were shorter both at brainstem and cortical levels, and it was also the case for the cortical responses to mice calls. Despite similar decreased responses to guinea pig whistles, the response latency, and the MI/spike did not differ between virgins and mothers for these heterospecific vocalizations. Last, the noise correlations between cortical recordings were decreased in mothers, suggesting that the firing rate of distant neurons was more independent from each other.

Similarities and differences with findings reported in other mice strains

Several studies reporting physiological changes in the auditory cortex in mother mice versus virgin mice have used the CBA/CaJ strain, mainly because (i) its auditory thresholds remain good for more than a year (Zheng et al. 1999; Hunter and Willot 1987; Jimenez et al. 1999) and (ii) the existence of a cortical representation of ultrasonic sounds (Shepard et al. 2015, 2016). In this mouse strain, whereas the initial study by Liu and Schreiner (2007) has not observed lower responses in mothers than in virgins, the study by Shepard et al. 2016 has reported that recordings obtained from the fields AI and AAF, displayed lower responses in mother mice than in naïve mice (especially those displaying BF below 40kHz). The larger proportion of single units showing inhibitory response to pup calls in mother mice described by Galindo-Leon et al. (2009) can potentially explain the lower responses observed in multi-unit recordings. These authors hypothesized that plasticity induced inhibitory responses for cortical neurons tuned at frequencies distant from the range of the pup USV.

In NMRI mice, no significant difference has been reported between the evoked and spontaneous activity obtained in virgin and mother mice (Rothschild et al. 2013). Similarly, only slight and non-significant decreases in evoked activity has been detected in pyramidal and parvalbumin positive neurons by Cohen and Mizrahi (2015) in the C57BL/6. In fact, the results of Marlin et al. (2015) were the only study reporting a strong increase in evoked responses and in trial-to-trial reliability in mothers compared to virgins, which might be the consequence of sampling more superficial layers and/or other cell types in their patch experiments. More recently, Tasaka et al. (2018) have also found a transient increase in firing rate but for neurons specifically activated by USV calls as a consequence of a pre-exposure performed 5-6 days before.

In the CBA mouse a reduction in the latency at pup call presentations (from 21.2 to 16.6ms) was observed by Liu and Schreiner (2007), an effect that was confirmed both for single units inhibited by pup calls and for LFP recordings (Galindo-Leon et al. 2009). This effect was also reported by Rothschild et al. (2013) (from 39.2 to 32.9ms) in the NMRI mice. Here, we found shorter cortical latencies both for pure tones and mice vocalizations, an effect also detected here at the brainstem level with pure tones as already described by Miranda et al. (2014).

Based upon MI quantifications, Liu and Schreiner (2007) reported that auditory cortex neurons of mothers were better than those of virgins in detecting and discriminating pup calls, an effect that was more pronounced at the response onset. In line with this result, we found that the value of MI/spike was higher in mothers than in virgins only for the pup calls (Fig. 6A). Thus, despite reduced responses to both adult and pup calls, cortical neurons were better to discriminate the pup calls, potentially based on the fact that the call-to-call differences in terms of response latency were larger in mother mice (Fig 4C). On the other hand, Tasaka et al. (2018) proposed that AI neurons are mostly playing a role in detecting pup calls without participating to their fine discrimination, a function which may occur in higher brain regions.

We found lower noise correlations in mother mice compared to virgins, in contrast with Rothschild et al. (2013) who reported higher noise correlations in mother mice. Besides methodological differences (two-photon vs. electrophysiological data) and potentially layer differences (sampling more superficial layers in two-photon imaging), these authors described noise correlations between closely adjacent neurons (less than 200µm apart) whereas the noise correlations reported here are between clusters of

neurons, which were on average 1000 μ m apart. It is not unrealistic to consider that, in mothers compared to virgins, the firing rate of neurons at close vicinity is more correlated whereas the firing rate of neurons at larger distances is less correlated. Note also that the temporal window used to compute noise correlations was much larger in two-photon imaging (250 ms) than in electrophysiology (65 ms).

Remarkably, it is interesting to note that the effects detected for the response to pup calls differed from effects detected for the responses to adult calls and guinea pig whistles. Despite close spectral and temporal parameters between pup and adult calls (see Methods), neurons of mother mice seem to be slightly better at discriminating the pup than the adult calls. It is possible that exposure to pup calls during the 9-10 days postpartum was sufficient to induce cortical plasticity specific to pup USV compared to the adult USV or the guinea pig whistles. In two studies (Shepard et al. 2016; Tasaka et al. 2018), postpartum induced changes have been investigated over time and the effects, especially the response strength, differed according to the number of days after parturition. Thus, testing our animals at different days post-partum might have revealed larger effects.

Potential mechanisms explaining our results

The changes detected in auditory cortex in mother mice are potentially the consequence of plasticity induced by the association between the calls emitted by pups and the large increase in concentration of various neuro-hormones and neuromodulators present during parturition and lactation. In their study, Marlin and colleagues (2015) reported that the increase in evoked responses and temporal reliability detected in mother mice can be replicated by pairing between pup calls presentations and either topical oxytocin application or oxytocin release by optogenetic stimulation in AI.

As this increase in evoked responses was not found by other studies (Rothschild et al. 2013; Cohen and Mizrahi 2015, Shepard et al. 2015, 2016) and in our data, other mechanisms than the oxytocin-induced facilitations should be envisioned. For example, neuropeptides such as oxytocin and vasopressin (Fliers et al. 1985, 1986; Petersson et al. 1998) and the steroidal hormone estradiol can activate neurons releasing neuromodulators, such as noradrenaline (Serova et al. 2011; Wade et al. 2013) which in turn promotes reduction in evoked responses in auditory cortex. Indeed, noradrenaline has been shown to decrease spontaneous and evoked activity by acting on α 1

receptors (Manunta and Edeline 1997; Gaucher and Edeline 2015). Furthermore, pairing protocols involving association between NA application or locus coeruleus stimulation and an auditory stimulus induced decreases in evoked responses specific for that stimulus (Manunta and Edeline 2004; Edeline et al. 2011). In addition, at several levels of the auditory system, NA application also tends to reduce the jitter of evoked responses, which can lead to a decrease in response latency (cochlear nucleus: Kössl and Vater 1989; auditory cortex: Manunta and Edeline 1997; see Fig. 3 in Edeline 2012).

Therefore, it is possible that neuromodulators or neuro-hormones promoted inhibitory mechanisms by decreasing the thalamo-cortical transmission or by a larger activation of intra-cortical (and/or sub-cortical) inhibitory neurons, and that these inhibitory mechanisms improved the cortical detection of pup calls over other types of acoustic stimuli (Galindo-Leon et al. 2009). Neuromodulators also impact the network dynamics (Metherate and Ashe 1993; Giocomo and Hasselmo 2007; Deliano et al. 2020) which can potentially explain the decrease in noise correlations found in mothers compared to virgin mice.

Interestingly, despite similar ABR thresholds, we also found significant effects of motherhood on the amplitudes and latencies of ABR waves, suggesting that neuromodulators and neurohormones impact the auditory system as early as the first relays in the auditory system (cochlear nucleus: Kössl and Vater 1989; inferior colliculus: Hurley and Pollak 1999, 2005). On the one hand, the reduced response latency observed at the cortical level can result from the reduced latencies observed in the brainstem. On the other hand, as the amplitude of the ABR waves IV and V were larger in mothers, the attenuated cortical responses cannot be explained by an action of neuromodulators at the brainstem level. Thus, the global effect observed in mothers at the cortical level is a combination of both subcortical effects and intrinsic cortical effects.

The specificity of the C57BL/6 model

The C57BL/6 mouse is a special case in the field of auditory neurosciences because its aged-related hearing loss can occur very early in age (3-5 months), starting in the highest frequencies (Mikaelian et al. 1974; Henry and Chole, 1980), which leads to a lack of CF above 24kHz for the eight nerve fibers of this strain at the adult stage (Taberner and Liberman 2005). As a consequence, at the level of the auditory cortex, there was no CF above 30kHz in electrophysiological (Tan and Wehr, 2009; Hackett et al. 2011; Cohen

and Mizrahi 2015; Moore and Wehr, 2013, 2018) and two-photon studies (Bandyopadhyay et al. 2010; Chen et al. 2011). Therefore, the cortical representation of ultrasonic frequencies (40-100kHz) does not seem to exist in this mouse strain, which explains why none of our BF was above 24kHz.

Nonetheless, we observed here that many cortical sites responded to the USV calls. In the CBA/CaJ mouse only 12% of the auditory cortex is allocated to ultrasonic frequencies, but more than 30% of the multi-unit recordings respond to the pup calls, including neurons with BF between 8 and 32kHz (see Fig 1 in Shepard et al. 2016). Similarly, in the inferior colliculus of CBA mice 60 to 80% of the cells with low frequency CF responded to ultrasonic calls (Portfors et al. 2009).

Several factors can potentially explain why neurons with low or middle frequency CF can respond to USV calls. In the IC, Portfors and colleagues (2009) showed that neurons can respond to the combination of ultrasonic tones if their difference is in the excitatory tuning curve of the neurons. They suggested that the quadratic and/or cubic intermodulation distortion component generated in the cochlea by ultrasonic vocalizations allow a large fraction of neurons to respond to these vocalizations.

Another possibility is that the response of cortical neurons is not primarily determined by the spectral content of natural stimuli, which has been largely documented in many species (cat: Bar-Yosef et al. 2002; rat: Machens et al. 2004; mice: Ahrens et al. 2008; bird: Woolley et al. 2006; guinea-pig: Laudanski et al. 2012; human: Bitterman et al. 2008). Among many acoustic cues, the rising slope of an acoustic stimulus can change the response strength and its latency (Heil 1997a, b, 2011). In our case, the very sharp rising slope of the adult and pup calls (1-5ms) or subtle variations in the frequency trajectory of the calls (Chong et al. 2020) could promote responses even if the neuron CF is far from the spectral content of the vocalizations.

To conclude, despite a lack of high frequency representation at the cortical level, cortical neurons of C57BL/6 mice can respond to pup and adult calls, and, more importantly, can display selective neuronal plasticity for communication sounds when they became significant. This suggests that the C57BL/6 is a suitable model for studying the plasticity of cortical representations involving communication sounds during motherhood and other natural situations.

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Authors Contribution

This work has been performed at the Paris-Saclay Institute of Neurosciences (NeuroPSI). CH, FO, JMC and JME designed the experiments. JR performed the experiment. JR, CH and FO analyzed the data. JR, JME, CH and JMC wrote the manuscript. All authors approved the final version of the manuscript.

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Figure Legends

Figure 1: ABR threshold, amplitude and latency of the waves in virgin and mother mice

A: The threshold of auditory brainstem responses (ABR) were similar in virgin and mother mice. Pure tones (at 4, 8, 16, 24 and 32 kHz) were presented at different intensities (between 70 and -10 dB SPL) and the threshold of wave III of the ABR was determined. Each point represents the mean threshold (\pm sem) of each group at the different frequencies.

B: Typical example of the ABR waves (labeled I to V) detected at 70dB SPL for a 8kHz pure tone (500 trials repeated at 10Hz).

C: Violin plots displaying the distribution of the amplitude of waves I to V in virgins and mother mice. The amplitude of waves IV were significantly larger in mothers than in virgins at the click, at 8 and 16 kHz. It was also the case for the amplitude of wave III at 8kHz.

D: Violin plots displaying the distribution of the latency of waves I to V in virgins and mother mice. The latencies of waves II to V were significantly shorter in mothers compared to virgins at click, 8 and 16 kHz.

In each violin plot, the open dot represents the median, the horizontal bar represents the mean and the vertical bar the 25th and 75th quartiles. * : p value <0.05; **: p value <0.01; ***: p value <0.001.

Fig 2: Quantification of spectro-temporal receptive fields (STRFs) at 75 dB

A: Typical examples of STRFs in response to pure tones in the primary auditory cortex of virgin (left) and mother (right) mice. Gamma tones (50 ms in duration) between 2.5 and 80 kHz were presented at 75 dB at a rate of 4Hz. The color gradient represents the neurons firing rate with the blue indicating the minimum firing rate (close to the level of spontaneous activity in dark blue) and the red indicating the maximum firing rate obtained for a range of frequencies. The thin white line indicates the evoked firing rate 6SD above the mean level of spontaneous activity. The maximum firing rate at a given frequency allows defining the neuron Best Frequency (BF). The bandwidth (bw), latency (la), and duration (du) have been quantified for each receptive field.

B: Distribution of the neurons' Best Frequencies (BF) in virgin and mother mice. The BF values were classified by octaves. The distributions of the BF values did not differ between virgin (blue) and mother (grey) mice.

C: Quantification of the receptive field parameters. Four parameters were quantified: the evoked firing rate, the bandwidth, the response latency at the BF and the duration of the receptive field. On average, the evoked firing rate was lower for the neurons recorded in the mother mice. The receptive fields bandwidth and their duration were significantly lower for neurons recorded in mother mice compared with neurons recorded in virgins. The response latency was also shorter in the auditory cortex neurons of mother mice.

In each violin plot, the open dot represents the median the horizontal bar represents the mean and the vertical bar the 25th and 75th quartiles. **: p value <0.01; ***: p value <0.001.

Fig 3: Typical examples of response to mouse pup (left) mouse adult (middle) and guinea pig (right) vocalizations

Time zero of the x-axis corresponds to the beginning of the pre-stimulus activity. The beginning to the vocalization is a 100ms for the pup and adult calls and at 200ms for the guinea pig whistles. The orange lines indicate the vocalization onset independently of this duration. Each vocalization was repeated 20 times. Note the different time scales between the pup and adult mouse calls and the guinea pig whistle. Note also that the spontaneous and the evoked firing rate were lower in mother mice (bottom) compared to virgin mice (top) for the three types of vocalizations.

Fig 4: Quantification of responses to pup and adult calls

A: On average, the spontaneous and evoked activities were significantly lower for the neurons recorded in mother mice. This was also the case for the number of spikes per trial (middle). The response latency to pup and adult calls was also shorter in mother mice (right). In each violin plot, the open dot represents the median the horizontal bar represents the mean and the vertical bar the 25th and 75th quartiles. * : p value <0.05; ***: p value <0.001.

B: Evoked responses (firing rate in spikes/s) for each pup (left) and adult (right) calls. The lower firing rate observed for the neurons recorded in mother mice (displayed in A) was present for the responses to each pup (left) and adult male (right) call.

C: Response latency for each pup (left) and adult (right) call. The small latency difference founded on average between neurons recorded in virgin and mother mice (displayed in A) was clearly detected in the responses to each call but was more visible for the response latencies obtained at presentation of the pup calls. Note that the mean latency to all pup calls (gray and blue dashed lines) and the latency to each pup call were larger in mothers than in virgins (2.72ms vs. 2.38ms) whereas it was not the case for the adult calls (3.98ms vs. 3.92ms).

Fig 5: Proportion of neurons responding to the pup and adult calls

A: Cumulative percentages of neurons showing significant responses to pup calls.

B: Cumulative percentages of neurons showing significant responses to adult calls.

Both for the pup and adult calls, there were no significant differences between the distributions obtained in virgins and mothers.

Fig 6: Quantification of mutual information (MI)

A: Mutual information per spike: On average, the mutual information per spike emitted at presentation of the pup vocalizations, was higher for neurons recorded in mothers than for neurons recorded in virgins. For adult calls, there is no significant difference.

In each violin plot, the open dot represents the median, the horizontal bar represents the mean and the vertical bar the 25th and 75th quartiles. * : p value <0.05; **: p value <0.01; ***: p value <0.001.

B: MI/Spike as a function of the number of significant responses to the pup (left) and adult (right) vocalizations: In virgin mice, there was a non-significant tendency for neurons responding to the largest number of vocalizations to have slightly larger values

of mutual information per spike. In contrast, in mother mice, there was a significant negative correlation between the value of MI/Spike and the number of calls.

Fig 7: Quantification of responses to heterospecific (guinea pig) vocalizations

A: On average, spontaneous and evoked activities (left) were significantly lower for the neurons recorded in mother mice. This was also the case for the number of spikes per trial (middle).

B: The response latency to guinea pig vocalizations was not different between mother and virgin mice (right).

C: The mutual information per spike emitted at presentation of the guinea pig vocalizations was not different between mothers and virgins.

In each violin plot, the open dot represents the median, the horizontal bar represents the mean and the vertical bar the 25th and 75th quartiles. * : p value <0.05; **: p value <0.01; ***: p value <0.001.

Figure 8: Quantification of Noise Correlation (NC) between pairs of recording sites

A1, B1 and C1: Distribution of NC values (i.e., Correlation of the mean firing rate of recording sites to each stimulus compared to all the single-trial responses of one recording site to that stimulus) of virgin (blue) and mother (grey) mice in response to pup calls (A1), adult calls (B1), and guinea pig whistles (C1). Mean NC values in mothers (0.19 for pup and adult calls, and 0.20 for guinea pig whistles) were significantly lower compared with those obtained in virgin mice (0.27 for pup calls, 0.28 for adult calls, and 0.28 for guinea pig whistles).

A2, B2 and C2: Stimulus-Specific Noise Correlation (SSNC) (i.e., Correlation of the firing rate of pairs of recording sites in response to the same stimulus) of virgin and mother mice in response to pup calls (A2), adult calls (B2), and guinea pig whistles (C2). On average, the NC values for each vocalization in mothers (0.20 for pup and adult calls, 0.27 for guinea pig whistles) were significantly lower compared with those obtained in virgin mice (0.29 for pup and adult calls, 0.40 for guinea pig whistles).

Highlights

- ABR thresholds were similar in mother vs. in virgin mice but latencies were shorter
- Evoked cortical responses were decreased in mothers compared to virgins
- Cortical response latencies were shorter in mothers than in virgins
- The MI per spike was higher in mothers than in virgins only for pup calls
- The noise correlations were lower in mothers than in virgins for all stimuli

