Biomagnetic Measurement System on Mice—Evaluation of System Performance by MCG and Application to MEG

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Biomagnetic Measurement System on Mice

-Evaluation of System Performance by MCG and Application to MEG-

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Abstract. We developed a biomagnetic measurement system on mice. Our initial model of the system has the magnetic field sensitivity of 1.3 pT/Hz1/2 in the white-noise region (10 Hz-10 kHz). And using the system, we succeeded to obtain magnetically the heart activity on mice. However, in its application to measure the brain activity on mice, it was necessary to improve the magnetic field sensitivity of the system. Therefore, we changed the material of the window cap, which holds a sapphire glass window on the dewar tail, to ceramic. The system noise was decreased and the magnetic field sensitivity of the system was improved to 0.75 pT/Hz1/2 in the white-noise region. For an initial measurement of the brain activity, we also developed a whisker stimulation system using a piezoelectric element to evoke somatosensory responses.

1. Introduction

A biomagnetic measurement system on mice using a dc superconducting quantum interference device (SQUID) magnetometer has been developed. We are going to use it for the magnetic studies of the brain activity (magnetoencephalogram; MEG) on genetically modified mice to evaluate the dysfunction caused by gene modification in the living body. The mice, whose genetic codes were almost completely revealed, are widely used in biological or behavioural studies of gene modification and a large variety of “disease-model” mice are now available. And the MEG detects the neuronal activity in good time and spatial resolution. The MEG is also a contact-free and non-invasive technique that has been widely used in neurophysiological screening on human. The use of MEG on experimental animals is expected to connect the results of the non-invasive screenings on human and the pathology on disease-model animals, and it would contribute to the medical diagnosis or treatment of human disease. Recently, our group [1] and Steinhoff et al. [2] developed biomagnetic measurement systems on mice. We succeeded to obtain the magnetic heart activity (magnetocardiogram; MCG) on mice using the developed system. However, in its
application to MEG measurement, more than 5000 times of signal averaging, corresponding to more than two hours measurement might be required to obtain the clear MEG waveform. Therefore, we improved the system noise. We also developed a whisker stimulation system to evoke the brain response in the somatosensory area of the brain, and investigated the requirements for the MEG measurement. The presented paper describes the improvement of the system noise and its performance with comparison of mice MCG data measured using the initial system and the improved system, and the whisker stimulation system.

2. Biomagnetic Measurement System

A. Dc SQUID

A low-Tc direct coupled dc SQUID magnetometer with Nb/AlOx/Nb Josephson junctions is adopted to suppress the magnetic flux noise. The outside/inside diameter of the focuser type pickup coil is 1 mm/100 μm, respectively, considering the lift-off distance (the distance between the pickup coil and the dewar tail) [3]. The effective diameter of the pickup coil is 320 μm. The small outside diameter is advantageous to the MEG or the MCG mapping on mice, considering the size of the brain or the heart (the size is less than 1 × 1 cm²).

B. System Configuration

The developed system consists of a single channel SQUID magnetometer and a non-magnetic measurement table. The system is installed in a magnetic shield box (dimension: 0.63 × 0.63 × 0.85 m³) made of high-permeability alloy. The shield box is placed in an electromagnetic shield room (dimension: 2.1 × 2.1 × 2.5 m³). A non-magnetic compact dewar was developed. The capacity of the dewar is 1700 cm³, and the amount of liquid helium evaporation is 90 cm³/h. The dewar has special structure to avoid the effect of thermal shrinkage, which contributes to keep the fixed lift-off distance. The table is arranged below the dewar and is set manually to the appropriate horizontal and vertical position. For the positioning, two laser beams indicate the horizontal center position of the pickup coil. On the table, a non-magnetic head stereotaxic apparatus is fixed to settle a mouse head correctly.

C. Magnetometer Installation

Figure 1 is the schematic representation of the SQUID magnetometer. The minimum lift-off distance is reduced to 700 μm. The short lift-off distance improves the spatial resolution and further prevents the attenuation of the magnetic field generated by a biomagnetic source. The minimum spatial resolution of the SQUID magnetometer is 500 μm, which was evaluated from the measurement of magnetic field generated by a direct current through meander lines. The SQUID magnetometer, embedded in a sapphire holder that is thermally connected to liquid helium through a oxygen free copper rod, is located in evacuated space neighboring a sapphire glass window (thickness: 100 μm) on the dewar. And the magnetometer was covered with a thin radiation shield plate made of phosphor bronze (thickness: 50 μm).
3. Improvement of System Noise
   
   A. Noise spectrum
   
   Our initial system has an aluminum window cap and the magnetic field sensitivity of 2.0 pT/Hz$^{1/2}$ at 1.3 Hz and 1.3 pT/Hz$^{1/2}$ in the white-noise region (10 Hz-10 kHz). The system noise, however, was still high for the MEG measurement. The radiation shield plate and the aluminum window cap mainly cause the system noise. Therefore, we changed the material of the window cap from aluminum to ceramic. The magnetic field sensitivity was improved to 1.12 pT/Hz$^{1/2}$ at 1 Hz and 0.75 pT/Hz$^{1/2}$ in 100 Hz-10 kHz. A spectrum of the system noise of the improved system are shown in Figure 2, and we confirmed the performance of the improved system with comparison between mice MCG data measured using the initial system and the improved system.

   B. MCG measurement
   
   We prepared two mice. Both mice are C57BL/NCij, wild type. One of the mice, mouse 1 was female (29 g, 6 month-age) and measured by the improved system. The other, mouse 2 was male (26 g, 6 month-age) and measured by the initial system. Unfortunately, we couldn’t use same mice for this comparison, because the life of mice is so short. The anesthesia was administered by Isofulrane (1.5-2.0%), oxide gas and nitrous oxide gas. Mice were laid down on their backs, and MCG data were measured at 16 points on their thorax. The distance between the thorax and the dewar tail was less than 1 mm. The electrocardiogram (ECG) data in the lead II configuration were also measured simultaneously. The MCG and ECG data were stored in a computer by 4 kHz sampling through a band pass filter of 0.08-1000 Hz and a notch filter of the power line frequency of 50 Hz, and were processed to a 400 Hz low pass digital filtering. The MCG data were averaged more than 400 times at the time points of R peak of the ECG as the trigger. Baseline correction was applied to the averaged MCG data.

   C. MCG Result
   
   Figure 3 is an example of the raw MCG data of mouse 1. The improvement of field sensitivity is clear. QRS complex and T wave of the MCG on mouse 1 are visible, though they are invisible on mouse 2. Figure 5 is the averaged MCG data of mouse 1 and mouse 2. The standard deviations of noise (during 50 ms before P wave in the averaged MCG data) are 1.91 on mouse 1 and 2.56 on mouse 2. The system noise was improved. It is a positional mismatch that the positions of the point, which shows the largest response, shift between mouse 1 and mouse 2.
4. Whisker Stimulation System

In the cerebral cortex of the brain, there are visual, auditory, somatosensory, olfactory, motor and other area. In the case of mouse, whisker somatosensory area occupies a great part of cerebral cortex. Therefore, the bigger response is expected even under anesthesia. Then we are going to obtain the magnetic somatosensory response (somatosensory evoked field; SEF) induced by the stimulation to the whisker, as the first MEG measurement on mice. We developed a whisker stimulation system using a piezoelectric element (dimension: $0.7 \times 6.1 \times 35.4$ mm$^3$). One of the whiskers is connected to the piezoelectric element using a nylon string. A tension of the piezoelectric element is applied to the whisker as the stimulation. We confirmed the performance of the system measuring the electric somatosensory response (somatosensory evoked potential; SEP). To measure the MEG, however, the stimulation system generates much magnetic noise. It was necessary to decrease the noise.

5. Discussion

We estimated the amplitude of the auditory response (auditory evoked field; AEF) on mice would be in the order of several pT from the MEG study of rats [4]. To measure the AEF using the initial system, over 5000 times of signal averaging might be required. But this time, the system noise was improved to about the half and we estimated that we could measure with below 1500 times of signal averaging using the improved system. If the SEF is twice the AEF in the amplitude, we would obtain the SEF with below 500 times of signal averaging, corresponding to about 15 minutes measurement. Timewise, it is enough possible to perform the MEG measurement. However, we have not succeeded yet in the SEF measurement due to the noise disturbance. We must decrease the noise generated from the piezoelectric element. Further improvements of the system noise are required to decrease the averaging number and to measure the weaker brain response. The longer sapphire holder of SQUID will decrease the coupling of the Johnson noise of the copper holder to the pickup coil. We should also examine the most appropriate anesthesia, which has less influence on the brain of mice.

6. Conclusion

A biomagnetic measurement system on mice using a dc SQUID magnetometer was developed to evaluate the dysfunction caused by gene modification. For the MEG measurement, the magnetic field sensitivity of the system was improved to 750 fT/Hz$^{1/2}$ in the white-noise region by changing the material of window cap to ceramic. And its performance was confirmed with the comparison of mice MCG data. And we also developed the whisker stimulation to evoke the SEF. We are now improving the shield method for the stimulation system. After the improvement, we will perform the MEG measurement using the developed systems.

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