APPLIED PHYSICS LETTERS **100**, 132601 (2012)

High-T_c superconducting quantum interference device recordings of spontaneous brain activity: Towards high-T_c magnetoencephalography

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(Received 6 March 2012; accepted 12 March 2012; published online 27 March 2012)

We have performed single- and two-channel high transition temperature (high-T_c) superconducting quantum interference device (SQUID) magnetoencephalography (MEG) recordings of spontaneous brain activity in two healthy human subjects. We demonstrate modulation of two well-known brain rhythms: the occipital alpha rhythm and the mu rhythm found in the motor cortex. We further show that despite higher noise-levels compared to their low-T_c counterparts, high-T_c SQUIDs can be used to detect and record physiologically relevant brain rhythms with comparable signal-to-noise ratios. These results indicate the utility of high-T_c technology in MEG recordings of a broader range of brain activity. *© 2012 American Institute of Physics*. [http://dx.doi.org/10.1063/1.3698152]

The first magnetic recordings of human brain activity were made with an induction coil[1] and led to a significant leap in neuroscience research. A few years later, the invention of the low transition temperature (low-T_c) superconducting quantum interference device (SQUID) revolutionized the field by improving the sensitivity of magnetic recordings by orders of magnitude.[2] In modern magnetoencephalography (MEG) systems, hundreds of low-T_c SQUID sensors are enclosed in a helmet that surrounds the subject's head and map the magnetic field emanating from the brain. Low-T_c SQUIDs are preferred because of their high fabrication yield and superior noise performance. A typical noise figure for such a SQUID is 1–5 $\mathrm{fT}/\sqrt{\mathrm{Hz}}$ at 10 Hz,[3,4] roughly one order of magnitude better than a similar high-T_c device. However, in order to keep the low-T_c SQUIDs operating at 4 K, thermal insulation limits the separation between the cold sensors and the room temperature environment to 18 mm at best (Elekta, Neuromag®). The possibility to operate high-T_c SQUIDs at 77 K has enabled some researchers to reduce this distance to just a few hundred microns.[5–7]

The first MEG recordings with high-T_c SQUIDs were accomplished some years after the discovery of high-T_c superconductivity when Zhang *et al.*[8] recorded the brain's response to auditory stimuli in 1993. Similar studies have proven high-T_c technology is sensitive enough to record such well-understood *evoked* MEG sources by averaging hundreds or thousands of stimulus-response signals.[9–11] However, recordings of *spontaneous* brain activity have yet to be demonstrated, perhaps because many spontaneous rhythms present themselves at frequencies below 20 Hz, where $1/f$ noise can be problematic for high-T_c SQUID technology. Furthermore, it is not possible to average spontaneous brain activity in the time-domain due to its inherently spontaneous nature.

Herein, we present MEG recordings of spontaneous brain activity in humans with single- and two-channel high-T_c SQUID magnetometer systems. We demonstrate time resolved modulation of the occipital alpha rhythm via visual stimulation as well as modulation of the mu rhythm in the motor cortex via muscle activation, both of which are well-characterized phenomena and are present in the 8–13 Hz range.

The most prominent sources of brain activity to which MEG is sensitive are current dipoles located on the cortical surface. The surrounding layers (including spaces filled with cerebrospinal fluid, the skull, scalp, etc.) add up to the roughly 1 cm distance between the surface of the head and this outermost active layer of an adult human's brain. Anatomy thus places a ∼1 cm lower limit on the brain activity source-to-room temperature spacing in typical MEG recordings.[12,13] Whereas thermal insulation moves low-T_c SQUIDs an additional 18 mm away from the sources of brain activity—leading to a total source-to-sensor spacing of nearly 3 cm—high-T_c SQUIDs can effectively operate at the anatomical limit of ∼1 cm.

The first non-vanishing term in a magnetic multipole expansion of a current dipole is the dipolar term. In the ideal case, the magnitude of the field generated by a dipole decays as $1/r^3$ as a function of distance, r, from the source. The absolute field strength available to a high-T_c SQUID is then a factor of 27 higher than that which is available to a low-T_c SQUID in MEG recordings. The higher noise levels typical of high-T_c SQUIDs are then compensated by higher signal levels. In a more thorough analysis, Tarte *et al.*[14] prove high-T_c SQUID-based systems are theoretically capable of a higher signal-to-noise ratio (SNR) than their low-T_c

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counterparts in magnetophysiological recordings. Furthermore, the reduced stand-off distance facilitates detection of higher order components of the magnetic multipole expansion, e.g., quadrupoles, that may be difficult to detect just a few centimeters from the scalp.[15]

The sensors used in our experiments were fabricated from epitaxial $YBa_2Cu_3O_{7-x}$ (YBCO) thin films grown on (100-oriented) 10×10 mm^2 $SrTiO_3$ (STO) bi-crystal substrates with a misorientation angle of 24°. The 300 nm thick YBCO thin films were grown by pulsed laser ablation and were patterned using standard photolithography and argon ion etching processes. A micrograph of one of the SQUID magnetometers is shown in Fig. 1(a) and a magnification of the "hair-pin" type SQUIDs in Fig. 1(b). The SQUIDs were directly coupled to 8×8 mm^2 single turn pick-up loops. The geometry and flux focusing of the superconducting loops resulted in a measured magnetic flux-to-field conversion of 5.3 nT/Φ_0. The SQUIDs could be operated (Magnicon GmbH, SEL-1/3 electronics) with a dc current bias as well as in bias-reversal mode,[16] enabling critical current fluctuations to be cancelled and the low frequency (1/*f*) noise to be substantially reduced. At 77 K, the critical current of one of the SQUIDs, having 3 μm wide Josephson junctions, was 80 μA and the voltage modulation was 32 μV. The noise performance of this SQUID magnetometer as a function of frequency is shown in Fig. 1(c). The noise at 10 Hz was about 9.1 $\mu\Phi_0/\sqrt{\text{Hz}}$ or 50 fT/$\sqrt{\text{Hz}}$. Also of note is the reduction of the 1/*f* noise with bias-reversal. These parameters and noise levels are typical of the SQUIDs we used in these experiments.

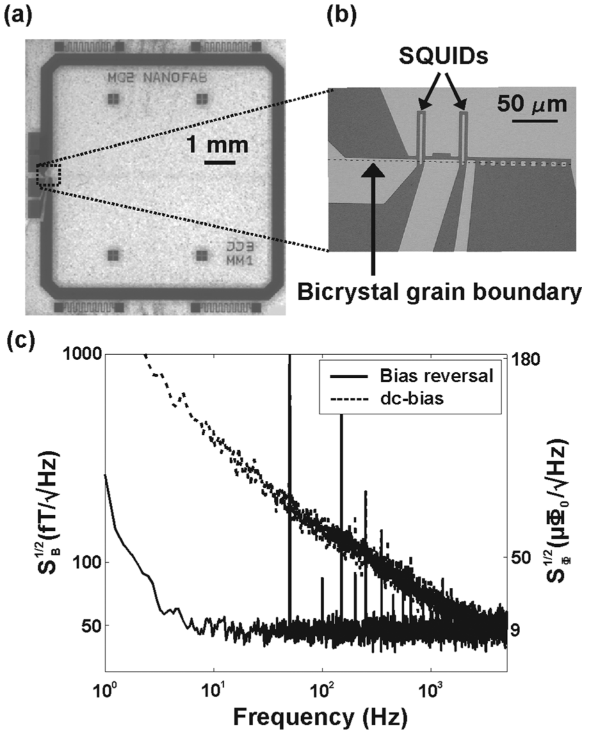

FIG. 1. SQUID magnetometer used for MEG. (a) Micrograph of one of the SQUID magnetometers made from YBCO. The large square is the pickup loop that feeds flux into the SQUID. (b) Zoomed-up view of the SQUIDs. Two SQUIDs are fabricated in the same pickup loop for redundancy; only one was used for each MEG channel during recordings. The bicrystal grain boundary (dashed line) crosses the 3 μm wide constrictions in the film, creating Josephson junctions. (c) Flux noise (right axis) and equivalent magnetic field noise (left axis) as a function of frequency with two biasing modes. The bias reversal mode (solid) significantly reduced the low frequency (1/*f*) noise as compared with the dc-bias mode (dashed). The noise level of this SQUID magnetometer at 10 Hz was 50 fT/$\sqrt{\text{Hz}}$.

The MEG measurements were performed in a three layer magnetically shielded room in order to reduce magnetic noise (MSR by Vacuum Schmeltze GmbH, with 2 mu-metal layers sandwiching a copper-coated aluminum layer, magnetic shielding factors of 10 000 and 50 000 at 10 Hz and 1 kHz, respectively). The SQUID magnetometers were independently mounted on a sapphire rod in identical non-magnetic epoxy-reinforced glass fiber cryostats (ILK Dresden). Each sapphire rod was thermally connected to a hermetically sealed liquid nitrogen bath (~0.7 liters) that could be pumped on to control the temperature in the range of ~70 to 77 K. The cold SQUID was separated from the room-temperature environment with a 200 μm thick sapphire window. The sensor could be moved towards or away from the window manually. The SQUID-to-scalp separation during the recordings was typically ~3 mm. The SQUIDs of the two-channel system could be independently placed at nearly arbitrary locations on the head, the only limitation being that they could not be placed closer than roughly 10 cm from each other (due to the size of the cryostats). The output of the SQUID electronics was sent to a pre-amplifier with a band-pass filter typically at 1–30 Hz and gain of 1000.

One of the most well-known of the spontaneous brain activities is the alpha rhythm, present in the 8–13 Hz range. Alpha rhythms during wakefulness signify cortical resting activity. Occipital (from the back of the head) alpha activity is observed when visual input is blocked, e.g., when a subject is relaxed and has closed eyes and becomes significantly attenuated upon resumption of visual input, e.g., opening of the eyes.[17,18] In a similar manner, the mu rhythm (also 8–13 Hz) is a resting rhythm of the motor cortex and is suppressed by, e.g., flexing the hands.[18]

The time trace in Fig. 2(a) shows a single-channel 64-s recording from the occipital region of an awake and alert human subject's head that demonstrates modulation of the alpha rhythm. The subject started with eyes shut, resulting in

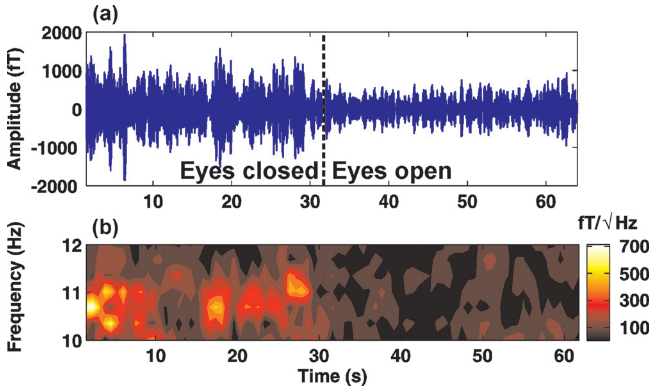

FIG. 2. High-T_c MEG recording of the alpha rhythm. (a) Time trace (band-pass filtered around the alpha band, 8–12 Hz) of a recording from the occipital region of an awake and alert subject. Alpha activity is suppressed when the subject opens his eyes after 32 s. (b) Spectrogram of the time-trace in panel (a). Again, the alpha activity at 10.5–11 Hz is substantially attenuated after the subject opens his eyes.

a high amplitude signal during the first 32 s of the recording, as expected. After 32 s, the subject was instructed to open his eyes, and consequently, the signal is attenuated. In order to present the frequency components of the signal more clearly, we plot the data as a spectrogram in Fig. 2(b). This figure was obtained by splitting the data into 3-s bins with a step size of 0.7 s. Each bin underwent a Fourier transform, the amplitude of which is plotted at its corresponding time slot. The main frequency components of the time trace in Fig. 2(a) are then visible as peaks in Fig. 2(b) at 10.5–11 Hz with maximum amplitude of roughly 700 fT/$\sqrt{\text{Hz}}$ and SNR $\sim$ 10. Such signals are within the known range for alpha rhythm activity (8–13 Hz). The clear attenuation of the alpha rhythm signals after 32 s (when the subject had open eyes) further indicates the signals recorded are emanating from spontaneous brain activity.

Fig. 3 presents 64-s spectrograms of spontaneous brain activity recorded with our two-channel MEG system. In this case, one high-T_c SQUID magnetometer was placed in the occipital region (O2/back right) of a subject's head, the other over the motor cortex (C4/$\sim$7 cm above the right ear). The subject started with open eyes and relaxed hands and was verbally instructed to both shut his eyes and flex his hands after 32 s. As expected, occipital alpha activity (Fig. 3(a)) at 10–12 Hz was suppressed until the subject shut his eyes. Simultaneous recordings of mu activity from the motor cortex (Fig. 3(b)) show strong 10–12 Hz signals that were suppressed upon flexion of the hands, also as expected. Further recordings of independently modulated alpha and mu rhythms were performed on this and another subject. Parallel electroencephalography recordings further corroborated these results.

This preliminary study suggests areas for further development. First and foremost, the position of each SQUID could be improved both by further reducing the spacing between the sensor and the room-temperature environment and by better localizing the sources of brain activity. Due to technical limitations, our present setup limited the SQUID to room-temperature standoff to roughly 3 mm. We have previously reduced this distance to just a few hundred micrometers[6,19] where the signal strength would be significantly higher.

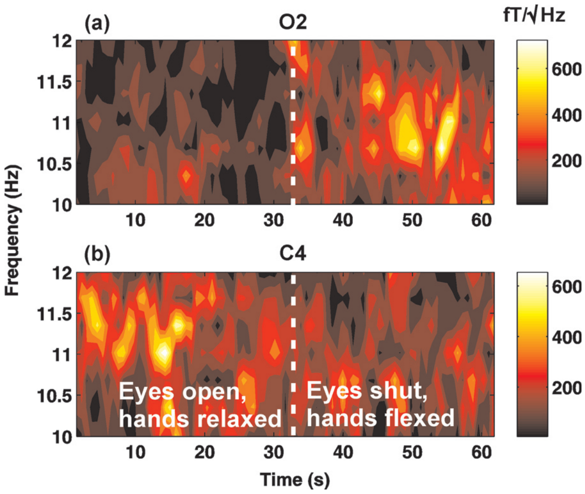

FIG. 3. Spectrograms of a two-channel MEG recording. The recording was made from the occipital (O2, panel (a)) and motor cortex (C4, panel (b)) of a human subject's head with two high-T_c SQUID magnetometers. The subject started with open eyes and relaxed hands. After 32 s, the subject was instructed to flex his hands and shut his eyes. (a) Spontaneous brain activity in the occipital region of the brain. Alpha activity at 10–12 Hz is absent during the first 32 s and exceeds 600 fT/$\sqrt{\text{Hz}}$ upon closing the eyes, as expected. (b) Spontaneous brain activity in the motor cortex recorded during the same 64 s as the alpha activity. Also as expected, the mu-rhythm is clearly attenuated when the subject flexes his hands.

Decreasing the noise levels of the SQUID sensors would further improve the SNR in MEG recordings. At present, the noise limit that we have achieved with our SQUID magnetometers is 25 fT/$\sqrt{\text{Hz}}$ above 40 Hz and 43 fT/$\sqrt{\text{Hz}}$ at 10 Hz. However, with this layout, the coupling efficiency between the pick-up loop and the SQUID is weak due to the inductance mismatch of the two elements ($L_{\text{SQUID}}/L_{\text{pick-up}}$ $\sim$ 0.001). This mismatch can be reduced significantly by employing a flux transformer with a multi-turn input coil coupled to the SQUID.[20,21] However, it should be noted that the present performance is sufficient to record physiologically relevant brain rhythms, and the SQUID magnetometers used in our MEG recordings were made via deposition and patterning of single superconducting thin films. Our fabrication process is, therefore, inherently simple compared to the multilayer structures required for more sensitive high-T_c SQUIDs.[20] That simplicity translates directly into high yield with our technology: We reliably fabricate SQUIDs with sufficient noise performance for incorporation in a full-head high-T_c MEG system.

Ultimately, one should aim for a competitive advantage over the state-of-the-art in MEG systems. In modern systems, most sensors are more than 20 mm from the subject's scalp because it is rare for a person's head to fit exactly inside the rigid helmet-shaped liquid helium dewars that low-T_c technology requires. High-T_c technology allows for both a reduction in this distance to less than a millimeter and a more flexible cooling system configuration. A modular set of distributed cooling systems based on state-of-the-art micro-cryocooling technology[22] could, for example, replace the bulky cryostats employed in these experiments. It is, therefore, possible to incorporate an array of our SQUID sensors into a flexible MEG helmet that fits snugly around arbitrary head sizes and shapes. Such an array of sensors in close proximity to the head is likely to increase the spatial resolution of MEG recordings and enable the study of new sources of brain activity, including higher-order and higher frequency sources of interest.[23–25] For example, high-T_c SQUID-based MEG systems may be used for high-sensitivity recordings of the gamma rhythm at frequencies approaching 100 Hz, well above the $1/f$ noise regime typical of this technology. Consequently, a flexible, full-head high-T_c SQUID-based MEG system may thus provide a closer look at the nature of brain activity.

In summary, we have demonstrated recordings of spontaneous human brain activity with single- and two-channel high-T_c SQUID MEG systems. We present modulation of two well-understood brain rhythms: the occipital alpha rhythm and the mu rhythm found in the motor cortex. The simple and high-yield bicrystal grain boundary-based YBCO SQUIDs were sufficiently sensitive to detect these spontaneous signals generated by the brain at frequencies below 20 Hz, yielding an SNR of $\sim$10. These results suggest that high-T_c technology may supplement or replace its conventional low-T_c counterpart in future MEG systems.

The authors acknowledge financial support from the European Commission Framework Program 7 (FP7/2007–2013) project MEGMRI (Grant agreement No. 200859), the European Union via Tillväxtverket and Regionala Utvecklingsfonden for MedTech West, the Knut and Alice Wallenberg foundation, and Kristina Stenborgs stiftelse.

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