Nano-MEG: Nano-scale patterned high critical-temperature superconducting sensor technology for next-generation neuroimaging with magnetoencephalography

Thilo Bauch[1], Edoardo Trabaldo[1], Silvia Ruffieux[1], Maxim Chukharkin[1,2], Christoph Pfeiffer[1,3], Alexei Kalaboukhov[1], Dag Winkler[1], Justin F. Schneiderman[4,*]

[1] Quantum Device Physics Laboratory, Department of Microtechnology and Nanoscience – MC2, Kemivägen 9, SE-412 96 Gothenburg, Sweden
[2] Chalmers Industriteknik, SE-412 88 Gothenburg, Sweden
[3] Department of Neuroscience and Biomedical Engineering, Aalto University, FI-00076 Aalto, Finland
[4] MedTech West and the Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Röda stråket 10B, SE-413 45 Gothenburg, Sweden;
*Corresponding author: justin.schneiderman@neuro.gu.se

ABSTRACT

We summarize unique neuroimaging capabilities with our 7-channel high critical temperature superconducting quantum interference device (high-T_c SQUID) on-scalp magnetoencephalography (MEG) system and unsurpassed magnetic field resolution in nanowire-based high-T_c SQUID technology. The improved proximity and dense packing of our on-scalp MEG system enables higher resolution and sensitivity to important brain functions, as compared to the state-of-the-art. The reproducibility, scalability, and sensitivity (theoretically down to 25 fT/√Hz, demonstrated to 60 fT/√Hz) of our grooved Dayem bridge-based high-T_c SQUIDs make them a promising core technology for future multi-channel on-scalp MEG systems. We conclude with future prospects beyond this ATTRACT Phase 1 project.

Keywords: magnetoencephalography, on-scalp MEG, SQUID, high temperature superconductivity, YBCO, nanowire, grooved Dayem bridge.

1. INTRODUCTION

Since its development in 1964 [1], the superconducting quantum interference device (SQUID) has become the most ubiquitous of superconducting sensor technologies, with application areas ranging from nanoscale materials science to astronomy [2]. The study of magnetic fields in biological systems—biomagnetism—was effectively born thanks to the SQUID. Presently, SQUIDs are being utilized globally to understand the human brain via mapping of the magnetic fields generated by neural currents i.e., magnetoencephalography (MEG) [3]. SQUID technology is currently based on low-critical temperature (low-T_c) superconductors. However, since the time of their discovery in 1986 [4], high critical-temperature (high-T_c) superconductors represented the ideal candidate for replacing their low-T_c counterparts, albeit a viable technology has yet to be fully realized.

MEG is a key technology for demonstrating a breakthrough with new and improved high-T_c SQUIDs. These sensors enable a unique combination of reduced sensor-to-source proximity and higher spatial sampling of the neuromagnetic field. Together, these improvements boost functional neuroimaging resolution and sensitivity to levels that are beyond reach for the state-of-the-art. In the future, full-head high-T_c SQUID-based MEG systems can provide unique information about how the human brain works and improve medical procedures [5].

During this project, a seven-channel on-scalp MEG system based on conventional high-T_c SQUIDs was finalized [6]. With it, we have demonstrated high resolution and sensitive functional neuroimaging studies of the human visual, audio [6], and somatosensory systems [7]. A case study on an epilepsy patient furthermore demonstrated sensitivity to twice the number of interictal epileptiform discharges (a critical signal for epilepsy treatment planning) than the state-of-the-art [8]. Finally, we have developed a new generation of high-T_c SQUIDs for MEG that can further improve our seven-channel and future systems. Based on grooved-Dayem bridge technology, this technical breakthrough enables flexibility in sensor design and simplicity in fabrication for a scalable sensor technology with state-of-the-art sensitivity, which can meet the market need in MEG and other application areas [9].

2. STATE OF THE ART

The most successful material for high-T_c SQUIDs is $YBa_2Cu_3O_{7-x}$ (YBCO), a ceramic oxide superconductor that demands very different technologies for the preparation of films and Josephson junctions when compared to low-T_c technology. YBCO films for low-noise magnetometers generally require epitaxial growth on a suitable substrate, and the fabrication of low-noise multilayer structures is challenging. Two different Josephson junction technologies are used to create the state-of-the-art in high-T_c SQUID magnetometers: bicrystal and step-edge grain boundary junctions [10]. Both have been developed and refined since the late 1980s, however, the sensor performance strongly depends on the film and grain boundary quality, and the grain boundary limits design flexibility. Fabrication of multiple low-noise sensors is labor intense, and the widespread utilization of high-T_c SQUIDs has therefore been limited, especially when compared to their low-T_c counterparts, e.g., in MEG.

The state-of-the-art in functional neuroimaging is fMRI and MEG. The former suffers from low temporal resolution (~1 s), which is due to its sampling of the slowly varying blood-oxygenation changes induced by neural activity. On the other hand, MEG directly measures neural activity and its temporal resolution is effectively unlimited; its spatial resolution is, however, moderate (~5 mm). This limitation is due to the low-T_c SQUIDs on which systems are presently based, which require an extreme cryogenic environment (T ~4 K) and thus thermal insulation between the sensors and the room temperature environment of the human head. This leads to a minimum source (i.e., neural currents) to sensor standoff distance of ~3 cm. The situation is worse for child subjects because the sensors must be mounted in a fixed 'one-size-fits-all' helmet that is far too big for children's relatively small heads. The ~$1/r^2$ dependence that magnetic field magnitudes have as a function of distance, r, from the sources means signals have weakened significantly by the time they reach the sensors.

Tab. 1. Nano-MEG projected neuroimaging breakthroughs.

Parameter	State-of-the-art	Nano-MEG
Avg. sensor-to-scalp distance (mm, adult/child)	29/40	1/1
Avg. spatial sampling (mm)	34	12
Signal gain	1	1-5
Avg. spatial information density (bits/source, adult/child)	1.5/1.6	2.1/2.4
Est. spatial resolution (mm)	~5	~2

Tab. 2. Nano-MEG projected GDB-based high-T_c SQUID breakthroughs.

Junction tech.	Bicrystal	Step-edge	GDB
Substrate	Bicrystal	Single crystal	Single crystal
Substrate cost	200 €	10 €	10 €
Alignment	To grain boundary	To etched step	None
Fabrication complexity	Medium (alignment)	Advanced (step preparation and alignment)	Simple

3. BREAKTHROUGH CHARACTER OF THE PROJECT

Our functional neuroimaging breakthrough comes from the far more moderate operating temperature of our high-T_c SQUIDs (T ~77 K). By flexibly mounting sensors on the scalp—i.e., on-scalp MEG—we sample higher signal levels and improve spatial resolution, regardless of the subject's head size or shape, c.f. Tab. 1.

With our new generation of high-T_c SQUID magnetometers based on grooved Dayem bridge (GDB) junctions, we can furthermore greatly simplify the fabrication of multiple magnetometers with state-of-the-art sensitivity. In contrast to step-edge junctions, no substrate preparation is necessary, which reduces the number of fabrication steps involved. GDB junctions can furthermore be made on single crystal substrates, which reduces the substrate cost by a factor of 20 in comparison to bicrystal grain boundary junctions that require expensive bicrystal substrates. Additionally, the lack of a grain boundary means that no alignment is necessary and enables new flexibility in design as the junctions can be placed freely on the chip. These properties (c.f. Tab. 2.) enable a more scalable and less labor intense fabrication of low-noise high-T_c SQUID magnetometers as required for multi-channel MEG systems.

4. PROJECT RESULTS

To date, we have completed construction and testing of our 7-channel high-T_c SQUID on-scalp MEG system as well as designed, fabricated, and tested a new generation of GDB-based high-T_c SQUIDs.

4.1. The 7-channel on-scalp MEG system

The 7-channel high-T_c SQUID-based on-scalp MEG system is presented in Fig. 1 (next page). The main components include the inner cryogen vessel, the outer vacuum jacket, the sensor array, and the electronics breakout box. The inner vessel has a sapphire window and wedges for supporting the high-T_c SQUIDs in a

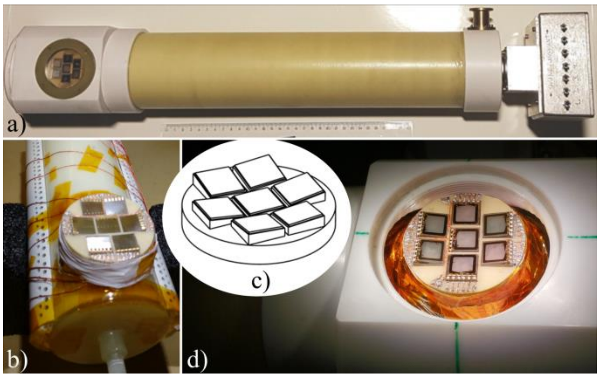

Fig. 1. The 7-channel high-T_c SQUID-based on-scalp MEG system. a) Side view of the cryostat with the sensor array behind the concave window (left), rigid outer vacuum enclosure (middle), and electronics breakout box (right). b) The exposed inner cryogen vessel with the cabling wrapped around it and the side-facing sensor array support in the foreground. c) Layout of the sensor array with the sensors on the perimeter tilted towards the center one in a concave pattern to match the curvature of an adult human head. d) The tail of the cryostat with the window removed, exposing the 7 sensors underneath.

concave pattern whose radius of curvature (8 cm) matches the average curvature of an adult human head. When filled with liquid nitrogen, the vessel can be attached to a vacuum pump for lowering the vapor pressure of the liquid nitrogen, and thus tune the operating temperature of the SQUIDs to between ~65 and ~78 K.

The seven sensors are conventional bicrystal grain boundary junction-based single layer high-T_c SQUID magnetometers with a size of 10 mm × 10 mm. The noise spectra of these magnetometers are presented in Fig. 2. The 50-130 fT/√Hz white noise levels were sufficient to demonstrate sensitivity to a variety of important brain signals including visual alpha modulation, auditory and somatosensory evoked fields [6, 7], and interictal epileptiform discharges [8].

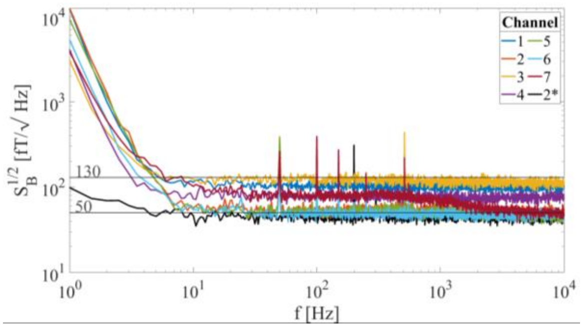

Fig. 2. Magnetic field noise of our 7-channel on-scalp MEG system [6]. All 7 SQUIDs have white noise levels between 50 and 130 fT/√Hz. 2* shows the noise recorded for Channel 2 when it was inside a superconducting shield: the higher 1/f noise in all other curves is typical for unshielded sensors.

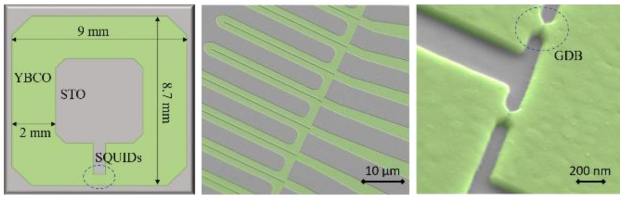

Fig. 3. GDB-based high-T_c SQUIDs. Left panel: Design layout of the washer-style pickup loop for coupling magnetic flux into the SQUIDs. Middle panel: Scanning electron microscope image of the SQUID array: 50 GDB SQUIDs were fabricated in series on the pickup loop. Right panel: Detail of two 50 nm × 100 nm GDB junctions closing the SQUID loop.

4.2. GDB-based high-T_c SQUIDs

With the novel grooved Dayem bridge junction-based magnetometers, we could achieve a roughly 10-fold improvement in the magnetic field sensitivity compared to conventional Dayem bridge-based high-T_c SQUID magnetometers. On a 5 mm × 5 mm substrate, a white magnetic field noise of roughly 100 fT/√Hz could be reached.

To further improve the noise levels, we switched to 10 mm × 10 mm substrates and tested a series of 50 GDB-based high-T_c SQUIDs coupled to the same washer-type pickup loop, see Fig. 3. As expected, the 10 mm × 10 mm sensors show an improvement in noise levels by a factor of ~2, c.f. Fig. 4. These sensors have noise levels comparable to those of state-of-the-art single layer high-T_c SQUIDs with the same pickup loop size, but have the advantage of a simpler, more scalable, and less labor intense fabrication process. Based on the noise levels of the best SQUIDs measured, 10 mm × 10 mm single layer magnetometers based on GDB junctions can reach magnetic field noise levels below 25 fT/√Hz. This is possible with a 3 mm wide pickup loop and a reduction in the number of redundant SQUIDs.

The next step is testing the performance of our 10 mm × 10 mm GDB-based high-T_c SQUID magnetometers in on-scalp MEG. Single- and 7-channel recordings of visual neuro-oscillation modulation as well as auditory and somatosensory evoked fields will be revealing in

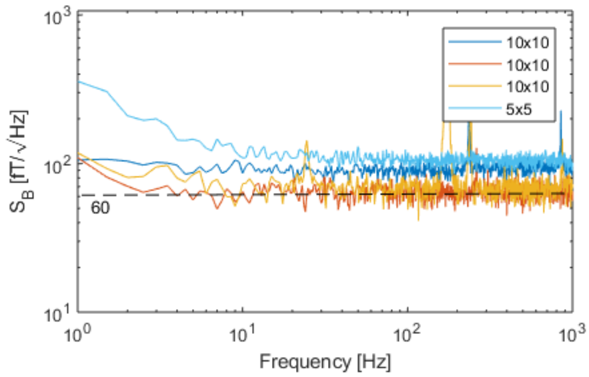

Fig. 4. Magnetic field noise of our GDB-based high-T_c SQUIDs on 5 mm × 5 mm and 10 mm × 10 mm substrates. The dashed line indicates the 60 fT/√Hz white noise level of the best magnetometer.

terms of improved sensitivity and resolution. While outside the scope of this project, benchmarking style comparison to a state-of-the-art MEG system will enable quantification of the gain available on-scalp and with our new generation of sensors [11].

5. FUTURE PROJECT VISION

Beyond this project, development of a full-head GDB-based high-T_c SQUID on-scalp MEG system is paramount. Such a system will be less expensive (savings of >2×), more user friendly (by eliminating liquid helium), more sensitive (signal gains of 1-5), and higher resolution (by >2×).

5.1. Technology Scaling

The path towards a full-head on-scalp MEG system at a Technology Readiness Level (TRL) of 5-7 in ATTRACT Phase 2 is straightforward thanks to the experience we have with system development [6] and the simplicity, flexibility, and scalability of the GDB-based high-T_c SQUID fabrication process [9]. We are constructing a 21-channel on-scalp MEG system and have evaluated various system designs for optimal sampling of child and adult subjects' brains [12]. More in-depth benchmarking and exploratory functional neuroimaging studies (in line with [6-8]) will strengthen the case for on-scalp MEG with our GDB-based high-T_c SQUIDs.

5.2. Project Synergies and Outreach

New collaborations will accelerate development and market readiness. We see potential synergy, and have initiated contact, with other ATTRACT projects including:

- *ThermoQUANT*, via collaboration on magnetic sensor technology,
- *Mixed reality for brain functional and structural navigation during neurosurgery*, via collaboration on supplementing neuro-surgical navigation with MEG-delineated eloquent brain tissue,
- *MAGRes*, via collaboration on providing MEG-based neuro-functional integrity measures for neuro-surgical follow-up,
- *MERIT-VA*, via collaboration on adding arrhythmia source information from magnetocardiography (MCG)—a second use of our MEG hardware—to catheter-based cardio-ablation workups.

Beyond ATTRACT Phase 1, additional organizations that can accelerate Nano-MEG towards TRL 5-7 include healthcare companies involved in functional neuroimaging technologies (e.g., EEG and MEG) as well as developers and companies in cryogenic cooling and superconducting sensor technologies.

In addition to Gold and Green Open Access publications, we reach out to the broader student and research communities to promote Nano-MEG and ATTRACT. At course lectures, conferences, and symposia, we communicate our research activities and results with talks and poster presentations.

5.3. Technology application and demonstration cases

In order to streamline future demonstrations of our Nano-MEG technologies, we target two functional neuroimaging paradigms with relevance to the *Health, demographic changes and wellbeing* Societal Challenge:

Epilepsy pre-surgical mapping: We have already demonstrated a doubling in the number of interictal epileptiform discharges detected with our on-scalp MEG system, as compared to the state-of-the-art, in an epilepsy patient [8]. This enables a significant improvement in hypothesis development for pre-surgical planning of epileptogenic zone resections. More extensive mapping of eloquent cortex can furthermore be used in planning to avoid damage to critical brain functions (language, sensorimotor, etc). We aim to execute a prospective, single-center, intention-to-treat study. A power estimation suggests ten surgical candidates will be sufficient for statistically significant results based on surgical planning hypotheses generated before and after inclusion of on-scalp data.

Social interaction: Despite it being one of the most important functions of the human brain, and its implication in a wide range of neuropsychiatric disorders and diseases (e.g., autism spectrum disorders, Alzheimer's disease, etc.), only a handful of functional neuroimaging studies include true social interaction. A significant limiting factor is the large footprints of advanced neuroimaging technologies. Our on-scalp MEG system is small enough to fit within the same lab environment as a state-of-the-art MEG system. We can thus demonstrate unique dual neuroimaging studies of two subjects interacting socially and naturally.

As a member of the Euro-BioImaging European landmark research infrastructure for biological and biomedical imaging, we aim to apply for the "Showcasing of New Technologies for EuBI" under the MEG technology area. With the coming inauguration of our med-tech collaborative lab at the Sahlgrenska University Hospital's Imaging and Intervention Centre, we will also apply to become a research node as an open-access facility.

5.4. Technology commercialization

We have initiated several utilization activities. These include a continually-updated Intellectual Asset Inventory, in which we document critical developments for potential utilization. Those provided the basis for a market verification project with the GU Research and Innovation Office and GU Ventures. A follow-up market analysis has been carried out by the Chalmers Innovation Office and collaborators. That activity led to a patent search and further innovation verification project wherein a (confidential) commercialization strategy has been formulated.

5.5. Envisioned risks

There are two main risks to the development of a full-head GDB-based high-T_c SQUID on-scalp MEG system. First, the noise of our conventional sensors is slightly worse in the on-scalp MEG cryostat, as compared to a shielded environment (c.f., Fig. 2). If this is the case for our GDB SQUIDs, then a local shield that surrounds the MEG cryostat can be used during cooling in order to reduce the likelihood of flux trapping while the sensors pass through their critical temperature. We can furthermore pump on the cryogen vessel in order to lower the operating temperature of the SQUIDs and thereby improve noise performance. Second, our conventional SQUIDs tend to trap flux while operating in on-scalp MEG recordings and the same may be the case for the GDB SQUIDs. Local on-chip heaters and a heating/cooling cycle that returns the sensors to low-noise performance should mitigate this risk.

5.6. Liaison with Student Teams and Socio-Economic Study

Authors DW and JFS are involved in a Chalmers School of Entrepreneurship MSc project with four students that are investigating a commercialization strategy for a separate project. Experience from developments therein will guide similar activities within an ATTRACT Phase 2 expert-driven socio-economic study. DW and/or JFS could facilitate this via supervision, interviews/lectures on our technology, etc.

6. ACKNOWLEDGEMENT

This project has received funding from the ATTRACT project funded by the EC under Grant Agreement 777222. We furthermore thank the Knut and Alice Wallenberg foundation (KAW 2014.0102), the Swedish Research Council (2017-00680), the Swedish Childhood Cancer Foundation (MT2018-0020), the Chalmers Excellence Initiative Nano, and the Swedish Infrastructure for Micro- and Nanofabrication (Myfab).

7. REFERENCES

1. Jaklevic, R.C., et al., *Quantum Interference Effects in Josephson Tunneling.* Physical Review Letters, 1964. **12**(7): p. 159-&.
2. Clarke, J. and A.I. Braginski, *The SQUID Handbook : Applications of SQUIDs and SQUID Systems*. The SQUID Handbook. 2006, Weinheim: Wiley-VCH.
3. Baillet, S., *Magnetoencephalography for brain electrophysiology and imaging.* Nature Neuroscience, 2017. **20**(3): p. 327-339.
4. Bednorz, J.G. and K.A. Muller, *Possible High-Tc Superconductivity in the Ba-La-Cu-O System.* Zeitschrift Fur Physik B-Condensed Matter, 1986. **64**(2): p. 189-193.
5. Schneiderman, J.F., et al., *On-scalp MEG*, in *Magnetoencephalography: From Signals to Dynamic Cortical Networks*, S. Supek and A. C., Editors. 2019, Springer International Publishing.
6. Pfeiffer, C., et al., *A 7-Channel High-Tc SQUID-Based On-Scalp MEG System.* IEEE Trans Biomed Eng, 2020. **67**(5): p. 1483-1489.
7. Andersen, L.M., et al., *On-scalp MEG SQUIDs are sensitive to early somatosensory activity unseen by conventional MEG.* Neuroimage, 2020. **221**: p. 117157.
8. Westin, K., et al., *Detection of interictal epileptiform discharges: A comparison of on-scalp MEG and conventional MEG measurements.* Clin Neurophysiol, 2020. **131**(8): p. 1711-1720.
9. Trabaldo, E., et al., *Properties of grooved Dayem bridge based YBa2Cu3O7-delta superconducting quantum interference devices and magnetometers.* Applied Physics Letters, 2020. **116**(13).
10. Faley, M.I., et al., *High-T-c SQUID biomagnetometers.* Superconductor Science & Technology, 2017. **30**(8).
11. Xie, M.S., et al., *Benchmarking for On-Scalp MEG Sensors.* Ieee Transactions on Biomedical Engineering, 2017. **64**(6): p. 1270-1276.
12. Boldizar, F. and U. Slipac, Chalmers MSc thesis, *Optimizing design of on-scalp MEG systems*. 2017.