Letter

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Optically pumped magnetometers enable a new level of biomagnetic measurements

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Abstract: The electrophysiological activities in the human body generate electric and magnetic fields that can be measured noninvasively by electrodes on the skin, or even, not requiring any contact, by magnetometers. This includes the measurement of electrical activity of brain, heart, muscles and nerves that can be measured *in vivo* and allows to analyze functional processes with high temporal resolution. To measure these extremely small magnetic biosignals, traditionally highly sensitive superconducting quantum-interference devices have been used, together with advanced magnetic shields. Recently, they have been complemented in usability by a new class of sensors, optically pumped magnetometers (OPMs). These quantum sensors offer a high sensitivity without requiring cryogenic temperatures, allowing the design of small and flexible sensors for clinical applications. In this letter, we describe the advantages of these upcoming OPMs in two exemplary applications that were recently carried out at Physikalisch-Technische Bundesanstalt (PTB): (1) magnetocardiography (MCG) recorded during exercise and (2) auditory-evoked fields registered by magnetoencephalography.

Keywords: biomagnetism; magnetocardiography; magnetoencephalography; optically pumped magnetometer.

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1 Introduction

Biosignals usually refer to small electric signals produced by the sum of electrical potential differences in biological tissue or cell systems such as the nervous system. This includes the electrical activity of the heart (electrocardiography), muscle activity (electromyography) or neuronal activity, of the peripheral nervous system (electroneurography) or of the brain (electroencephalography). These signals are measured as potential differences between electrodes attached to the skin and are widely used in clinical diagnosis. Alternatively, the magnetic field generated by the currents of the same electrical activity can be measured using sensitive magnetometers. Although electric and magnetic biosignals originate from the same neurophysiological processes, there are important differences [1, 2]. Magnetic fields are less distorted by skin, bones or other tissues, and are not affected by their conductivity, which results in a better spatial resolution of magnetic methods. As described above, electrical methods rely on a reference electrode attached to the body, while magnetic methods are reference-free, which often makes the interpretation easier. Most widely used among the magnetic methods so far is magnetoencephalography (MEG), a functional neuroimaging technique for noninvasive mapping of brain activity [1, 3]. MEG has been in development since the late 1960s and is applied clinically for instance to localize abnormal brain activities, as during epileptic seizures, or due to Parkinson's or schizophrenia. In addition, magnetic field measurements are also used to study biosignals from heart magnetocardiography (MCG), muscles (magnetomyography, MMG), and peripheral nervous system (magnetoneurography, MNG), in analogy to their electrical counterparts [4].

Magnetic biosignals are extremely small—magnetic heart signals on the skin surface are a million times smaller than the Earth's magnetic field (48 μT in Central Europe) in the pT range and magnetic brain signals are again smaller by a factor of thousand, thus in the fT range. Therefore, biomagnetic measurements gain strongly from dedicated magnetic shields (often large enough to walk in). For this

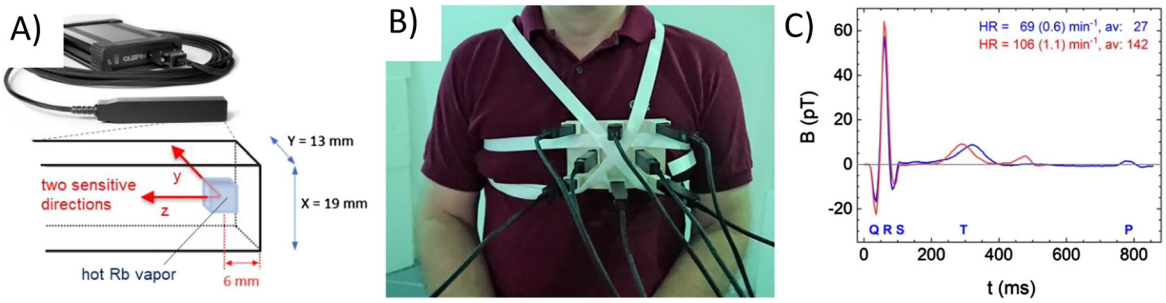

Figure 1: A) Commercial OPM (QZFM-gen-1, QuSpin Inc.) with a schematic of vapor cell and sensitive directions with respect to sensor housing. B) Exemplary multichannel arrangement of eight commercial OPMs fixed on the chest of a subject. C) Pilot measurement of averaged heart signals at rest (blue) and during exercise (red). Corresponding heart rate (HR) and number of averages (av) are indicated. The typical features as the QRS-complex, the T-, and P-wave are clearly visible and indicate no broadening from motional artifacts.

typically passive shielding by a few layers of high-permeability Mu-metal and one layer of aluminum are used, sometimes combined with active compensation of the Earth's magnetic field by external coils. In commercial magnetically shielded rooms (MSR) with 2 + 1 layers, i.e., two layers of Mu metal and one layer of aluminum a shielding factor of >1000 above 1 Hz is achieved (Ak3b, VAC, Germany [5]). In Physikalisch-Technische Bundesanstalt (PTB's) 8 + 1-layer room (BMSR-2), an overall (active + passive) shielding factor of 6×10^6 at 0.01 Hz, that exceeds 1×10^8 above 6 Hz is achieved [6], with residual fields of less than 1 nT and respectively small gradients—unique conditions for evaluation of novel sensors in biomagnetism.

Most common types of magnetometers in biomagnetism for several decades were superconducting quantum interference devices (SQUIDs) [7] requiring complex cooling in a cryogenic vessel which must be regularly filled with liquid helium (or nitrogen). Recently, new optically pumped magnetometers (OPMs) have been developed that reach a similar sensitivity as SQUIDs, in the order of 10–20 fT/$\sqrt{\text{Hz}}$ [8] and even below [9]. OPMs do not rely on any cooling but rather on slight heating, for this, they can be built as individual miniaturized sensors. This meets two important criteria in terms of practical manageability. First, it enables to place them close to the skin and, second, to adapt flexibly to the individual shape of the body [10, 11].

2 Compact OPMs for biomagnetic applications in medicine

OPMs comprise a class of sensors that have the following three-stage process in common: first, so-called "optical pumping", typically by a laser beam, serves to prepare an ensemble of atoms in a collective spin state. Second, the resulting collective magnetic moment precesses with the Larmor frequency in the external magnetic field. Third, the atoms are interrogated by the same or an additional laser beam, by means of changes in their optical properties. As atomic samples, typically gaseous atoms in vapor cells, and more recently also artificial atoms such as nitrogen-vacancy centers in diamond are used [12, 13]. Although invented already in the late 1950s, OPMs have been improving drastically in the past two decades. Triggered by the commercial availability of highly stable, tunable diode lasers, the so-called spin exchange relaxation-free (SERF) mode [14] was realized for the first time [9]. Additionally, millimeter-sized pretuned diode lasers, together with microelectromechanical systems technology of vapor cell production paved the way for miniaturization of OPMs [8, 15, 16]. This resulted in the first commercial micro-manufactured vector-OPMs in 2016 [17, 18]. In 2018, QuSpin Inc. (USA) introduced even smaller sensors with a miniscule housing size of 5 cm^3. Their sensitivity of about 10–20 fT/$\sqrt{\text{Hz}}$ and bandwidth of 135 Hz are sufficient for the analysis of many aspects of brain and heart biosignals. While losing to SQUIDs [19] in bandwidth, sensitivity, dynamic range and multichannel capability, they challenge SQUID-based systems in usability and require no maintenance by qualified personnel. So far commercial OPMs can be easily combined to a multichannel system of several tens of sensors [20]. In contrast commercial SQUID-based MEG-systems typically have several 100 channels.

3 Exercise-MCG registration enhanced by OPMs

Ultracompact OPMs assembled in a multisensory array enable a new level of biomagnetic investigations. While

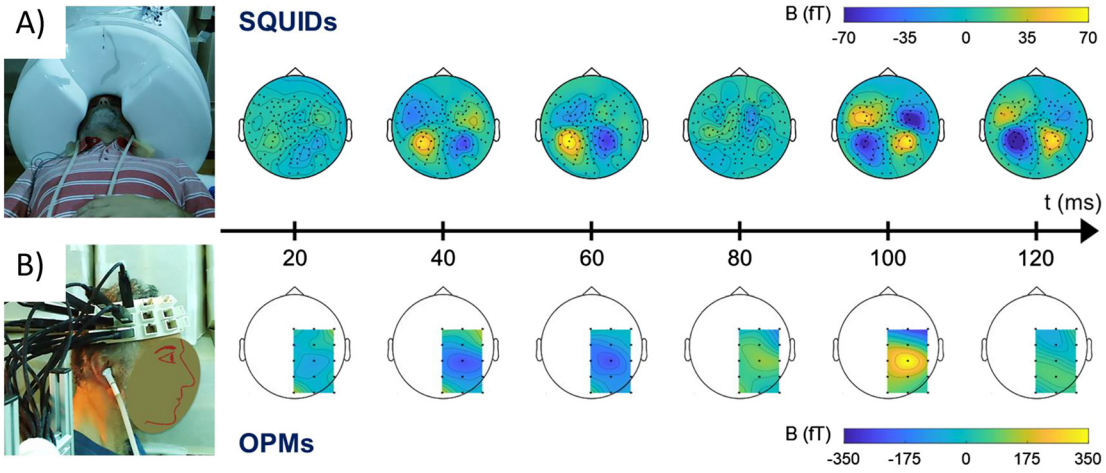

Figure 2: MEG registration of auditory-evoked brain signals. The photos show the subject in the respective MEG system, the contour plots on the right depict the radial component of the magnetic flux density B at instances after the acoustic stimulation. A) SQUID-MEG registration on a lying subject with PTB's 128-channel SQUID-based MEG-system. B) OPM-MEG registration on an upright sitting subject, whose head is partially covered by an OPM-array of 15 sensors.

SQUID-based systems [21] and early OPM systems [22, 23] have a fixed geometry and typically require the subject to be located below the SQUID system, the flexibility in placing ultracompact OPMs facilitates adaptation to the individual shape of the body and the placement of the sensors from different sides at the same time. This novel flexibility is especially important for exercise MCG. Already MCG at rest profits from the fact that the sensors can be attached to the body on top of the clothes and at the same time, for example, on chest and back. But for exercise MCG [24], the advantages go even further because as the sensors are attached to the body, the subject can move without changing the relative position between sensors and body. Thus, registration of MCG also during the exercise becomes feasible, and does not lead to artifacts from lateral or radial changes in the relative position between sensors and field source. The only remaining sources of motional artifacts are movements of the sensors in the gradient of the background field. But if the latter are asynchronous with the heartbeats, these artifacts can be averaged out. To avoid motional artifacts in stress MCG, chemically induced stress is often used instead, which is way less convenient for the subject [25, 26].

A pilot measurement with commercial OPMs (QZFM-gen-1, released by QuSpin Inc. in 2016, Figure 1A) confirmed that MCG can be recorded with the anticipated advantages. For this purpose, a 3D-printed sensor holder with hook-and-loop fasteners was fixed to the chest of the subject on top of the T-shirt (Figure 1B). The subject located in PTB's BMSR-2 was then pedaling on an ergometer. For evaluation, we consider the signal measured by an OPM in radial direction. Averaging over many heart beats at rest and during exercise (Figure 1C) indicates that indeed the shape of the heartbeat is not degraded due to motional artifacts upon averaging. But also, single heart beats can be detected with a signal-to-noise ratio (SNR) of more than 100 at rest. To suppress motional artifacts during exercise also in single heart beats, a gradiometric sensor arrangement is needed.

4 MEG of auditory-evoked brain signals registered by SQUIDs and OPMs

OPMs which are lightweight and flexible can be combined in a wearable sensor helmet, adapted to the individual head shape, as was demonstrated in a seminal work by Elena Boto et al. [11]. This enables for instance to record MEG during movement disorders.

To assess the performance of OPM systems in MEG, we benchmark them against nonportable SQUID systems and record brain signals from the same subject using both systems in sequence. In the measurements considered here, we used a commercial 128-channel SQUID-MEG System (Eagle Technologies), while the OPM system consisted of 15 commercial OPMs (Figure 1A) which were inserted into a 3D-printed helmet, derived from anatomical images of the subject. Both MEG measurements were performed in a commercial MSR (Ak3b, VAC, Germany [5]). To obtain reproducibly repeated brain signals, we evoked them by auditory stimulation with a sequence of tones delivered by

flexible tubes to the ears. First, the supine lying subject had its head inside a SQUID-based MEG system (Figure 2A), and the stimulated brain signals were recorded for 20 min. Second, the subject could sit upright while wearing an OPM helmet (Figure 2B) and the measurements were repeated. The 2D-projected field maps obtained from both measurements (250 repetitions of 1 kHz stimuli) are compared in Figure 2 at instances after the acoustic stimulation. At 100 ms post stimulus, two dipolar structures are visible in the SQUID field maps, which are attributed to the auditory cortex. One pole of the dipolar field is fully covered by the OPM array, and both measurements exhibit a good agreement. The peak amplitudes registered by the OPMs (350 fT) are five times larger than those registered by the SQUIDs (70 fT), which is expected from the closer proximity [27]. The SNR obtained with OPMs and SQUIDs was similar, if most OPMs are considered. Only two OPMs showed about twice the normal noise level on that day, which was still acceptable.

5 Conclusion

We have presented two exemplary cases in order to demonstrate the benefits from using OPMs in biomagnetism. The new technology does not rely on cryogenic liquids and maintenance by qualified personnel. In perspective, it is therefore much cheaper in operation. Beyond this, the newly possible flexibility opens new options. The sensors can be arranged in 3D-printed sensor holders and adapted to the individual shape of the body. This results in closer proximity to the field source and fixed relative positions. Also positions, which are difficult to access simultaneously with superconducting sensors, are now accessible. This enables for instance the registration of heart signals on the chest and on the back. Furthermore, the subjects can maintain a comfortable position during the measurement, i.e., sit upright or even move, as for the investigation of brain diseases with movement disorders can hardly be avoided. Especially interesting is also the registration of MCG during exercise, because this may give new insights for the diagnosis of coronary artery disease [26].

OPMs are also for myography and neurography very promising [28], as flexibility is especially important here to adapt to arms and legs. Here, but also in many other applications, OPMs—due to their small size—can be operated in much smaller shields, e.g., tabletop units.

The next steps to bring the new technology towards medical practice will require dedicated research to validate the methods and diagnostic options [29]. Highly desired from biomedical research are commercial integrated OPM-based multichannel systems [30], which work reliable with a high fidelity.

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