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Optically pumped magnetometers reveal fasciculations non-invasively

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HIGHLIGHTS

- First evidence that quantum sensors (optically pumped magnetometer OPM), can non-invasively detect fasciculations in neuromuscular patients.
- Proposal of the necessary technical solutions to detect other forms of pathological spontaneous activity.
- Introduction of magnetomyography as a new clinical neurophysiological diagnostic tool.

ABSTRACT

Objective: This proof-of-principle-study evaluated the extent to which spontaneous activity (SA) of the muscle can be detected via non-invasive magnetomyography (MMG) with optically pumped magnetometers (OPM).
Methods: Five patients, who together exhibited all forms of SA (fibrillations, positive sharp waves, fasciculations, myotonic discharges, complex-repetitive discharges) with conventional needle electromyography (EMG), were studied by OPM-MMG and simultaneous surface EMG (sEMG) while at rest, during light muscle activation, and when a muscle stretch reflex was elicited. Three healthy subjects were measured as controls. SA was considered apparent in the OPM-MMG if a signal could be visually detected that corresponded in shape and frequency to the SA in the respective needle EMG.
Results: SA in the context of fasciculations could be detected in 2 of 5 patients by simultaneous OPM-MMG/sEMG. Other forms of SA could not be detected at rest, during light muscle activation, or after provocation of a muscle stretch reflex.
Conclusions: Results show that fasciculations could be detected non-invasively via a new method (OPM).
Significance: We show that other forms of SA are not detectable with current OPM and propose necessary technical solutions to overcome this circumstance. Our results motivate to pursue OPM-MMG as a new clinical neurophysiological diagnostic.

1. Introduction

Spontaneous activity (SA) of muscle tissue is a diagnostic hallmark of neuromuscular diseases. However, skin and subcutaneous fat prevent detection of SA by surface electromyography (sEMG), necessitating insertion of painful needle electrodes into the

Abbreviations: CRD, complex repetitive discharge; OPM, optically pumped magnetometer; EMG, electromyography; sEMG, surface electromyography; MMG, magnetomyography; MD, myotonic discharge; OPM-MMG, optically pumped magnetometer magnetomyography; SA, spontaneous activity; PSW, positive sharp wave; MEG, magnetoencephalography; SQUID, superconducting quantum interference device.

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muscle. New, non-invasive, and painless methods are therefore needed that overcome the limitations of invasive needle EMG. An elegant new method to overcome the limitations of *electro*myography (*E*MG) could be to measure the *magnetic* field generated by muscle action potentials, so-called *magneto*myography (*M*MG). According to Biot–Savart law (Garg, 2012), every electric current generates a magnetic field, which result to be much less affected by the tissue between the muscle fiber and the sensor. In addition, the measurement is contactless and could provite spatial flexibility (Fig. 1). Consequently, in theory, SA, including positive sharp waves (PSW), fibrillations, myotonic discharges (MD), complex-repetitive discharges (CRD), and fasciculations, should be detectable using MMG (Llinás et al., 2020; Reincke, 1993). This possibility was raised in the initial 1972 magnetometry work (Cohen and Givler, 1972), but was not pursued due to the technical limitations of the conventional SQUID (superconducting quantum interference device) magnetic sensors, which require cryogenic cooling to −269 °C and lack spatial flexibility (Ustinin et al., 2018). However, the newly developed and improved optically pumped magnetometers (OPM) (Broser et al., 2018; Sander et al., 2020) now provide the ability to record muscles in complex anatomical situations using flexibly arranged sensors and without cryogenic cooling (Broser et al., 2021; Elzenheimer et al., 2020). Here, as a proof-of-principle, we performed an OPM-MMG study in patients with 5 different forms of SA. Simultaneous surface EMG and conventional needle EMG before or after OPM-MMG were used to evaluate how well PSW, myotonic discharges, fibrillations, or fasciculations were detected.

2. Methods

The affected muscles of 5 patients with known typical findings of SA (PSW, fibrillations, fasciculations, myotonic discharges, complex-repetitive discharges) were examined. Patients' neuromuscular diseases were: Myotonia congenita, myotonic dystrophia 1 (DM1), Pompes Disease in combination with TTR-amyloidosis, brachial plexus avulsion, and Charcot-Marie-Tooth disease type 2 (HMSN II) (Table 1). Furthermore, three healthy subjects were measured as controls. A previously described OPM System (QZFM-gen-1.5, QuSpin Inc., Louisville, CO, USA) was used to record magnetic fields in combination with simultaneous surface EMG recordings (2 active electrodes adjacent to the distal OPM sensors, a reference, and a ground electrode; Fig. 1). All OPM recordings were conducted in a magnetically shielded room (Ak3b, VAC Vacuumschmelze, Hanau, Germany) during 3 minutes of rest, 1 minute of light muscle activation, and 1 minute of triggering of a muscle stretch reflex with a custom-built non-magnetic hammer. The small size of the OPM devices (13 × 19 × 85 mm) allowed for easy handling and flexibility to adapt the sensors to the specific geometrical situation. The employed OPMs were capable of concurrently measure two components of the magnetic field vector: the y-axis, longitudinal to the muscle, and the z-axis, ortogonal to the muscle (Fig. 1). They provided a magnetic field sensitivity in the order of 15 $fT/\sqrt{Hz}$ in a bandwidth of 3–135 Hz, an operating range below 200 nT, and a dynamic range of a few nanotesla. The analog output signals of the OPM system were recorded using the data acquisition electronics of an MEG System (CTF Omega 275, Coquitlam, BC, Canada). Simultaneously, surface EMG was recorded. The OPM system had an intrinsic delay of 3.8 ms, which was corrected offline. Following a cross-design, conventional needle EMG (Ambu© Neuroline Concentric 28x0, 45 mm, Natus Keypoint EMG-system) was recorded immediately before or after the simultaneous OPM-EMG to confirm the presence of SAs. Simultaneous needle EMG-OPM examinations (i.e., a direct comparison to the gold standard) could not be performed since no magnet-free monopolar or bipolar EMG electrodes were commercially available.

Data were analyzed with the BESA software (Brain Electric Source Analysis; 3–100 Hz Filter, 50 Hz Notch) and SA was considered measurable if a signal could be visually detected that corresponded in shape and frequency to the known SA detected by the respective needle EMG.

2.1. Data availability

The anonymized data of all patients and controls are stored locally and any raw data can be made available on reasonable request.

2.2. Standard protocol approvals, registrations, and patient consents

This study was registered and approved by the ethics committee of the University of Tuebingen (project number 692/2020B01). All patients and healthy controls consented to par-

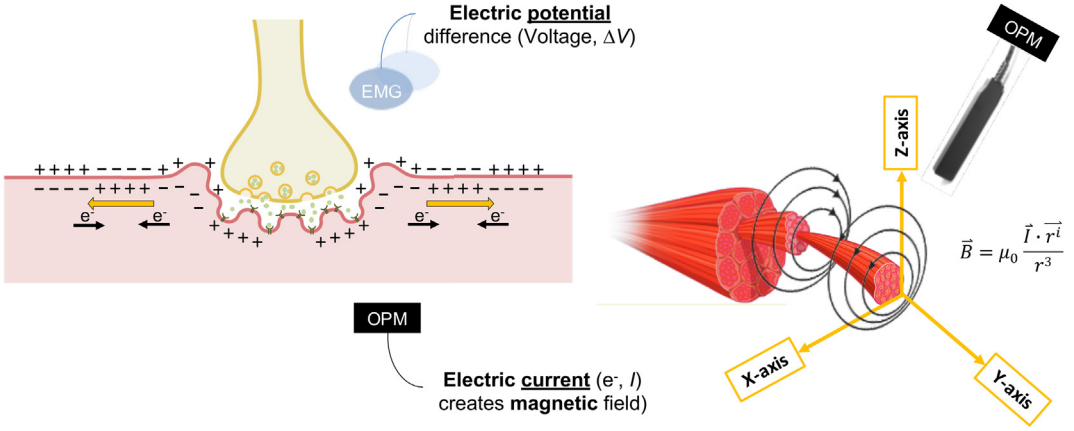

Fig. 1. Basic principles of electromyography (EMG) and magnetomyography (MMG). Left: Schematic drawing of a neuromuscular junction with two action potentials (yellow arrows) propagating from the neuromuscular junction along the muscle fiber. While the EMG measures potential differences (ΔV), the optically pumped magnetometer magnetomyography (OPM-MMG) indirectly measures the electric current (I) that goes along with a magnetic field. Right: Simplified illustration of electric currents (I) and their accompanying magnetic flux density (B). The flux density depends in magnitude on the distance (r) and the intensity of the current (I) and is oriented circularly around the direction of the current flow. Note that the MMG measures magnetic flux density as a result of currents, rather than potential differences as EMG does. Magnetic fields have an orientation; thus, in principle, they have vectorial components in all three geometrical directions (X, Y, and Z).

Table 1
Patient characteristics and needle electromyography (EMG) and magnetomyography (MMG) findings. M (male), PSW (pathologic sharp waves), fibs (Fibrillation), Fasc (Fasciculation), CRD (complex-repetitive discharge), MD (myotonic discharge), BMI (Body mass index).

Patient number(sex, age in years)	**Diagnosis**	**BMI** (kg/m^2)	**Muscle**	**needle EMG-findings**					**MMG-findings**				
				Pathologic spontanous activity					**Pathologic spontanous activity**				
				PSW	*fibs*	*Fasc*	*CRD*	*MD*	*PSW*	*fibs*	*Fasc*	*CRD*	*MD*
#1 (M, 58)	Dystrophia myotonica 1 (DM1)	23.1	Rectus femoris left	–	–	–	–	++	–	–	–	–	–
#2 (M, 58)	Myotonia congenita	21.2	Rectus femoris left	–	–	–	–	+++	–	–	–	–	–
#3 (M, 63)	Pompes Disease + TTR-Amyloidosis	20.1	Rectus femoris left	+	–	++	++	–	–	–	+	–	–
#4 (M, 34)	Brachial plexus avulsion	25.7	Biceps brachii left	+++	++	–	–	–	–	–	–	–	–
#5 (M, 55)	Charcot-Marie-Tooth disease type 2 (HMSN II)	21.6	Rectus femoirs left	–	–	+++	–	–	–	–	+	–	–

ticipate in the study and consented to publication of anonymized data.

3. Results

SA in the context of fasciculations were detected in 2 of 5 patients by simultaneous OPM-MMG/sEMG (Fig. 2). Specifically, on visual inspection of the recordings, patient #3 showed 17 fasciculations in OPM-MMG and 19 in EMG; patient #5 showed 146 fasciculations in OPM-MMG and 138 in EMG. Other forms of SA could not be detected. At rest, during light muscle activation, or after elicitation of a muscle stretch reflex, only the physiological muscle signals were apparent, as shown in previous studies (Broser et al., 2018). Surface EMG also detected fasciculations in 2 of 5 patients (patients #3 and #5, see above), but it failed to detect other forms of SA. Needle EMG detected all forms of SA in all 5 patients. Patient recordings were compared with those of the 3 control subjects, revealing no differences in the signal other than fasciculations.

4. Discussion

This small proof-of-principle study is, to the best of our knowledge, the first to investigate whether SA, in principle, is detectable by noninvasive MMG in patients with various neuromuscular diseases. The main results and conclusions are as follows:

- First evidence that OPM-MMG can non-invasively detect fasciculations in neuromuscular patients.
- Other forms of SA were not visually detectable in our patient cohort with our current commercially available OPM setup.

Why were the other forms of SA not detectable? We assume this is largely due to (1) the low signal-to-noise-ratio (SNR) of the recorded signals, in combination with our setup, and (2) to the comparatively low bandwidth (135 Hz) of the employed and current commercially available OPMs (for comparison, for needle EMG, a bandwidth of 10 kHz is recommended for SA recording). For fasciculation, numerous muscle action potentials from an entire motor unit (1–2 cm^2, approx. 2000 muscle fibers in the rectus femoris muscle) sum up over a period of 5–69 ms (Mills, 2010). This spatial and temporal signal summation leads to strong signals that can be measured both magnetically, despite considerable noise (compare Fig. 2c), and electrically on the skin, despite signal attenuation by skin and fat. By contrast, other forms of SA exhibit low or variable spatiotemporal summation and have a higher discharge frequency than fasciculations: Myotonic discharges occur at a frequency of about 40–100 Hz (Stålberg et al., 2019), which is theoretically measurable with the employed OPM setup. However, due to the low spatial and temporal summation, they likely do not reach a sufficient signal-to-noise ratio to be detectable with the here used setup. For fibrillations, the measurability is likely even more limited because a typical signal duration of 1–2 ms is too short for the highest frequencies detectable with the employed OPM setup (135 Hz) (Stålberg et al., 2019). In addition to these two major factors, the unknown magnetic geometry of SA in the muscle may be a further factor, as OPMs may need a special alignment to the muscle to optimally register SA. However, the geometry of magnetic SA signals is currently unknown.

Regarding the geometry and the investigation of other muscles, it is important to consider the angle between the longitudinal axis of a muscle and its muscle fibers, the so-called pennation angle. Muscle fibers are not always parallel to the longitudinal axis of a muscle, as for example in the biceps brachii muscle, but may also be oriented oblique, as for example in the rectus femoris muscle. The magnetic field of an oblique muscle fiber (pennation angle > 0°) is oriented differently compared to a muscle fiber running parallel to the muscle axis (pennation angle = 0°), which influences detection of the corresponding magnetic field.

A limitation of our study is that simultaneous needle EMG-OPM examinations, that would have allow a direct comparison to the gold standard needle EMG, could not be performed since no magnet-free monopolar or bipolar EMG electrodes are currently commercially available. Consequently, we used surface EMG and performed conventional needle EMG before or after the OPM-MMG examination. Any quantitative comparison of the OPM-MMG with sEMG regarding detecting fasciculations should be made only with caution, as the study was designed to merely detect SA (here fasciculations), and not to compare OPM and sEMG.

Our results demonstrate the feasibility and the current limitations of OPM-MMG as a new clinical neurophysiological diagnostic tool. We also outline necessary technical improvements for future MMG studies. In addition, *ex vivo* MMG studies on muscle tissue with SA may allow further characterization of the muscle physiology and magnetic signal geometry, as well as the necessary sensitivity and bandwidth for OPM-MMG.

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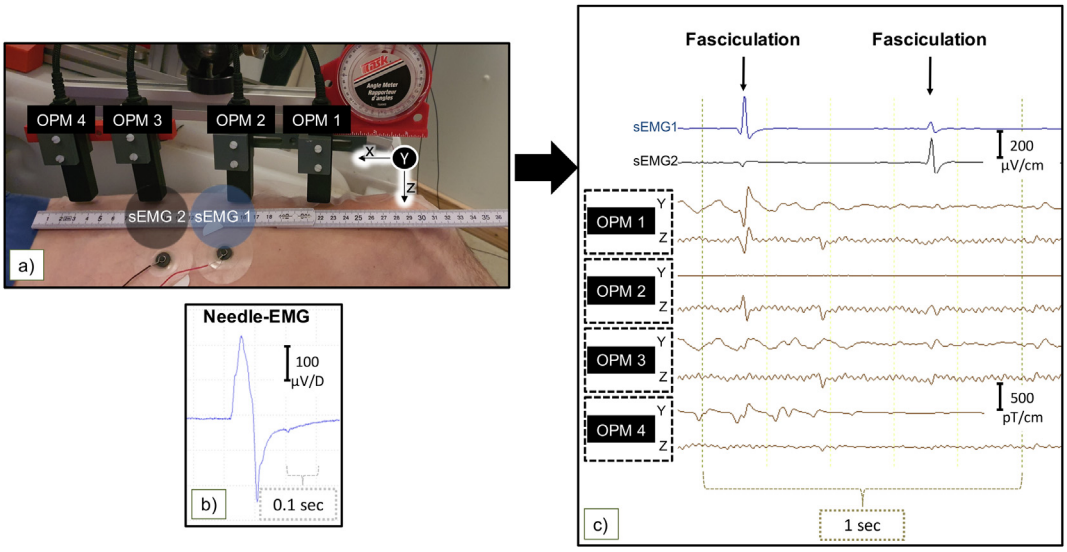

Fig. 2. Simultaneous optically pumped magnetometer – electromyography (OPM-EMG)-Setup with recording of fasciculations. a) Picture of a patient with fasciculations. Optically pumped magnetometer (OPM) 1–4 were placed from distal (OPM 1) to proximal (OPM 4). Medial to OPM 1 and 2, two surface EMG-electrodes were also placed. An additional reference electrode was attached to the ipsilateral lateral knee. **b)** Fasciculation recorded in the needle EMG of patient #5, who also showed fasciculation in a simultaneous OPM-EMG (right). **c)** Representative example two fasciculations with simultaneous OPM-EMG. Note that the measurement of the Y-component of the flux density of OPM 2 was not acquired due to technical issues (saturation of the analog-to-digital converter of the OPM); therefore, only a flat line is shown. Further examples, such as a representative fasciculation of patient #3, are provided in the supplementary material.

Declaration of Competing Interest

JM received lecture fees and travel support from UCB, Eisai, Desitin, Alexion and the German society for ultrasound (DEGUM), all unrelated to the current study. All other authors have no competing interests.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.06.009.

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