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Letter

Dear Editor, to improve the safety and efficacy of non-invasive brain stimulation techniques, we need to embrace automation and precise targeting of cortical structures. Multi-locus transcranial magnetic stimulation (TMS) enables the stimulation of nearby cortical regions electronically, without physically moving the coil set [1–3]. This technology opens the possibility to engage with local cortical networks at millisecond and millimeter scales and to create automated closed-loop mapping protocols [4,5]. However, existing mTMS coil sets have two major issues: a limited range for electronic targeting (30-mm diameter region) and heavy construction (approximately 5 kg for a 5-coil set), mainly due to cabling. Therefore, the manual placement of the coil set on the scalp is slow and physically demanding, requiring highly trained personnel to manipulate the coil sets. Collaborative robots improve the reproducibility and accuracy of TMS coil placements [6,7]; they can compensate automatically for patients' head movements and can be flexibly programmed to be guided by suitable algorithms. Yet, traditional robotized TMS systems can shift the stimulation focus only physically and are limited by robot velocities that are safe for human applications to avoid harmful collisions (around 0.2 m/s) [8]. Furthermore, commercial robotic TMS solutions rely on closed-source platforms associated with a specific robotic arm, which can be costly and difficult to implement without the necessary flexibility for researchers to incorporate novel algorithms on demand.

We developed an open-source platform combining rapid mTMS electronic targeting with accurate and autonomous robotic handling. The robot control module was developed in Python 3.11 and designed to operate with the open-source neuronavigation software InVesalius [9]. The transformation matrix between the robot and InVesalius is computed by a closed-form solution, described in Supplementary Material S1. For safe robot operation, we implemented five software layers and a force and torque sensor control, described in **S2**. The algorithm for robotized TMS coil positioning, defined as the robot control module, is freely available at https://github.com/biomaglab/tms-robot-control. We developed the control platform with an Elfin E5 collaborative robot (Han's Robot Co Ltd, China), which has 6 joints, a 5-kg payload, an 80-cm maximum operation range, and a repeatability accuracy of ±0.05 mm. The developed robot control module can be adapted to any commercial collaborative robot thanks to the software's modular architecture. The robotic TMS coil positioning and head movement compensation were implemented with a closed-loop control, as illustrated in Fig. 1a. The algorithm defines the robot's trajectory to move the coil to the desired target. If the patient moves beyond the threshold specified in InVesalius (default is 2 mm and 2°), the control system can detect the disturbance and adjust for head movements by utilizing the targeting feedback from the neuronavigation positioning guide. The robot-control equations are described in **S3**. We characterized the positioning stability of our robotic mTMS system, described in **S4**. Also, we characterized the accuracy of the produced induced electric field by the system [10]. To demonstrate the combination of robotized transducer placement with the mTMS electronic targeting, we performed a motor mapping experiment with the experimental setup shown in Fig. 1b. Three healthy volunteers (age range: 32–35 years) with no reported neurological disorder participated in this study, which was conducted at the ConnectToBrain Laboratory at Aalto University. The study was approved by the local ethics committee in accordance with the Declaration of Helsinki; all participants gave informed consent prior to the experimental procedure. Neuronavigation was performed with InVesalius connected to eight Flex13 tracking cameras (OptiTrack, NaturalPoint, Inc., USA) installed in the laboratory room. The tracking cameras were positioned such that the head and coil navigation markers were visible for any mTMS coil array position. T1-weighted MRIs (volumetric gradient echo sequence; voxel size $1 \times 1 \times 1$ mm^3; $240 \times 240 \times 240$ acquisition matrix) were acquired in a Skyra 3T scanner (Siemens Healthcare, Germany). Electromyography (EMG) data were recorded from the right abductor pollicis brevis (APB) muscle with a NeurOne amplifier (24-bit resolution, 5-kHz sampling frequency; Bittium Biosignals Ltd., Finland) and circular surface electrodes (24-mm diameter; Spes Medica, Italy) placed on a belly–tendon montage [11]. The hotspot coil placement was defined as the placement on the scalp resulting in the highest MEP amplitudes. On the hotspot, we measured the resting motor threshold (RMT) as the minimum intensity needed to elicit MEPs in the APB larger than 50 μV peak-to-peak in at least five out

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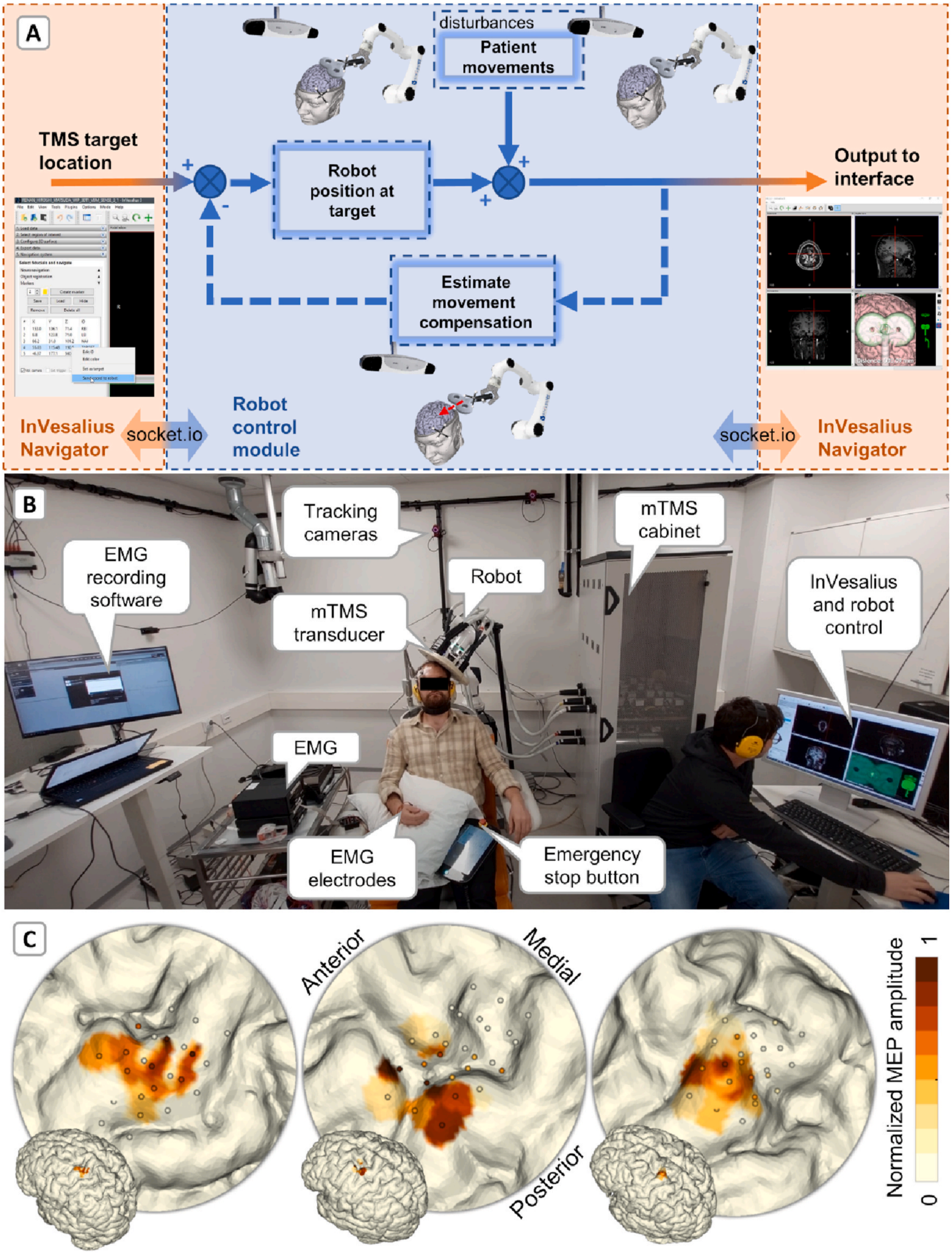

Fig. 1. Robotic–electronic mTMS control and experimental set-up. (A) Schematic diagram of the closed-loop robot control algorithm for mTMS coil set positioning. The robot control module (blue box) receives a target coordinate and detects and corrects head movements. The orange boxes show the user interface (InVesalius) with the robot control module. (B) Photo of the experimental setup with all components for robotized mTMS motor mapping. (C) Robotic–electronic mTMS motor mapping for three volunteers. The colored dots are the stimulated brain targets projected on the individualized MRI for each participant. The color scale is normalized to the maximum MEP amplitude of each participant. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of ten pulses [12,13]. Based on the hotspot, we created three physical targets: 1) the hotspot, 2) on the medial and 3) lateral side along the left precentral gyrus. Then, we created 3 × 3 square grids of brain targets for the three targets, resulting in a total of 27 brain targets. Then, the robot control module autonomously positioned the mTMS transducer on each of the physical targets and applied five single mTMS pulses, with a randomized interstimulus interval of 2–4 s for each brain target. The stimulation intensity was set at 110% of the RMT. The motor maps were generated with the average MEP peak-to-peak amplitude across the five pulses and interpolated with a gaussian interpolation method with 4-mm radius and 3-mm sharpness. Fig. 1c shows the resulting motor maps obtained with the robotized mTMS for three volunteers.

We leverage the high accuracy and autonomous operation of the collaborative robot to enable effortless and accurate positioning of mTMS coil sets. Our robotized-electronic system attains higher accuracy than manual positioning and exhibits stability and accuracy comparable with existing robotized TMS systems [10,14,15]. The robot control allows hands-free placement of mTMS coil arrays on a target location with real-time and automatic compensation for head movements. The robotic–electronic targeting enables the automation of mTMS protocols, such as hotspot hunting and motor mapping with closed-loop algorithms with minimal dependency on user experience and subjective analysis [4,16]. Our open-source platform for combined electronic–robotic applications is an important step in increasing the safety, accuracy, and reproducibility of TMS procedures. This platform offers new prospects to create closed-loop [17,18], operator-independent brain stimulation protocols capable of covering large cortical brain areas, potentially resulting in improved treatments for neurological disorders.

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CRediT authorship contribution statement

Renan H. Matsuda: Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Victor H. Souza:** Software, Project administration, Methodology, Investigation, Formal analysis, Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing. **Thais C. Marchetti:** Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **Ana M. Soto:** Writing – review & editing, Writing – original draft, Software, Investigation, Methodology. **Olli-Pekka Kahilakoski:** Writing – review & editing, Writing – original draft, Software, Methodology. **Andrey Zhdanov:** Writing – review & editing, Writing – original draft, Software, Methodology. **Victor H.E. Malheiro:** Writing – review & editing, Writing – original draft, Software, Methodology. **Mikael Laine:** Writing – review & editing, Formal analysis, Investigation, Methodology, Writing – original draft. **Mikko Nyrhinen:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Heikki Sinisalo:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Dubravko Kicic:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration. **Pantelis Lioumis:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **Risto J. Ilmoniemi:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Oswaldo Baffa:** Writing – review & editing, Writing – original draft, Supervision, Resources, Conceptualization, Funding acquisition, Methodology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Risto J. Ilmoniemi is a patent holder for mTMS-related technology. Victor H. Souza and Oswaldo Baffa have a patent application for neuronavigation technology. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.03.022.

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