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A Custom Robot for Transcranial Magnetic Stimulation: First Assessment on Healthy Subjects

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***Abstract*— In this paper, a custom robotic system for Transcranial Magnetic Stimulation is assessed in clinical conditions on healthy subjects. A motor cortex mapping is performed using the robotic system with comparison to a manual approach using a neuronavigation system. Stimulation accuracy, repeatability are evaluated as well as the feeling of the system operator and the subject in terms of comfort, tiredness, stress level, ease-of-use. Very encouraging results are obtained on all these aspects, which strengthens the idea of developing robotic assistance for TMS.**

I. INTRODUCTION

Transcranial Magnetic Stimulation (TMS) is a noninvasive stimulation technique of the cortex. The stimulation results from a rapidly changing magnetic field generated with an external coil (Fig. 1) which is applied onto the skull to locally induce electric currents in the brain. The first TMS device was created more than 25 years ago [1]. Single pulse and repetitive TMS have been applied in clinical research for the treatment of neurological and psychiatric diseases. The efficiency of TMS has been demonstrated in the case of severe depression for patients whose drug medication has failed [2] and has been approved for clinical treatment in the US, Canada and Israel. Its effect on several other pathologies, such as the auditory hallucinations of schizophrenia or chronic neuropathic pain has shown promising results [9], [10]. However, TMS is not yet widely accepted because its efficiency varies substantially between subjects. The variability is partially due to how the stimulation gesture is performed [3]. Up to now [4], [5], the most accurate method has been to position the coil manually with the help of a neuronavigation software [6], [7]. This tool combines preoperative MR images and peroperative data from an optical localizer (Fig. 4) in order to display in a graphical interface the actual position of the coil with respect to the subject's brain. Even with such an assistance, it remains difficult to obtain an accuracy of a few millimeters in a repeatable manner. The main reason is that each procedure lasts more than 30 minutes with a coil that weighs more than 2 kg. A static positioning system is sometimes used to hold the coil. In such a case, it is not possible to follow continuous trajectories nor to compensate for involuntary motions of the subject during the session.

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Fig. 1. Close-up view of a stimulation coil with a figure-of-eight shape.

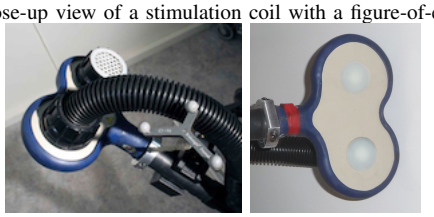
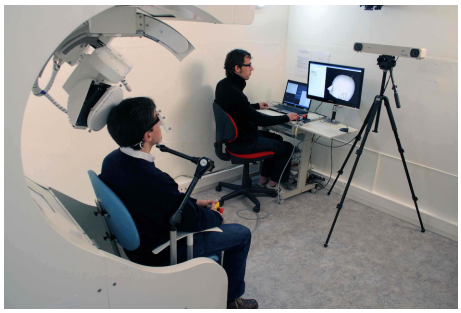


Fig. 2. The custom robotic system: the robotic device on the left, the software for the operator in the middle and the optical localizer on the right.



A custom robotic system was previously proposed in [8], with details on its design and control. Its accuracy was then only tested on a phantom, in lab experiments. The purpose of this paper is to present the first results of a clinical study with healthy subjects. The objective is to assess the level of performance of the robotic device in a standard TMS procedure and to evaluate the feeling of the user and the subject when interacting with the robot.

The main features of the proposed robotic system to improve safety, comfort for the subject, and the ease-of-use for the operator are outlined in section II. The design of the experimental assessment is then introduced in section III, before detailing and discussing the results in section IV. Conclusion on the interest of the use of a custom robotic system for TMS are finally derived from the experimental results, and future work is outlined.

II. MAIN FEATURES OF THE ROBOTIC SYSTEM

A. Hardware features

The robotic system is composed of a custom-designed robot, an external magnetic stimulation system, and an optical localizer (Fig. 2).

The stimulation is delivered using a custom Magstim coil (The Magstim Company Ltd, Whitland, South West Wales) connected to a Magstim Super Rapid stimulator. The coil

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equipped with force sensors is mounted at the tip of the robotic arm. The arm is equipped with six active joints, using a spherical architecture for the first three joints. In this way, the stimulation coil can perform only spherical movements around the head of the subject, avoiding any unwanted collision. Safety is also obtained by monitoring the output of the force sensors to control the force applied by the coil on the subjects head, and by restricting the amplitude and speed of the joints.

The optical localizer, a Polaris system (NDI, Waterloo, Canada) is used to follow a marker located on the subject's forehead. Any head movement can therefore be compensated for. In the following, a marker located on the stimulation coil is also used for control purpose: a vision-based control loop [8] enables us to suppress in particular the influence of the robot flexibilities. The control loop is implemented with a realtime software using Adept SMI6 SmartMotion modules, with a supervision software running on a Windows XP laptop. It is connected to the controller by a IEEE 1394 FireWire link and to the Polaris camera by a serial link in order to monitor the head motions and the coil displacements at 10 Hz.

To optimize the comfort of the subject, his head is not immobilized but simply supported by a chin strap to provide a restful position allowing natural movements for the duration of the session. The robotic system includes a mobile seat that eases the installation of the patient: once the seat is in its most forward position, and the robotic arm is placed in a lateral position, the subject can easily enter in the system. The seat can be then automatically adjusted to modify the subject position with respect to the robot base and consequently optimize the accessibility of the stimulation targets.

B. Software features

The key element of the robotic system for man-machine interactions is a software developed specifically for session planning and control. During the planning phase, MR images of the subject's head can be processed to provide 3D reconstructions of the brain and skull thanks to the Medipy framework [12]. These reconstructions can be manipulated to define the location of anatomical landmarks, necessary for head registration, as well as the location of stimulation targets.

At the beginning of the stimulation session, the software allows the operator to register the subject's head with respect to the MR images and the robot. A two-step process is implemented in the software. First, a rough computation is achieved with a point-to-point registration using anatomical landmarks. Then a surface matching is performed with an ICP algorithm, following [13]. The level of accuracy of the registration, with a RMS error in the order of 2 mm, is comparable to the registration with a commercial software such as Brainsight 2 (Rogue Research Inc, Montreal, Canada).

After registration, the subject is placed at the center of the robot workspace. Once the stimulation session protocol is loaded, the session can start. The operator can visualize the stimulation targets and the coil displacement during the whole session. All the robot positions are recorded for *a posteriori* analysis.

III. Design of the assessment experiment

A. Assessment criteria

We reported previously the results of lab experiments conducted with the robot using a phantom model [8]. The behavior of the robotic system appeared as satisfactory, but obviously several aspects require an evaluation in clinical conditions:

- First, the impact of the natural movements of the subject on the stimulation accuracy needs to be evaluated.
- Second, we need to estimate how the operator of the stimulation system is influenced by the introduction of a robotic system, since it may induce longer sessions, a more complex procedure with associated tiredness and/or a higher level of efforts to succeed in doing the full procedure.
- Third, we can question the subjects about their perceived levels of comfort and stress, as they may be affected by the installation inside a robotic system that is permanently moving during the session.

B. The experiment

Considering the assessment criteria, we selected for our evaluation of the robotic system a motor cortex mapping protocol involving healthy subjects using TMS.

Motor cortex mapping is a well-known, complex TMS protocol used in neurology and neuroscience for the measurements of Motor Evoked Potentials [11]. It can be performed with the robotic system and with a commercial neuronavigation system. As a consequence, with such an experiment, a direct comparison of the manual technique using neuronavigation versus the robotized approach can be performed.

During a motor cortex mapping, the operator has to move the coil over the patient's motor cortex at a large number of positions, typically one hundred, delivering a stimulus at each position, to record electrophysiological responses measured at a hand muscle. For such a protocol, it is not mandatory to define targets as a regular grid. Decision was made to choose a 10 x 10 periodic grid centered on the right thumb muscle area with a constant interspace of 10 mm (Fig. 3). The idea is to define a positioning task that covers a large set of positions and orientations of the coil from the top of the head to its side.

Ten participants were involved in the study. Each participant had two sessions with the robot, one session with pre-contraction of the recorded thumb muscle and one session without pre-contraction. Repeating the protocol twice allows us to get a first evaluation of the stimulation repeatability. Notice that the pre-contraction of the muscle affects the results in terms of mapping geometry, which is not exploited in this analysis. The two sessions were then repeated using manual neuro-navigated positioning.

Fig. 3. The predefined mapping of the cortex

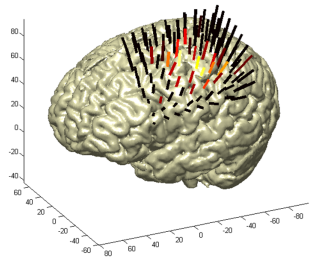
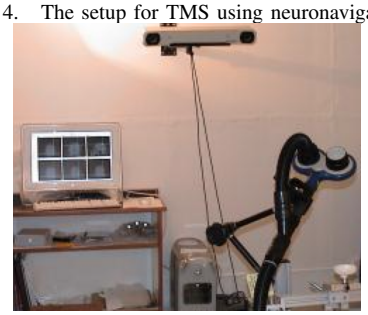


Fig. 4. The setup for TMS using neuronavigation.



Five trained operators performed the robotic and the manual sessions in an random order. The electromyography (EMG) response provided by a KeyPoint device (Natus Medical Inc, USA) was analyzed by an independent operator after each stimulus in order to determine and record the maximum and mininimum response as well as the times of minimum and maximum responses.

The manual positioning assistant was the Brainsight 2 neuronavigation system (Fig. 4) where the operator was allowed to trigger the stimulus based on its own decision. The robot software was programmed to automatically trigger the stimulus when the distance between planned coil and actual coil's location reached a pre-defined position and angular tolerance. The same tolerance values were used as in the display provided by the neuronavigation system. The NDI Polaris camera of the neuronavigation system was used to record the coil position in both settings.

The comparison is achieved by considering absolute accuracy and repeatability of both techniques. Accuracy is here defined as the discrepancy between the planned and the actual positions of the coil center, the so-called hot spot, on each point of the grid. Repeatability measurement is obtained by comparing the coil center position between the two sessions of each subject.

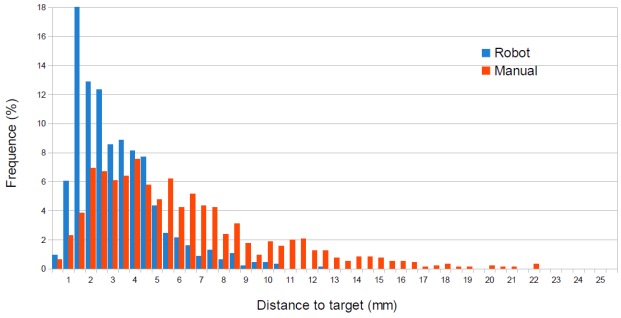
Motor cortex mapping is a long protocol. Therefore it also helped assessing the feedback of the operator on the robotic system use. Moreover, as it was performed on healthy volunteers, the protocol also allows to evaluate subject feeling. Both the participants and the operators were asked to evaluate fatigue, easiness and acceptability of the protocol using visual analogical scales.

TABLE I

PERCENTAGE OF STIMULATION BELOW A GIVEN DISTANCE BETWEEN COIL HOT SPOT AND TARGET.

	50 %	80 %	90 %	95 %
Robot	3 mm	4.5 mm	5.5 mm	6.5 mm
Manual	5.5 mm	9 mm	12 mm	15 mm

Fig. 5. Histogram of the accuracy without pre-contraction



IV. RESULTS AND DISCUSSION

A. Results

The histogram of the distances to target during the sessions with and without pre-contraction of the hand muscle are represented in Fig. 5 and 6. As mentioned earlier, these two plots have to be analyzed as identical experimental protocols in terms of accuracy. A third plot is computed from the variation of the position of the coil center between the two experiments (Fig. 7). The introduction of the robotic system improves by a factor of 2 the accuracy and the repeatability ($p < 0.01$). The average accuracy is about 3 mm, in the order of the registration error, with respect to 6 mm with a manual positioning. If we consider a 5-mm threshold as the maximum acceptable error, 90% of the grid is valid with the robotics approach, to compare with less than 50% in manual conditions (Table 1). The repeatability evaluation leads to the same conclusions in terms of efficiency of the robotics approach. The session duration was not significantly different between the two conditions (81min for both).

The comfort of the two setups was considered identical by the subjects, as well as the level of stress. On the opposite, the robotics approach has been considered as less tiring and effortful ($p = 0.04$), more pleasurable and comfortable to use ($p < 0.01$) compared to the manual positioning by the operators. This difference even tended to increase from the first to the second session (with and without pre-contraction).

B. Discussion

This experimental evaluation brings very interesting results concerning the use of a custom robotic system for TMS sessions.

The influence on the stimulation accuracy is obvious. The robotic system helps lowering the average position error. It can also strongly limit the maximum repeatability error as illustrated in Fig. 7 where errors up to 24 mm have been recorded in the manual conditions, compared to 10 mm using

Fig. 6. Histogram of the accuracy with pre-contraction

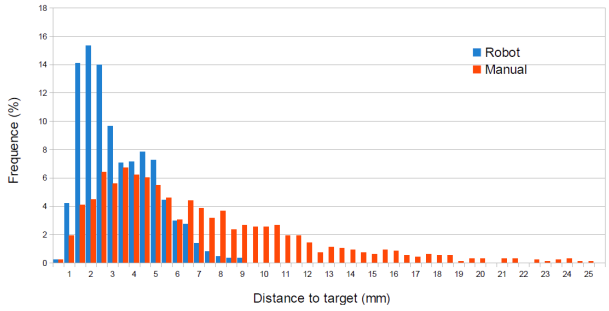
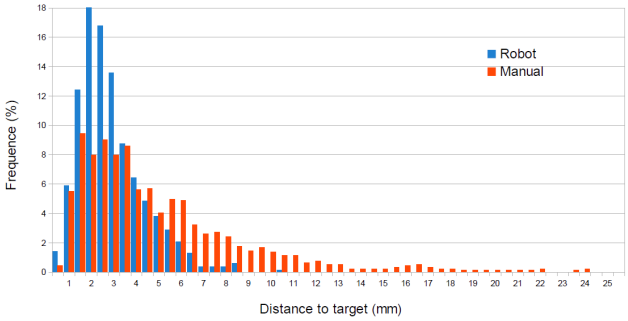


Fig. 7. Repeatability between the two consecutive sessions



the robotic system. This can be explained by the difficulty of positioning the coil for instance on the side of the head. The coil is then not supported by the head, so the operator has to maintain without any assistance the 2-kg coil in a static position.

It may look surprising that the session duration is not improved. After analysis, two main reasons appeared. First, the manual analysis of the EMG responses is very time-consuming. This part of the task is not influenced by the use of the robot in the current conditions, so the possible time decrease of the experiment is limited. Second, the robot is currently controlled using a vision loop. The coil displacements are then pretty slow and constitute a limit in the time reduction of the stimulation protocol.

Finally, it is very encouraging to see the comfort, stress level were not modified by the introduction of a new device in the TMS room. In the same way, the operators considered the system less tiring, more pleasurable and comfortable use. It tends to show the validity of the design choices in term of hardware and software solutions.

V. CONCLUSIONS

The presented experimental assessment on healthy subjects is very encouraging for the development of robotic assistance in TMS. Using a custom robotic system allowed to significantly improve the accuracy. This looks promising for therapeutic repetitive TMS protocols, like in psychiatry or neurology, where a large number sessions are required for the same patient. Similarly to a brain mapping protocol, physicians need repeatability, absolute accuracy, good user and subject feeling.

The results are also very interesting in terms of acceptability of the device by the operators and the subjects. This is a very important element since the introduction of a new device could constitute an obstacle in a clinical use.

The duration of TMS sessions was not improved with the robotic system. The use of a vision loop for the device control constitutes a limit to reduce the duration of the robot movements. Therefore a next step is now to improve the robot mechanical properties, particularly in terms of stiffness, so that open loop control can be used. A new version of the robot is being developed with that purpose.

The system is already installed in three TMS centers to gather pre-clinical data required for regulatory approval. Further clinical testing will be also performed.

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REFERENCES

[1] A. T. Barker, R. Jalinous, and I. L. Freeston, "Non-invasive magnetic stimulation of human motor cortex," *The Lancet*, vol. 325, no. 8437, pp. 1106–1107, 1985.

[2] A. Gershon, P. Dannon, and L. Grunhaus, "Transcranial magnetic stimulation in the treatment of depression," *American Journal of Psychiatry*, vol. 160, no. 5, pp. 835–845, 2003.

[3] S. Lisanby, L. Kinnunen, and M. Crupain, "Applications of TMS to therapy in psychiatry," *J. Clin. Neurophysiol.*, vol. 19, pp. 344–360, 2002.

[4] R. Ahdab, S. Ayache, P. Brugieres, C. Goujon, and J.-P. Lefaucheur, "Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patents with chronic pain and depression," *Clinical Neurophysiology*, vol. 40, pp. 27–36, 2010.

[5] R. Sparing, D. Buelte, I. Meister, T. Paus, and G. Fink, "Transcranial magnetic stimulation and the challenge of coil placement: A comparison of conventional and stereotaxic neuronavigational strategies," *Human Brain Mapping*, vol. 28, pp. 82–96, 2008.

[6] U. Herwig, C. Schonfeldt-Lecuona, A. Wunderlich, C. von Tiesenhausena, A. Thielscher, H. Walter, and M. Spitzera, "The navigation of transcranial magnetic stimulation," *Journal of Psychiatric Research*, pp. 123–131, 2001.

[7] S. Neggers, T. Langerak, D. Schutter, R. Mandl, N. Ramsey, P. Lemmens, and A. Postma, "A stereotactic method for image-guided transcranial magnetic stimulation validated with fMRI and motor-evoked potentials," *Neuroimage*, vol. 21, pp. 1805–1817, 2004.

[8] L. Zorn, P. Renaud, B. Bayle, L. Goffin, C. Lebossé, M. de Mathelin, J. Foucher, "Design and evaluation of a robotic system for transcranial magnetic stimulation," *IEEE Transactions on Biomedical Engineering*, Vol. 59, no. 3, pp. 805–815, 2012.

[9] E.M. Khedr, H. Kotb, N.F. Kamel, M.A. Ahmed, R. Sadek, and J.C. Rothwell, "Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain," *J Neurol Neurosurg Psychiatry*, vol. 76, pp. 833–838, 2005.

[10] J. Brunelin, E. Poulet, B. Bediou, L. Kallel, J. Dalery, T. D'Amato, et al., "Low frequency repetitive transcranial magnetic stimulation improves source monitoring deficit in hallucinating patients with schizophrenia," *Schizophrenia Res.*, Vol. 81, pp. 41–45, 2006.

[11] P.E. Tarapore, M.C. Tate, A.M. Findlay, S.M. Honma, D. Mizuiri, M.S. Berger, S.S. Nagarajan, "Preoperative multimodal motor mapping: a comparison of magnetoencephalography imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation," *J Neurosurgy*, Vol. 117, no. 2, pp. 354–362, 2012.

[12] Medipy - A medical image processing framework, http://code.google.com/p/medipy/

[13] P. J. Besl and H. McKay, "A method for registration of 3-d shapes," *Pattern Analysis and Machine Intelligence*, vol. 14, pp. 239256, 1992.