Project Name: SP-STIM

Rewiring dysfunctional brain circuits with personalized stimulation

Scientific Report

Coordinators of the project:

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Hosting entities: IETR – UMR CNRS 6164 | LTSI – UMR 1099 INSERM

Context

The SP-STIM project aimed to investigate the potential application of electromagnetic wave (EMW) as a novel non-invasive neuromodulation modality, from the PKSTIM project pilot findings. The use of radiofrequency (RF) frequencies is not clearly understood as no clear mechanism of action on the central nervous system has been identified for low dose exposure. However, recent studies show that RF fields have neuroinhibitory effects that can be used for neuromodulation[1]. In addition, RF techniques allow to use electromagnetic focusing/beamsteering techniques to focus the wave inside dispersive tissues, enabling the focus of EMW into the targeted area. The objective of this one-year project was two-fold: develop and deepen existing theory on focusing the EMW into brain tissues to draw the possible limits in term of exposure; and assess *in vitro* the effect of amplitude modulated RF EMW on neuronal activity, to validate the possible use of these high frequencies to modulate brain activity.

Computational neuro-EM models for non-invasive stimulation

To optimize the delivery of EMW into brain tissues and ensure ICNIRP guidelines restriction on the level of tissue heating/exposure to EMW, we assessed the theoretical limit of EMW focusing in brain tissues using numerical models. Indeed, previous head models were designed during the PKSTIM project and firstly used to dose and study transcranial electrical stimulation. During the present project, these models were used in RF RWM modeling using COMSOL Multiphysics. To draw the theoretical limits, a perfect mirror boundary was used to focus perfectly the waves back to the target. Doing so, we demonstrate the ability to focus

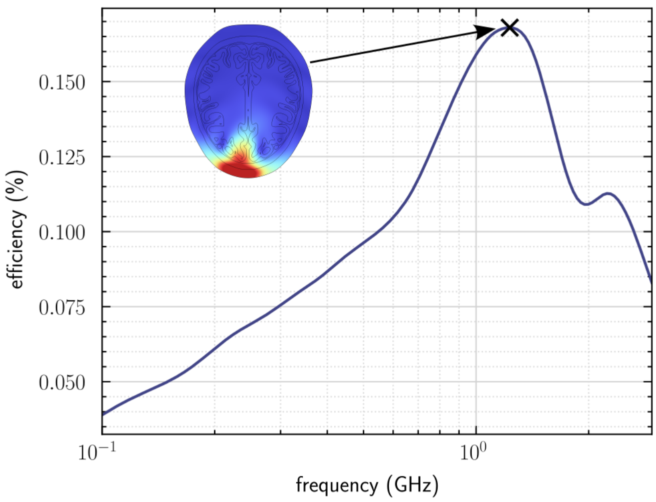

Figure 1: Efficiency frequency profile for a perfectly focused EMW in a frontal cortical area. A clear maximum is visible at 1.28 GHz.

[1] Ahsan, F. *et al.* EMvelop stimulation: minimally invasive deep brain stimulation using temporally interfering electromagnetic waves. *J. Neural Eng.* **19**, 046005 (2022).
Rektorová, I., Pupíková, M., Fleury, L., Brabenec, L. & Hummel, F. C. Non-invasive brain stimulation: current and future applications in neurology. *Nat Rev Neurol* 1–18 (2025).
Yaghmazadeh, O. *et al.* Neuronal activity under transcranial radio-frequency stimulation in metal-free rodent brains in-vivo. *Commun. Eng.* **1**, 15 (2022).

the waves into a focal spot with the general λ /2 size, with an efficiency clearly frequency-dependent as illustrated in Figure 1. Therefore, we highlighted the optimal operating frequency to target cortical area being around 1.4 GHz, while lower frequencies should be used to target deeper brain structures, which is something expected due to the increase in loss in tissues with frequencies. We further investigated the impact of adding a layer of material with a specific relative permittivity that could be used as a matching layer. Doing so, we underlined the changes in optimal operating frequency when using such material, enabling an increase in efficiency but also to design both material and antenna to optimally deliver the EMW into the desire area. The setup for the 2D simulation and results are presented in Figure 2. The results of this section (related to D1 and D2 of the initial proposal) are included in an article in progress, that we aim to submit to the IEEE TBME review.

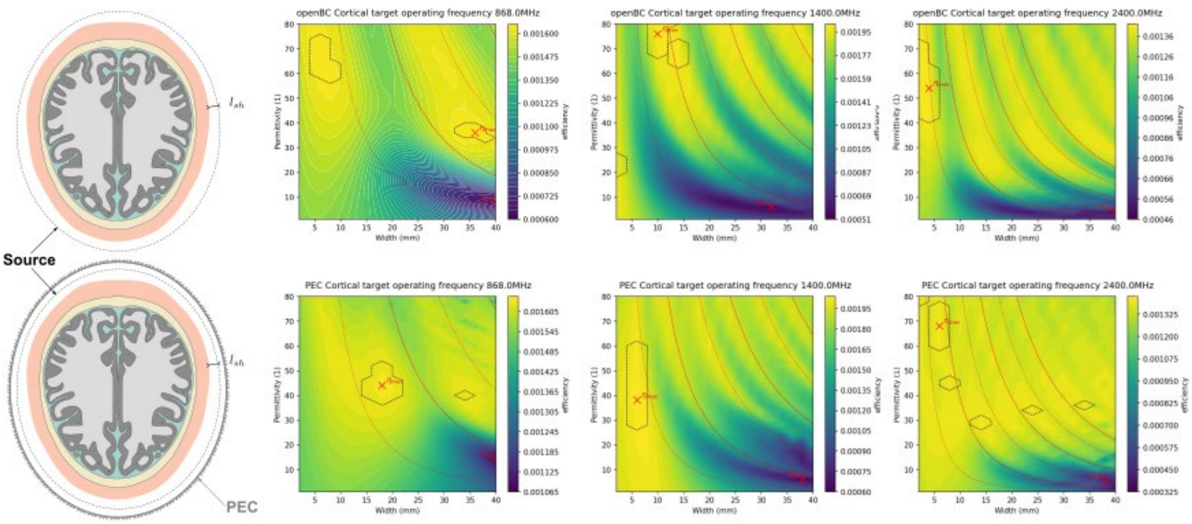

Figure 2: Setup of the 2D model with open and PEC based perfect mirror boundary conditions and the related efficiency maps to target a cortical area. Note the match between the highest efficiencies and the λ /4 multiples draw in dotted res lines.

In vitro neuronal exposure to amplitude modulated radio frequency electromagnetic waves

Exposure of neuron from Sprague-Dawley rats cultured in IMS, Bordeaux were used to assess the effect of amplitude modulated radiofrequency electromagnetic waves (AM-RF EWM) on neuronal activity. The neuron were cultures on a multi-electrode unit plate to record their activity and disposed in a transverse electromagnetic cell (TEM cell), place into an incubator to keep the temperature at 37° C during exposure. This experimental setup enabled to expose the cell while efficiently record their activity (Figure 3.A). The exposure protocol consisted in 4 consecutive trials of 15 minutes being S1: SHAM; E1: exposure to non-modulated 1.4 GHz EMW for comparison to the modulation; S2: SHAM/after effect of E1; E2: AM-RF exposure

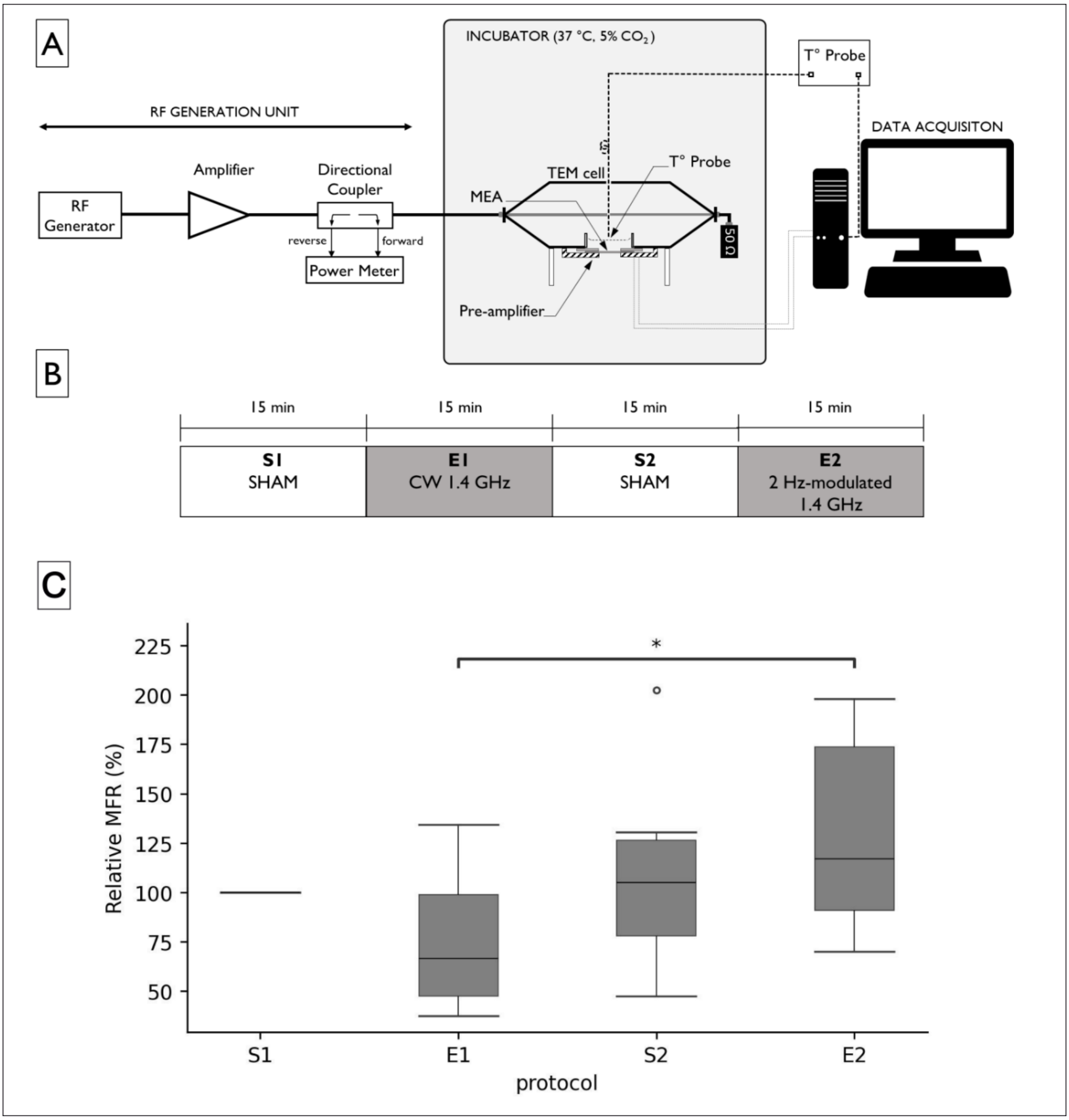

Figure 3: ***A) Experimental setup.*** *The RF generator was coupled to an amplifier to deliver exposure within the incubator in which the TEM cell containing the neuronal culture was placed. A power meter connected to the amplifier via a directional coupler was used to monitor incident power in real time during exposure.* ***B) Exposure protocol.*** *Temporal course of the exposure, which involved two "Sham" epochs without any stimulation (S1 and S2), and two Exposure epochs (E1 and E2). E1 and E2 both involved exposure to 1.4 GHz RF, but amplitude modulation at 2 Hz was only present during the E2 epoch. Each epoch lasted 15 minutes.* ***C) Relative mean firing rates of active electrodes for the 7 cultures across protocols.*** *A non-significant decrease is visible in E1, while an increase is visible in E2 with significant increase between E1 and E2 (p<0.05, Conover's multiple comparison test).*

(Figure 3.B). The active recording electrodes – having a firing rate above 0.5 Hz – were used to calculate the mean firing rates and were compared across protocols and show a significant difference between the E1 and the E2 conditions only, marking and increase in firing rate between both ($p<0.05$, Conover's multiple comparison test). The results are however hard to justify a direct modulatory effect of AM-RF EMW since no reliable phase entrainment was found in all cultures.

Summary

Resulting grant applications

A joint ANR project, STIMNET (420,000 euros over 3 years), has been submitted in as a direct continuation of the collaborative research efforts that have been initiated in PKSTIM between LTSI and IETR. This proposal has been very favorably reviewed but did not pass the second evaluation step. A resubmission is planned.

Based in part on preliminary findings on SPSTIM and PKSTIM**, ERC Starting Grant "BESSEL"** was obtained in 2024 (one of the work packages of the project is relevant to the findings of SPSTIM).

Publications

Journal papers:

1. Gaugain G, Al Harrach M, Yochum M, Wendling F, Bikson M, Modolo J, et al. Frequency-dependent phase entrainment of cortical cell types during tACS: computational modeling evidence. J Neural Eng. 2025;22: 016028. doi:10.1088/1741-2552/ad9526

Preprints:

1. Gaugain G, Modolo J, Nikolayev D. Accurate evaluation of neural sensitivity to weak alternating electric fields requires protocols accounting for input dependence. bioRxiv; 2025. p. 2025.11.24.690108. doi:10.1101/2025.11.24.690108

2. Gaugain G, Canovi A, Orlacchio R, Gannes FP de, Nikolayev D, Modolo J. 1.4 GHz amplitude-modulated radiofrequency electromagnetic waves effects on neural cultures. bioRxiv; 2025. p. 2025.10.10.680616. doi:10.1101/2025.10.10.680616

Conferences:

1. Gaugain G, Modolo J, Nikolayev D. Improving precision of computational electromagnetics for transcranial stimulation. Proc. ICECOM 2023, Dubrovnik, Croatia: 2023.

Technological transfer

In SP-STIM, we have achieved several advances towards this objective that suggest that a prototype implementing a novel form of non-invasive neuromodulation with significant IP and technology transfer potential is a realistic perspective as the next step of the PKSTIM and SPSTIM projects. We already have an expression of interest in this innovative approach from a leading company in the field, NeuroElectrics. A discussions are underway with SATT Ouest Valorisation for the maturation project.

International visibility

The results of SP-STIM project were presented in flagship international venues (see the list above) and led to the creation of new international collaborations with the following researchers and reinforce the existing collaborations with the companies:

- Prof. Marom Bikson, CCNY, New York, USA
- Prof. Warren Grill, Duke University, USA
- Prof. Angel Peterchev, Duke University, USA
- Prof. Risto Ilmoniemi, Aalto University, Finland
- Dr. Satoshi Nakasono, CRIEPI, Tokyo, Japan
- Prof. Flavio Fröhlich, University of North Carolina, USA
- Pr. Bradley Voytek, University of San Diego, USA