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Deep Transcranial Magnetic Stimulation for the Addiction Treatment: Electric Field Distribution Modeling

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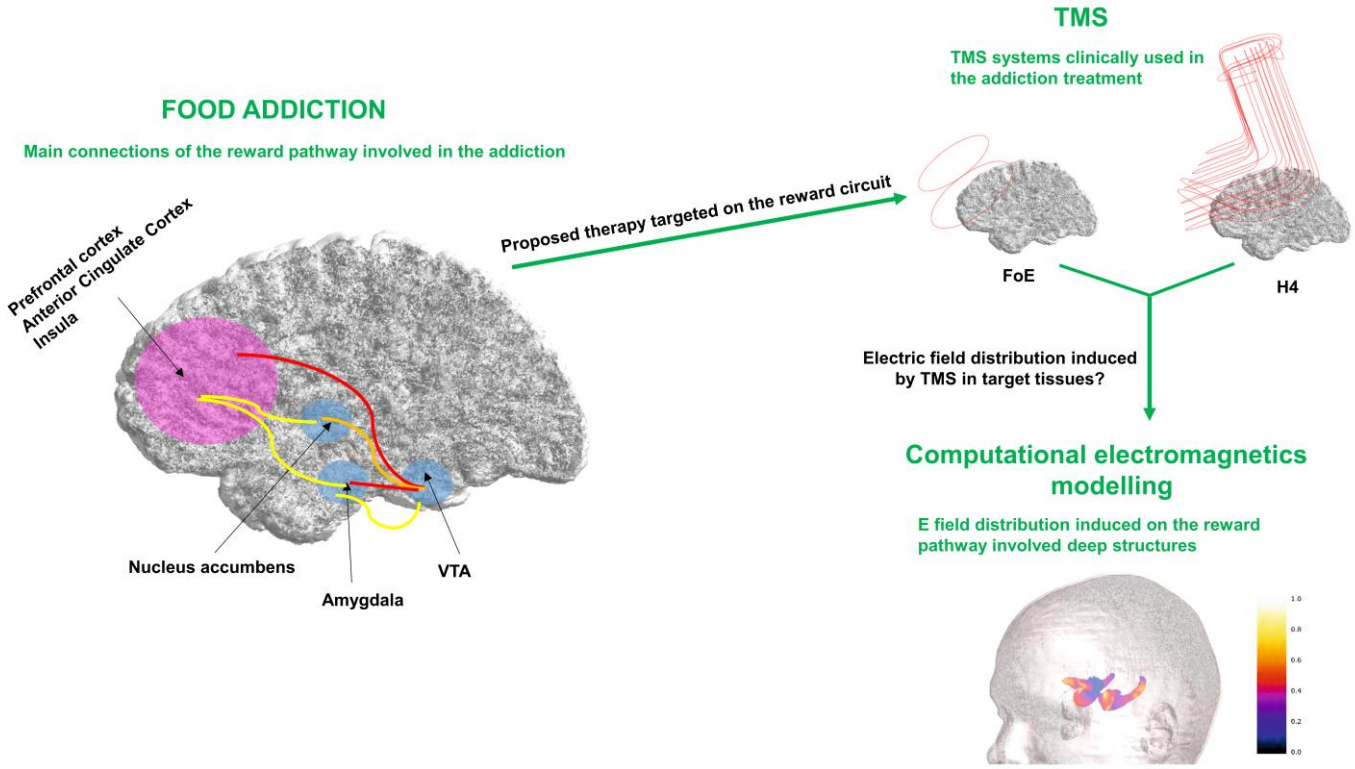

dTMS H4 coil for the addiction treatment: assessment of the electric field in cortical and subcortical targets

Take-Home Messages.

- Deep Transcranial Magnetic Stimulation (dTMS), administered through H4 coil, has been recently proposed for the addiction treatment and it's aimed to stimulate bilaterally the prefrontal cortex and to activate the reward pathway.
- Computational electromagnetic models help in gaining knowledge on the mechanism laying behind neurostimulation, by providing a detailed electric field distribution induced in cerebral tissues.
- Simulations demonstrates that H4 induces the highest electric fields at cortical level, targeting preferentially prefrontal cortex and the anterior cingulate cortex and then supporting its use for addiction treatment.
- This work represents, in contrast with prior works based on homogenous tissue phantoms, a powerful and informative tool for both planning, optimization and outcomes evaluation of clinical protocols based on dTMS systems for addiction treatment.
- Deep TMS coil H4 can be specifically used to target cortical and subcortical structures involved in food craving related disorders.

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Deep Transcranial Magnetic Stimulation for the Addiction Treatment: Electric Field Distribution Modeling

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Abstract Deep Transcranial Magnetic Stimulation (dTMS) is a neurostimulation technique for deep brain structures that has recently been successfully applied in the clinic for treatment of addiction. In contrast to conventional magnetic stimulation, which uses planar coils (figure-of-8) to target specific superficial regions of the brain, dTMS requires the design of complex three-dimensional coils in order to induce deeply penetrating fields. Recent clinical studies have focused on the use of H4 coils, which utilizes a left-right symmetric structure for bilateral stimulation of the prefrontal cortex, and demonstrated efficacy for therapy such as smoking cessation. The mechanism of activity, however, remains poorly understood, in part because the affected regions of the brain are not known in detail. To this purpose, computational techniques applied to highly detailed inhomogeneous tissue phantoms, provide a powerful tool for testing coil efficacy. In this work we quantified both electric field **E** distribution and its penetration depth in the prefrontal cortex, induced by a specific Hesed-coil, H4, designed for the addiction treatment and by the traditional figure-of-8 coil for comparison. Results show that H4 coil preferentially targets insula and cingulate cortex. Moreover, it can induce in the deepest tissues E amplitude ranging between the 20-40% of the cortical peak and it can penetrate the cortex up to 4 cm with a E>50% of the cortical peak, thus noticeably increasing the penetration depth of the traditional TMS systems.

Keywords **— Dosimetry, Magnetic stimulation, Computational electromagnetics, Finite element methods, noninvasive treatment, electromagnetic induction.**

I. Introduction

The recent advances in neuroimaging have allowed a more precise identification of anatomical and functional alterations in specific brain regions thus contributing to a better understanding of their role in the time of onset and the progression of different neurological disorders [1]. That paved the way to a more rational and focused development of techniques such as Deep Brain Stimulation (DBS), Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) for brain modulation. Among them, TMS, by combining a non-invasive and safe approach for prefrontal cortex (PFC) stimulation, has been increasingly considered a valuable and efficient tool for the treatment of neuropsychiatric disorders, whose progression is clinically linked to imbalanced activity of that region [2]. However, conventional TMS, usually administered through a "Figure-of-Eight" (FoE) coil system, allows stimulation of the only brain regions placed just below the skull, and, therefore, it is not the most adequate tool for reaching specific deeper subcortical networks that are known for their affected activity in all the mood disorders. In the attempt to overcome this constraint, deep TMS (dTMS) was proposed [3][4]. This technique, based on the use of large coils with a complex 3D path, by inducing a non-focal distribution over the cortex, allows to reach deeper brain targets than traditional and focused FoE based TMS systems. In the last few years, in particular, dTMS started to be successfully used in the treatment of a growing number of mood disorders, including substance use disorder (for a review on the clinical use of dTMS coils see [5]). Literature and criteria defining substance use disorder considers food addiction similar to drug addiction, sharing most of evidence on underlying common neurobiological mechanisms [6]. For this reason, studies that have successfully applied dTMS for the treatment of drug disorders [7][8] sound as a promising basis to extend the use of that therapy for the treatment of food related pathologies. Neuroanatomy of food craving is little explored, however, the growing literature on the neural substrate of drug craving suggests that the craving-related activated structures include prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, hypothalamus, amygdala, hippocampus, nucleus accumbens and ventral tegmental area (VTA) [9][10]. These structures, as

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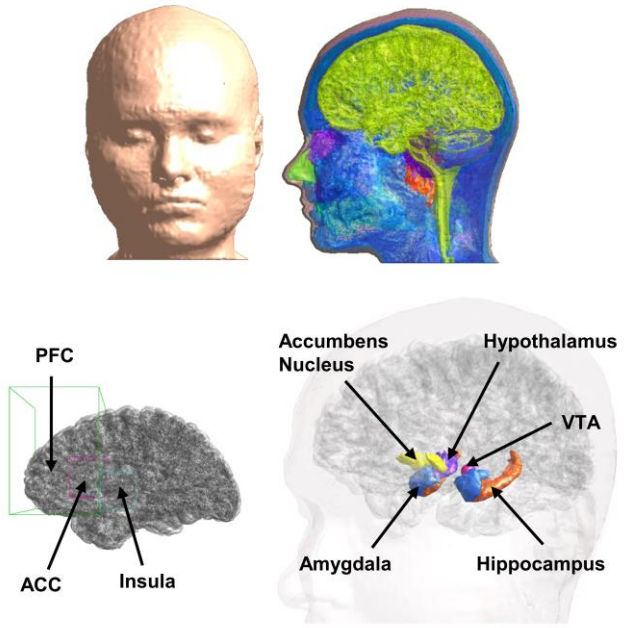

Fig. 1. MIDA model. Top: surface and internal organs representation; Bottom: Segmentation masks of brain target structures for addiction treatment. PFC: prefrontal cortex; ACC: anterior cingulate cortex; VTA: ventral tegmental area.

documented by the few computational studies that have investigated the detailed distributions of electric field induced by dTMS coils [11]-[16] can be reached with an electric field amplitude higher than the 20% of the maximum at cortical level at expense of a much more broad distribution over the cortex. Among dTMS coils, the family of coils called Hesed (H) coils are thought to target both prefrontal cortex areas and the over mentioned sub-cortical structures, thus encouraging their application for the addiction treatment, including food addiction.

In particular, the dTMS H-coil named "H4", among the other H-coils [5], was precisely designed to bilaterally stimulate a specific cortical target for the addiction, namely the prefrontal cortex, between the entorhinal cortex and the insula, and was successfully used in a pilot study for smoking cessation [8]. Despite that, the mechanism lying behind the proven efficacy of this coil is still poorly understood, in part because of the limited knowledge of the regions most affected by the stimulation. This translates into a limited and unspecific knowledge of the electric field (**E**) distribution induced into the complex brain anatomy.

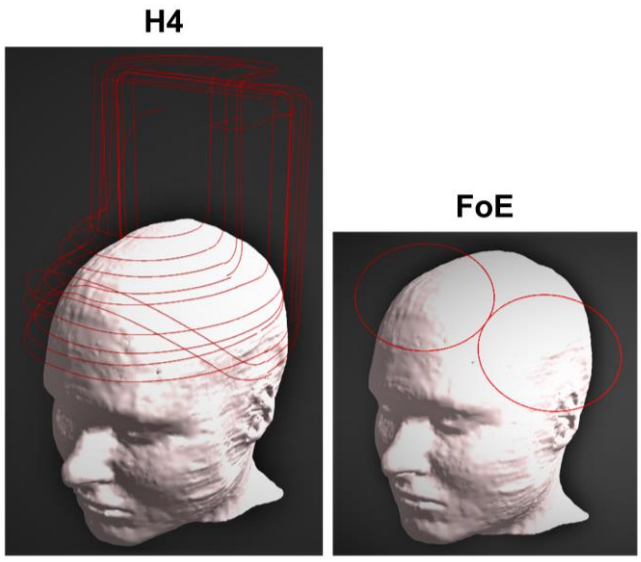

Fig. 2. H4 (left) and FoE (right) coil models placed over MIDA model.

In contrast with most of the previous decades works, based on homogenous tissue phantoms, this work aims to quantify, by means of computational electromagnetic techniques, the **E** distribution induced by H4, in a new and highly detailed anatomical head model.

The **E** distributions were also compared with the one induced in the same targets by a conventional FoE coils system, traditionally used for the TMS therapy. Moreover, in order to evaluate to which extent the individual variability affects the **E** distributions, the analysis of the **E** induced by H4 was also performed on other two highly detailed anatomical models, commonly used in the most advanced computational electromagnetic studies.

II. Methods

A. Human and coil models

A multimodal imaging-based anatomical model, named MIDA (Fig. 1) [17], of the head and neck, segmented and reconstructed from three different MRI modalities at a 500 μm isotropic resolution was used in this study. The model derives from scans of one healthy 29-years old female volunteer. The head model distinguishes, among other tissues, the cortex (in which we identified prefrontal cortex, anterior cingulate cortex and insula), hypothalamus, amygdala, hippocampus, nucleus accumbens and ventral tegmental area. The dielectric properties of each of them have been assigned according to literature data [18][19] at the dTMS single pulse typical frequency [20], i.e. 5 kHz.

The H4 coil was modelled according to the available manufacturer specifications as current paths. It is composed of 12 windings and the current flows clockwise in each winding. The FoE coil model was also derived by a clinically used coil and consists of two adjacent current circular loops, modelled as two single current paths [16], of 10 cm diameter, placed tangentially to the head. A distance of 1 cm to account for the thickness of the realistic coil insulation not included in the model was kept. The current flows in opposite directions in the two windings. Following the experimental studies protocol, both coils were placed with their centers moved from the left motor hand cortex, where the motor threshold (MT, here supposed to be equals to 100 V/m) was determined, 6 cm toward the left prefrontal cortex (Fig. 2).

The current intensity delivered was then adjusted in order to obtain 120% of the MT (i.e. 120 V/m).

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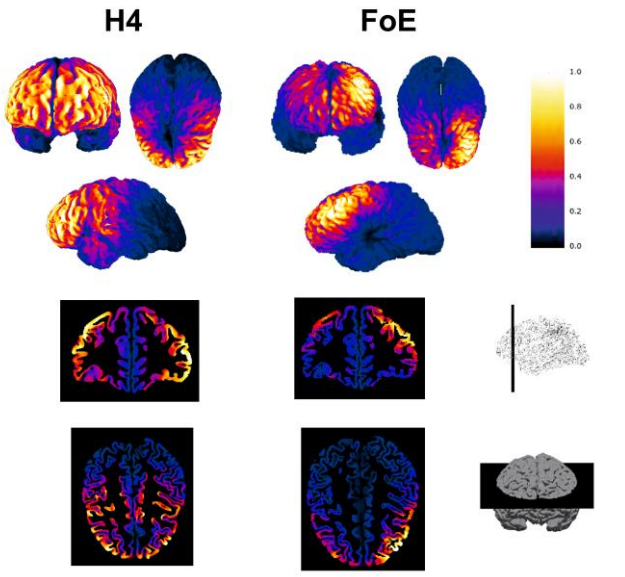

Fig. 3. Normalized (to E_{max}) **E** amplitude distributions induced by H4 (left) and FoE (right) coil over MIDA cortical surface. 3D surface (top row) and slice field view (bottom row).

According to repetitive TMS (rTMS) safety guidelines (see the first guidelines [21] and the related consensus statements and comments [22][23][24]), this threshold, if used in combination with adequate frequency and duration of trains, has been proven efficacious in avoiding both spread of excitation and seizures, thus assuring that both the field produced by the simulated coils and the resulting induced fields are within the limits preventing acute adverse effects in humans.

B. Simulations

Simulations were conducted using the magneto quasi-static low-frequency solver of the simulation platform SIM4life (by ZMT Zurich Med Tech AG, Zurich, Switzerland, www.zurichmedtech.com), which uses a Biot-Savart solver based on the scalar potential finite element method. In the low frequency range, the pertinent dimensions of the computational domain are smaller than the free space wavelength; therefore, the magnetic vector potential **A** is decoupled from **E**. Moreover, since the conduction currents are dominant in the human body for the conditions here studied, **E** can be calculated from the scalar potential Φ, which is given by (1):

$$-\nabla\cdot\sigma\nabla\Phi=j\omega\nabla\cdot(\sigma A) \quad (1)$$

where σ is the tissue conductivity and ω is the angular frequency of the frequency of the field. **A** is calculated using the Biot-Savart's law whereas the finite element method is used to solve for Φ. The computational domain was discretized using a uniform hexahedral meshing algorithm, made available by the computational software, with a maximum mesh step of 0.5 mm.

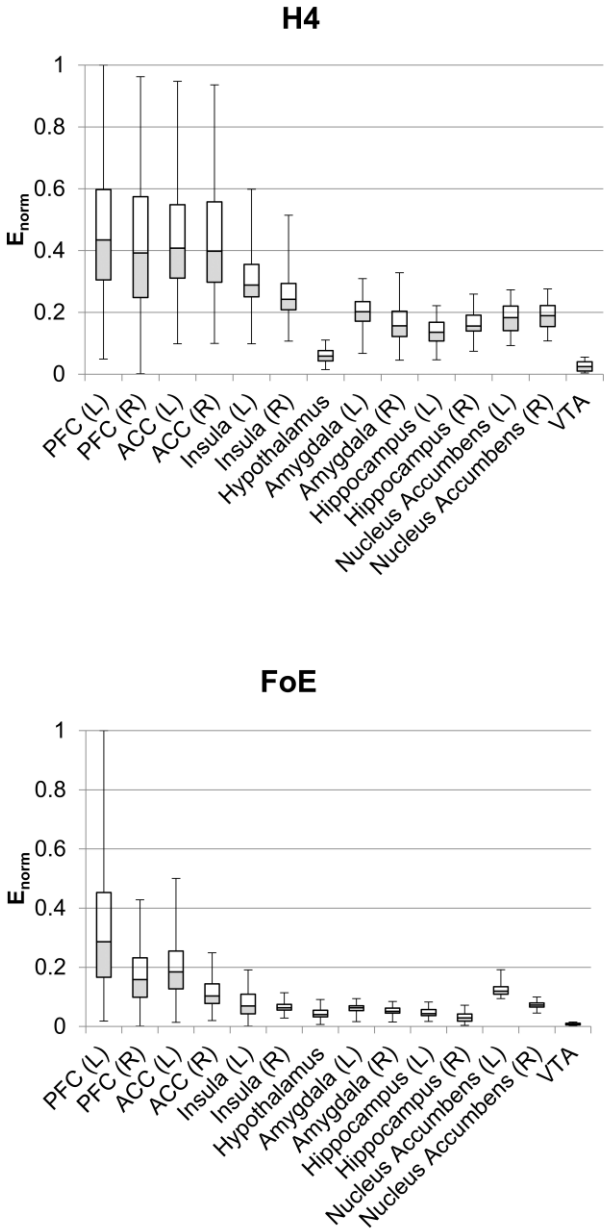

Fig. 4. Descriptive statistic of the normalized **E** amplitude induced by H4 (top) and FoE (bottom) coils over cortical and subcortical MIDA structures PFC: prefrontal cortex; ACC: anterior cingulate cortex; VTA: ventral tegmental area; L: left; R: right.

C. Electric field analysis

The **E** amplitude distribution was estimated in the brain regions target of the dTMS for addiction treatment (detailed in Fig. 1). In all these brain structures, the descriptive statistics of the **E** amplitude distribution (i.e. min, 25th, 50th, 75th and 99th percentiles of the distribution) and its penetration depth were quantified. This last is defined as the maximum depth in the frontal lobe of the brain where the induced **E** amplitude was equal or greater than the 50% (d_{50}) or the 70% (d_{70}) of the maximum (here intended as the 99th percentile) amplitude of **E** in the cortex (in the following named "E_{max}") [13]-[15].

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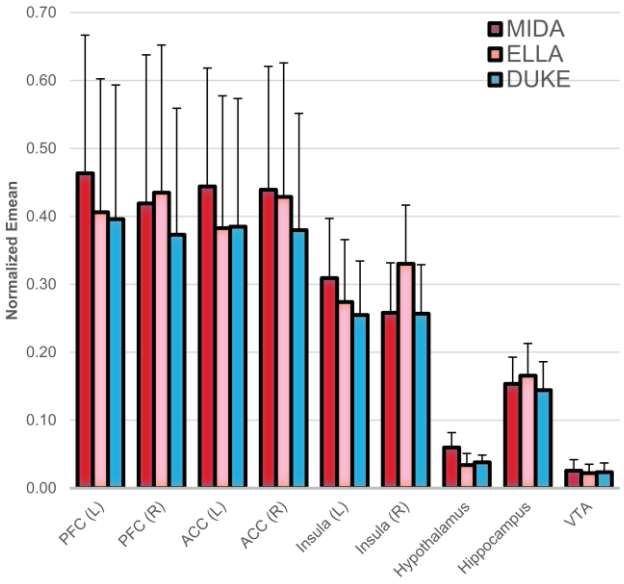

Fig. 5. Mean (bars) and standard deviation (whiskers) of the normalized (to cortical Emax) electric field distributio induced by H4 on the three different models

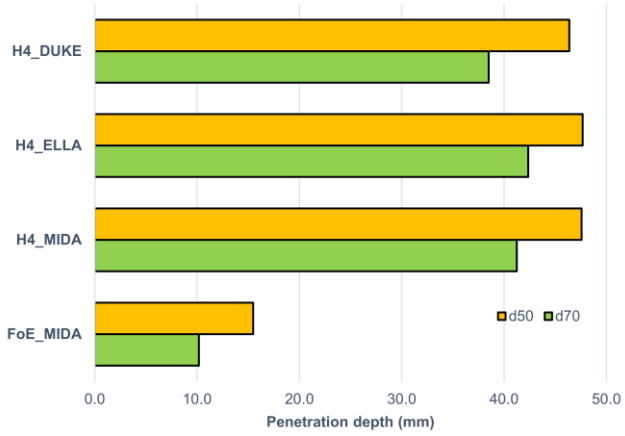

Fig. 6. Penetration depth at 50% (d50) and at 70% (d70) of E_{max} in the frontal lobe from the surface of the cortex for the two coil systems over MIDA and for H4 also on Duke and Ella models.

D. Effect of human variability on electric field distribution

In order to evaluate to which extent the human variability affects the **E** amplitude distribution induced by the H4 coil, the same analysis performed on MIDA model was repeated on two adult anatomical voxel models belonging to the Virtual Family [25], namely an adult 34-years old male model "Duke" and an adult 26-years old female model "Ella". In particular, the **E** amplitude distribution was estimated in some brain regions target of the dTMS for addiction treatment that can be distinguished in all the three models and the penetration depth in the PFC for each of them was calculated.

III. Results

Fig. 3 shows the normalized (to E_{max}) **E** amplitude distribution induced by the two coil systems over MIDA cortex. Panels in the figure show that **E** amplitude distributions induced by H4 coil are much more widespread than the ones due to the FoE coil and involve both hemispheres. H4 coil is able to induce higher **E** amplitude over a broad area of the frontal lobe, specifically over the more lateral region (anterior cingulate cortex and entorhinal cortex) of both hemispheres. Conversely, FoE induces a more focused **E** amplitude distribution with maxima over a small volume of the superior PFC only on the hemisphere over which it is positioned.

In order to quantify more precisely the **E** amplitude distributions in cortical and subcortical structures target of stimulation, Fig. 4 illustrates the descriptive statistics (minimum, 25^{th}, 50^{th}, 75^{th} and 99^{th} percentile) of the **E** amplitude distributions normalized respect to E_{max} in the cortex. From this figure, one can note how H4 coil preferentially targets the bilateral prefrontal cortex and the bilateral anterior cingulate cortex, followed by insula (peak of **E** amplitude around the 50-60% of E_{max}), amygdala and nucleus accumbens (peak of **E** amplitude around 30% of E_{max}), hippocampus (peak of **E** amplitude> 25% of E_{max}), and ventral tegmental area and hypothalamus (peak E around 10% E_{max}). The same trend can be identified by comparing the median normalized **E** amplitude values, with a cortical maximum median value over the anterior cingulate cortex (median of **E** amplitude around 40% of E_{max}) and a decrease of more than 20% in the subcortical structures. FoE targets, as expected, preferentially the left hemisphere over which it is positioned, with a maximum over the left PFC. In detail, it can reach the left anterior cingulate cortex with a peak of **E** amplitude around 50% of the cortical peak, whereas in all the other target regions the induced **E** amplitude is always below the 20% of the maximum.

Fig. 5 shows the comparison between mean and standard deviation of the normalized (for each model to the respective cortical E_{max}) **E** amplitude distribution induced in the target tissues that are identifiable in all the three models. The figure shows that the **E** amplitude distributions were slightly influenced by the anatomical differences, with a general trend of the spatial distributions of the field amplitude similar among the different human models.

Fig. 6 shows the maximum depth of the point in the frontal lobe whose **E** amplitude is equal or greater at 50% (d_{50}) or at 70% (d_{70}) of E_{max} for both coils on MIDA and for all the three human models for H4 coil. The calculation of the penetration depth in the MIDA model revealed that H4 coil can penetrate the prefrontal cortex up to 4.2 cm with an

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E>70% of E_{max} and up to 4.8 cm with an E>50% of E_{max}. Moreover, the penetration depth of H4 coil resulted quite similar across the different human models. FoE showed, on the contrary, a minor capability to induce higher **E** amplitude level in depth of the frontal lobe, being d70 around 1.0 cm and d50 around 1.6 cm..

IV. Discussion

The recent introduction of dTMS systems for the treatment of neurological disorders is not always fully supported by a concurrent and detailed estimation of the electric field induced in the main structures target of the stimulation, thus hampering a full understanding of therapeutic outcomes and, in perspective, their diffusion. In this work we characterized the electric field distribution induced by a novel model of H-coil, designed to stimulate bilaterally the prefrontal cortex, in a new highly detailed model of human head, in which one can distinguish small structures involved in the reward circuit of addiction.

For the treatment of addictive disorders, stimulation targets include the regions belonging to the mesolimbic dopamine circuit, which originates in the ventral tegmental area and projects to the reward circuit including nucleus accumbens, amygdala, hippocampus, insular, anterior cingulate and prefrontal cortex. Results of this study show that both FoE and H4 coil systems target preferentially the PFC, with an expected net prevalence of the side over which it is positioned for the FoE and a bilateral symmetry for the H4. That could support the use of those systems for the addiction treatment, in view of the frontal lobe disruption identified in various forms of substance dependence such as nicotine, cocaine, alcohol, heroine and also food [26][27]. Moreover H4 seems able to target with high **E** amplitude the anterior cingulate cortex (Fig. 3), being the median value higher than the one calculated in the whole PFC. Interestingly, that is one of the main target of the stimulation, based on neuroimaging studies which reported a decreased metabolic activity in the anterior cingulate cortex which may underlie some deficits in prefrontal cortex seen in individuals with eating disorders [28]. On the contrary, FoE focuses high electric field amplitude in a small region of the PFC (Fig. 3), corresponding to the dorsolateral prefrontal cortex, as already observed in a previous computational study [16].

The cortical electric field due to H4 coil spread also to the entorhinal cortex and more in depth to the insula, being median levels only 10% lower than the ones induced in the PFC (Figs. 3- 4). This region is indeed the main target for which this coil has been designed [5] and insula is the main cortical area activated by food cues [29].

At subcortical levels, overeating is thought to be related to the hyperactivity of circuits involved in the reward sensitivity, conditioning and control [30]. Hypothalamus and its projection to the surrounding nuclei in particular has been identified as the main controller of food intake and play a crucial node for homeostatic, satiety and reward-related inputs that together govern motor programs that activate feeding behavior [31]. Increased neural activation of amygdala, hippocampus, nucleus accumbens and VTA, besides the over mentioned insula and PFC, have been identified in obese patients in response to pictures of high-calorie foods [32]-[35]. Our results suggest that FoE induces on these structures an **E** amplitude lower than the 20% of the cortical peak and it agrees with previous computational studies, even if the coil pairs was differently positioned [12][16]. H4 coil can reach the same limbic subcortical structures with an **E** amplitude substantially higher than FoE, up to 35% of the cortical peak. Invasive brain stimulation techniques, such as DBS, have showed positive results into directly stimulating these structures with electric field amplitude lower than the values here calculated [37], when referred to a hypothetic cortical threshold of about 100 V/m [36]. That means that the structures involved in the impairment of the reward system in obese patients can be reached with a not negligible **E** amplitude [38], whose effects could be either inhibitory or excitatory depending on the neurotransmitter release conditioned (GABA or glutamate, respectively) [39].

As to laterality, H4 results (Figs. 3-4) do not suggest any appreciable differences between left and right side. This is an expected result given the symmetry of the manufactured coil.

Our data (Fig. 5) seem to indicate a little influence of the human variability on the **E** amplitude distribution induced on different subjects, being the maximum difference in normalized mean **E** levels limited to 7%. These differences are probably and uniquely linked to the anatomic changes that results into different distances between the analyzed regions and the coil, being equal all the other parameters (health condition, dielectric properties, coil position, etc…).

Results of penetration depth in prefrontal cortex (Fig. 6) are as such to indicate that H4, similarly to other coils belonging to the same dTMS family (see e.g. [12][14][15]), can substantially increase the penetration depth of **E** amplitude with distance from the cortical surface and penetrate the cortex up to 4-5 cm with an **E** amplitude higher than the 50% of the cortical peak. It represents a substantial improvement with respect to the traditional TMS system, based on figure-of-8 coils (Fig. 5), as already discussed in a previous computational study comparing a Hesed-coil system (namely H1) and a traditional figure-of-8 [16]. In view of the typical decreased grey matter concentration in patients with addiction [40], that result can be helpful for the TMS based treatment optimization, given that grey matter volume loss of the rewarded pathways correlate with obesity degree [40].

V. Conclusion

This study supports the use of H4 for targeting cortical and subcortical structures involved in addictive disorders, including food craving related disorders. The computational approach here used, by specifically quantifying the electric field distribution in a detailed anatomy, represents a powerful and informative tool for both planning,

optimization and outcomes evaluation of clinical protocols based on dTMS systems for food addiction treatment.

Future extensions of this work will comprehend the use of a fat head model, in order to evaluate how the variability of anatomical characteristics encountered in these patients (larger skull size, decreased grey matter concentration, etc..) would affect the generality of the results.

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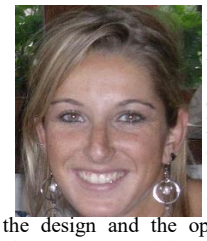

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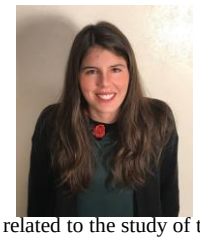

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