Effect of skin conductivity on the electric field induced by transcranial stimulation techniques in different head models

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Abstract
This study aims at quantifying the effect that using different skin conductivity values has on the estimation of the electric \((E)\)-field distribution induced by transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in the brain of two anatomical models. The induced \(E\)-field was calculated with numerical simulations inside MIDA and Duke models, assigning to the skin a conductivity value estimated from a multi-layered skin model and three values taken from literature. The effect of skin conductivity variations on the local \(E\)-field induced by tDCS in the brain was up to 70%. In TMS, minor local differences, in the order of 20%, were obtained in regions of interest for the onset of possible side effects. Results suggested that an accurate model of the skin is necessary in all numerical studies that aim at precisely estimating the \(E\)-field induced during TMS and tDCS applications. This also highlights the importance of further experimental studies on human skin characterization, especially at low frequencies.

1. Introduction

Transcranial magnetic and electric stimulations are techniques that use electric or magnetic fields for the treatment of several neuronal and psychiatric disorders (Ilmoniemi et al 1999, Nitsche and Paulus2001). Differently from other clinical applications, such as deep brain stimulation (Okun and Zeilman 2014, Paffi et al 2015a), transcranial stimulation techniques have the great advantage of being non-invasive treatments.

Among them, the most widespread ones are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). In TMS applications, an intense sinusoid-like pulsed current, varying in time at a rate of a few kHz, flows through a coil placed on the scalp. Time-varying current generates a time-varying magnetic field that, in turns, induces an electric \((E)\)-field inside the brain. If the \(E\)-field induced in specific cortical regions overcomes a threshold level, it is thought to directly activate neuronal axons (Kammer et al 2011), even though other interaction mechanisms are not excluded (Bungert et al 2017). TMS is generally used for the treatment of schizophrenia (Rotenberg et al 2014, Ray et al 2015, Bais et al 2017), Parkinson’s disease (Chen and Chen 2019, Nardone et al 2020), tinnitus (Schoisswohl et al 2019) and depression (Valero-Cabré et al 2011, Habib et al 2018, Kumar et al 2018). Other interesting possible applications are currently under investigation, including obsessive compulsive disorder (Zhou et al 2017, Carmi et al 2018), post-stroke rehabilitation (Watanabe et al 2018, Zhao et al 2018, Fisicaro et al 2019, He et al 2020), chronic pain (Yang and Chang 2020), dependencies, addiction and dementia, (Najib et al 2011, Horvath et al 2014, Lefaucheur et al 2014).

Conversely, tDCS makes use of a low-intensity (260 \(\mu\)A–2 mA) direct current flowing between two metallic electrodes placed on the scalp (Priori et al 1998, Nitsche and Paulus 2001, Nitsche et al 2008). The induced \(E\)-field penetrates deep inside the brain but its strength is several orders of magnitude lower than in TMS so that it modulates the spontaneous neuronal activity (Nitsche and Paulus 2001, Knotkova et al 2019) by means of
mechanisms allowing neuronal detection of weak signals (Gammaitoni et al 1998, Paffi et al 2013). Possible clinical applications for tDCS are the treatment of psychiatric disorders, such as depression (Kečk et al 2016, Brunoni and Palm 2019) and, depending on the electrodes position on the scalp and polarity of stimulation, beneficial effects have been found when applying tDCS to patients affected by schizophrenia (Mondino et al 2015, Fröhlich et al 2016), neuropathic pain (David et al 2018), for stroke rehabilitation (Elsner et al 2018, Fleming et al 2018) and Parkinson’s disease (Fregni et al 2006, Nitsche et al 2008, Lattari et al 2017, Dobbs et al 2018). For both techniques, the accurate placement of the coil or the electrodes in correspondence of the target brain region can be supported by the use of neuro-navigation systems, which grant to visualize a 3D model of the subject’s brain and track the position of the coil/electrodes with respect to it (Comeau 2014, Krieg et al 2017, De Witte et al 2018). Further optimization of a TMS or a tDCS treatment derives from an accurate knowledge of the E-field distribution inside the brain. This allows to predict the stimulated brain areas, as well as to optimize both stimulation techniques during the treatment. In fact, especially in TMS applications, the most advanced neuro-navigation systems include real-time E-field calculation while placing the coil over the scalp, in order to simultaneously facilitate the best coil position and the best stimulation parameters (Hannula et al 2005, Ruohonen and Karhu 2010, Nummenmaa et al 2013, Comeau 2014, Paffi et al 2015b). Both real-time and offline dosimetric calculations have always played a key role to optimize TMS and tDCS applications and to understand their interaction with the neuronal tissue. Many papers were published in the last years aiming at numerically evaluating the E-field distribution induced by TMS (Deng et al 2013, Opitz et al 2014, 2016, Paffi et al 2015b, Bungert et al 2017, Laakso 2018, Gomez et al 2020, Weise et al 2020) and tDCS (Datta et al 2009, 2010, 2011, Truong et al 2013, Patrizzini et al 2011, 2015, Manoli et al 2017, Fiocchi et al 2018, Opitz et al 2018, Laakso et al 2015, 2018a, Puonti et al 2019) inside the brain. These papers used different calculation methods and human head models, that spanned from simple homogeneous or multilayered spheres (Miranda et al 2003, 2006, Deng et al 2013) up to realistic patient-specific or standard anatomical models obtained from magnetic resonance images (Starzyński et al 2002, Salinas et al 2009, Datta et al 2009, 2010, 2011, Chen and Mogul 2010, Parazzini et al 2011, 2015, Truong et al 2013, Paffi et al, 2015b, Fiocchi et al 2018, Laakso et al 2015, 2018a, 2018b, Gomez et al 2020). Neuro-navigation systems usually consider spherical geometries or anatomical head models that count for few tissues, given the need of a real-time E-field computation (Paffi et al 2015b, Krieg et al 2017). The offline dosimetric studies, like those used for the treatment planning, may consider patient-specific and semi-specific models (Colella et al 2020) as well as standard detailed anatomical head models. These models include a fine and detailed representation of different tissues and brain structures and are obtained from high-resolution MRIs scans (1 mm or less), such as those from the Virtual Population (Gosselin et al 2014), the Japanese models (Nagaoka et al 2004), MIDA (Iacono et al 2015), and others (Makris et al 2003), or are based on freely available online anatomy atlas, such as the Alvar model by Laakso and co-workers (Laakso 2018).

Although the available anatomical models are getting increasingly accurate and realistic, the assignment of dielectric properties to different tissues remains an important question. Comprehensive databases are available to furnish a reference value for permittivity and conductivity of different human tissues (Gabriel et al 1996, 2009, Hasgall et al 2018), nevertheless, there is no agreement on the value used by the different dosimetric studies currently published, especially regarding the conductivity of the skin. This wide range of values used for skin conductivity is partially due to the lack of an accurate knowledge of skin dielectric properties, especially at DC or in the low frequency (LF) range, up to 10 kHz (De Santis et al 2015, 2016). Furthermore, skin properties strongly depend on internal, physiologic or pathologic conditions, and on external, environmental or experimental factors (Tarao et al 2012). In fact, skin conductivity is highly variable with hydration level, corneum layer thickness, healthy or ill status, subject age, gender and the body part considered. Moreover, factors external to the body, such as environmental temperature and humidity or the presence of sponges and electrodes, can considerably modify skin conductivity (Tarao et al 2012).

The impact of skin conductivity on the estimated induced E-field was studied for safety assessment purposes under a uniform B-field, corresponding to the reference level for the general public (ICNIRP 2010) at frequencies up to 1 MHz (Schmid et al 2013), and it was found to be less than 15% at the level of the Central Nervous System (CNS). However, differences up to a factor of 100 were found in specific regions of the skin where pain receptors are located (Schmid et al 2013).

When simulating TMS applications, authors may not consider an accurate skin model and include the head’s outer tissues (skin, fat, muscle) in a single layer of scalp (De Lucia et al 2007, Thielchers et al 2011, Datta et al 2013, Opitz et al 2014, Gomez et al 2020, Weise et al 2020). This choice is acceptable when assuming that the induced primary E-field, which is proportional to the time derivative of the magnetic B-field, predominates over the secondary E-field, related to the charge accumulation at the interface between two tissues. Nonetheless, variability in skin thickness was shown to affect the induced electric field in the brain with changes below 5%, and up to 11% locally in the skin (Rashed et al 2019). A recent study on a simple multilayered sphere revealed that a 15% change in the skin conductivity, caused a variation of about 1% on the induced E-field in the brain,
however much less than those induced by other sources of variability, such as the uncertainty in coil positioning (Gomez et al 2015, 2018). In a preliminary study (Colella et al 2019) with the TMS coil placed at the top of the head of two anatomical models, the authors found that skin conductivity affected the maximum and the average E-field in the brain in a negligible way with respect to the anatomical differences. Despite the low percentage variations found in previous studies, further investigation of local differences is needed, specially where pain receptors are located, as this would be the site of possible side effects onset.

However, variability over the skin conductivity in realistic anatomical models deserves to be further investigated in different anatomical regions for an accurate estimation of the induced E-field, not only to assess TMS efficacy but also to control possible side effects, particularly on the local pain receptors on the skin (Rossini et al 2015). Beside the global statistical values on the E-field in single tissues, sensitive observables comparing local E-field distributions should be considered as well (Armstrong 1978).

For what concerns tDCS, the effect of outer tissue layers on the E-field induced in the brain is instead supposed to be much higher than in TMS, due to the capacitive coupling. This was also confirmed by a recent sensitivity study on a simplified anatomical model that included five different tissues (Saturnino et al 2019). Moreover, since the clinical response to tDCS varies from patient to patient, due to inter-individual differences in the E-field generated inside the brain (Laakso et al 2015, Mikkonen et al 2018), it is of paramount importance to quantify how much the E-field would be affected by different skin properties.

In a recent work (Huang et al 2017), in vivo intracranial recordings in epilepsy patients were used, for the first time, to validate computational head models. Validation was carried out in patient-specific models, including five different tissues, by assigning them the conductivity values that minimized the error between measurements and simulations, thus proposing a range of skin conductivity values supported indirectly by experiments.

Herein we proposed an alternative approach to estimate the skin conductivity in detailed generic anatomic head models, for which experimental validation is not feasible. It is based on numerical simulations on a multilayered skin model (De Santis et al 2015) and was used to estimate an average skin conductivity value suitable for the two realistic and accurate anatomical models: MIDA (Iacono et al 2015) and Duke (Christ et al 2010).

Beside this value, after an extensive literature review, we herein considered other three skin conductivities, which represented the whole range of values assigned in the literature. By means of computational simulations we rigorously quantified, with global and local sensitive observables, the influence of skin conductivity on the E-field distribution induced inside MIDA and Duke, by TMS and tDCS applicators placed on the motor cortex.

The final aim of the present work is to demonstrate the importance of an accurate skin model for a precise estimation of the simulated E-field. Moreover, we provide reliable indications on which conductivity value should be used once the level of detail considered when modeling the skin is known. This would be a solid support to all the numerical studies that want to correlate the induced E-field to the therapeutic response and/or to possible side effects.

2. Models and methods

2.1. Brief review of skin conductivity values used in literature

As reported in De Santis et al (2015), skin consists of several layers (stratum corneum, cellular epidermis and dermis) with different thicknesses and conductivities, thus an homogenization procedure is often considered (De Santis et al 2016).

In the literature dealing with LF dosimetry (from DC to 10 kHz), skin conductivity $\sigma_s$ assumes several values (from 0.0002 S m$^{-1}$ up to 0.465 S m$^{-1}$) spanning more than three orders of magnitude, as summarized in table 1.

The lowest value of $\sigma_s$ found in literature is 0.0002 S m$^{-1}$, it is reported in the generic IT’IS database (Hasgall et al 2018) and refers to the dry skin as predicted by the dispersive model of Gabriel et al (1996) from 10 Hz to 10 kHz.

The highest $\sigma_s$ is 0.465 S m$^{-1}$. It was derived in Wagner et al (2004) and typically refers to the scalp, a thick homogeneous tissue that incorporates the skin and the subcutaneous adipose tissue (SAT), as well as the fat and the muscle. Two noteworthy intermediate values for $\sigma_s$ are 0.08 and 0.17 S m$^{-1}$. The latter is reported in the low-frequency IT’IS database (Hasgall et al 2018) and was obtained by extrapolating experimental values in accordance with the dispersion characteristics of biological tissues (Yamamoto and Yamamoto 1976).

The value 0.08 S m$^{-1}$ is used in two models in which skin and fat are considered as a unique tissue (Laakso et al 2015, 2018a), and corresponds to the conductivity of the fat as reported in Gabriel et al (2009).

2.2. A multi-layered model for skin conductivity estimation

To restrict the range of possible $\sigma_s$ to be used in numerical simulations, the level of detail chosen to model the skin should be considered. As an example, both Duke and MIDA models have an average skin thickness of...
Table 1. Values of skin conductivity ($\sigma_s$) (1st column) and related reference (2nd column) used in numerical studies (3rd column) dealing with different kinds of exposure (4th column) and frequencies (5th column).

| $\sigma_s$ (Sm$^{-1}$) | Reference for $\sigma_s$ | Papers | Kind of exposure | Frequency (Hz) |
|------------------------|--------------------------|--------|-----------------|----------------|
| 0.0002                 | ITIS database (Hasgall et al 2018); (Gabriel et al 1996) (dry skin) | (Tarao et al 2012, Lu and Ueno 2017, Fiocchi et al 2018) | Contact currents; short magnetic dipole; tDCS; TMS | $< 10^4$ |
| 0.00045                | Gabriel et al (1996) (wet skin) | Aonuma et al (2018) | TMS | $10^4$ |
| 0.012                  | Parazzini et al (2011) | Parazzini et al (2012, 2014, 2015) | tDCS | 0 |
| 0.08                   | Gabriel et al (2009) (Same as fat) | Laakso et al (2015, 2018a) | tDCS | 0 |
| 0.1                    | Dimbylow (1998) | Dimbylow (1998, 2003), Hirata et al (2010, 2011), Laakso and Hirata (2012), Tarao et al (2012), Laakso et al (2014) | Uniform B; contact currents; TMS | $30–10^6$ |
| 0.17                   | ITIS database, low freq (Hasgall et al 2018); (Yamamoto and Yamamoto 1976) | — | — | $1–10^6$ |
| 0.20                   | Dawson et al (1998), Gabriel et al (2009) | Dawson et al (1998), De Santis et al (2015) | Uniform B | $1–10^4$ |
| 0.22                   | Haueisen et al (1997) | Im et al (2008) | tDCS | < 2 |
| 0.25                   | Truong et al (2013) | Bungert et al (2017) | TMS | $< 10^4$ |
| 0.29                   | Huang et al (2017) | Huang et al (2017) | tDCS | 1 |
| 0.33                   | Salinas et al (2009) | Salinas et al (2009) | TMS | $< 10^4$ |
| 0.43                   | Haueisen et al (1997) | Holddeker et al (2006), Im et al (2012), Neuling et al (2012), Sadleir et al (2010, 2012), Wagner et al (2014) | TMS, tDCS, | 0; 10 |
| 0.465                  | Wagner et al (2004) | De Lucia et al (2007), Chen and Mogil (2010), Opite et al (2011, 2014), Thielischet al (2011), Datta et al (2013), Windhoff et al (2013), Janssen et al (2013, 2015), Gomez et al (2020), Weise et al (2020) | TMS, tDCS | $< 10^4$ |
1.5 mm at the level of the head (see supplementary figure S9 (available online at stacks.iop.org/PMB/66/035010/mmedia)). Thus, the lowest $\sigma$ in table 1 (0.0002 S m$^{-1}$), that well describes the stratum corneum (Gabriel 1997, Birgersson et al 2013), which is approximately 14 $\mu$m thick, should not be extended to the whole 1.5 mm thick skin. On the other hand, the highest $\sigma$ in table 1 (0.465 S m$^{-1}$) is appropriate only in simplified models, where a single thick compartment (scalp) including skin, subcutaneous adipose tissue (SAT), fat, and muscles is considered.

Therefore, to estimate what skin conductivity value should be assigned to Duke-like or MIDA-like models, a 1.5 mm thick multi-layered skin model was placed inside two metallic parallel plates (see supplementary figure S10) and simulated with Sim4Life (v. 4.4, ZMT Zurich MedTech AG, Zurich, Switzerland). The following layers were considered: stratum corneum (14 $\mu$m; $\sigma = 0.0002$ S m$^{-1}$), cellular epidermis (61 $\mu$m; $\sigma = 0.009$ S m$^{-1}$), dermis (1 mm; $\sigma = 0.526$ S m$^{-1}$), and SAT (remaining thickness; $\sigma = 0.0417$ S m$^{-1}$). Thicknesses and conductivities at 1 kHz for each layer were taken from the experimental data of Tsai et al (2019) and Xu and Mandal (2015). Further details are given in the Supplementary material. The calculated equivalent $\sigma$, resulted equal to 0.08 S m$^{-1}$. Taking into account the variations associated to each layer, as those reported in Tsai et al (2019), the estimated $\sigma$ ranged from 0.07 to 0.1 S m$^{-1}$. Therefore, we performed a first set of numerical simulations assigning to the skin 0.08 S m$^{-1}$. To account for the wide range of values reported in literature three more $\sigma$ values were considered: 0.0002, 0.17 and 0.465 S m$^{-1}$.

The same values were used for both stimulation techniques, as $\sigma$ increases by less than 2% from 10 Hz to 10 kHz (Gabriel et al 1996).

2.3. Head models

The anatomical models used in this work are Duke, a 34 year old male whole body model, belonging to the Virtual Population (Christ et al 2010), and MIDA, a 29 year old female model of head and neck (Iacono et al 2015).

From the whole Duke model, we extracted only the head and the neck, down to the carotid sinus, thus counting 38 different tissues, including all the basic head structures, such as the cerebrospinal fluid (CSF), gray matter (GM) and white matter (WM).

The MIDA model includes 115 separate structures, with a detailed representation of nerves and vessels.

However, to compare results obtained with the two models, we considered the same level of anatomical detail for MIDA and Duke by reducing the MIDA model to 38 different anatomical structures. This was done by merging together all tissues characterized by the same dielectric properties. By doing so, the dielectric discontinuities of the model are not altered.

Both surface-based head models were imported in the commercial software Sim4Life (Sim4Life-v4.4, SIMulation 4 LIFE Science Platform) and discretized with a maximum spatial step of 1 mm in the three orthogonal directions. Dielectric properties of all the tissues (except the skin) were taken from the ITIS database (Gabriel et al 1996, Hasgall et al 2018) at 3 kHz for TMS and 10 Hz for tDCS. The latter is the lowest frequency at which measurements have been conducted (Gabriel et al 1996).

2.4. tDCS electrodes model

tDCS electrodes were modeled as two rectangular pads of 5 cm $\times$ 7 cm that consisted of a metallic contact, modeled as Perfect Electric Conductor (PEC), and a saline soaked sponge ($\sigma = 1.4$ S m$^{-1}$) between the electrode and the scalp (see figures 1(a) and (b)). The cathode, colored in black in figure 1, was placed over the contralateral supraorbital region, while the anode, colored in red, was placed over the primary motor cortex (M1) (Nitsche et al 2008). M1 is anterior to the central sulcus and is one of the most commonly targeted areas in both tDCS and TMS (Opitz et al 2011, Thielscher et al 2011, Laakso et al 2014). The different positioning of the anode between MIDA and Duke, see figures 1(a) and (b), is due to the anatomical differences in the cortical circuimevolutions, specifically in the central sulcus.

The electromagnetic (EM) problem was solved with the EM simulation software Sim4Life using the electro ohmic quasi-static solver, which solves the Laplace equation. Simulations were performed injecting a current of 1 mA into the head.

2.5. TMS coil model

The two head models were exposed to a commercial figure-of-eight coil (PN9925-00, MagStim Eden Prairie, MN), modeled as a current pathway made of two coplanar windings, 9 turns each, with the internal diameter of 6 cm and the external diameter of 8.6 cm, as described in Paffi et al (2015b) (figures 1(c) and (d)). The coil was placed at a distance of 5 mm from the scalp in correspondence of M1 (Jansen et al 2015).

According to the specifications of the neurostimulator (‘MAGSTIM® RAPID2, P/N 3576-23-09, OPERATING MANUAL’), the frequency was set to 3 kHz and the current amplitude was such to obtain a $B$-field
of 1.2 T on the scalp surface just below the coil. The problem was solved using the Magneto Quasi-Static (MQS) module included in the LF solver of the EM simulation software Sim4Life.

2.6. Observables
For each different tissue, the $E$-field distribution was considered. Starting from that, the mean value, the maximum value and the percentiles were extracted to compare results obtained with different head models and $\sigma_s$. To avoid numerical artifacts, the 99th percentile was used as an estimation of the maximum value of the $E$-field ($E_{\text{max}}$), as suggested by the ICNIRP guidelines of 2010, (ICNIRP 2010). To estimate $E_{\text{max}}$, other papers proposed either to use a dynamic approach (De Santis and Chen 2014) or to use the 99.9th and even the 99.99th percentile (Soldati and Laakso 2020). However, looking at the probability distributions of the $E$-field intensity inside the WM and the GM in our simulations, we decided to follow the ICNIRP guidelines and to use the 99th percentile (see supplementary material and figures S1–S8). Beside this global evaluation, to compare voxel-by-voxel the $E$-field distribution obtained with different $\sigma_s$ and to quantify differences in regions that are distant from the stimulation focus, we calculated the symmetric mean absolute percentage error (SMAPE) (Armstrong 1978) defined as:

$$\text{SMAPE}(i, j, k) = \frac{|E_{\nu}(i, j, k) - E_{\text{REF}}(i, j, k)|}{\frac{E_{\nu}(i, j, k) + E_{\text{REF}}(i, j, k)}{2}} \times 100,$$

where $i$, $j$ and $k$ are the indexes of the single voxel, while $E_{\nu}(i, j, k)$ and $E_{\text{REF}}(i, j, k)$ are the intensity of the $E$-field for the evaluated conductivity ($\sigma$) and the reference conductivity ($\sigma_{\text{REF}}$) computed in the voxel $(i, j, k)$. For the sake of convenience, we used as the reference skin conductivity ($\sigma_{\text{REF}}$) the lowest one: 0.0002 S m$^{-1}$.

Figure 1. Position of the tDCS electrodes (panels (a) and (b)) and the TMS coil (panels (c) and (d)) in correspondence of the primary motor area (M1) of MIDA (panels (a) and (c)) and Duke (panels (b) and (d)).
3. Results

3.1. tDCS

Probability distributions of the calculated $E$-field intensity inside the tissues involved in the stimulation, i.e. GM and WM, for MIDA and Duke are shown in Figure 2, together with the average value ($E_{\text{mean}}$) and the 99th percentile ($E_{99}$), reported in the inset of each panel.

Comparing the different anatomical models, for both tissues, one can see that the distributions are very similar, with a maximum value around 1 V m$^{-1}$ for almost all the investigated conductivities, as expected from literature (Parazzini et al 2011, Truong et al 2013). Higher values are induced in MIDA, probably due to the smaller size of the head (23 cm $\times$ 21.6 cm $\times$ 16.3 cm vs 23.4 cm $\times$ 24 cm $\times$ 18 cm), with maximum differences between the models equal to about 12% for both $E_{99}$ and $E_{\text{mean}}$. This result was in line with those obtained in Parazzini et al (2014), where both peak and median values of the $E$-field amplitude were higher in a child model than in adult ones. Both in Duke and MIDA, an increase of $\sigma_s$ led to a reduction of the induced $E$-field in the inner structures due to a higher voltage drop across the skin layer. Maximum variations on $E_{99}$ and $E_{\text{mean}}$ were, respectively, about 40% and 25% for MIDA model and 40% and 30% for Duke. This implied that the choice of skin conductivity might affect the predicted induced $E$-field in the brain even more than the considered anatomical model.

Moving to the local differences, Figure 3 shows the SMAPE on a sagittal plane passing through the center of the cathode for MIDA (upper row) and Duke (bottom row), calculated between each conductivity value and the ‘reference’ value of 0.0002 S m$^{-1}$. Maximum differences were in the frontal region below the anode, and might reach values as high as 70% even inside the brain, revealing that prediction of stimulated areas strongly depends on the correct choice of skin conductivity.

3.2. TMS

The same analysis on statistical values conducted for TMS application revealed that the induced $E$-field in the brain (GM and WM) was less sensitive to both the anatomical model and the skin conductivity than it was in tDSC (data reported in supplementary tables S1 and S2).
Variability between MIDA and Duke reached 11% for $E_{99}$ and 1.5% for $E_{\text{mean}}$ inside GM, whereas, for both models, the effect of skin conductivity on $E_{99}$ and $E_{\text{mean}}$ in the brain (GM and WM) was negligible, less than 1% (data reported in the Supplementary material). This was expected given that the induced E-field follows closed streamlines, as the eddy currents. Therefore, just below the coil, it is almost tangential to the air-skin and skin-SAT boundaries and is only slightly affected by the conductivity contrast at the interfaces (Chen et al 2013, De Santis et al 2015, 2016).

However, looking at the SMAPE on the sagittal plane of the left hemisphere at 1 mm from the center of the head, shown in figure 4, we could see that there were some regions where the SMAPE was quite large. Particularly, it was higher than 10% in a region deep inside the brain, when comparing the two extreme values used for $\sigma_s$ (see figures 4(c) and (f)). Similar findings were obtained in Colella et al (2019) with the coil placed on the top of the head. Such SMAPE distributions could be explained by the fact that the effect of skin conductivity variations is more relevant on the normal component of the E-field than it is on the tangential one, and in the deep brain regions the induced E-field is mainly oriented orthogonally to the interfaces between GM, WM and CSF. The region where the SMAPE resulted to be higher than 10% was calculated to be of about 26.1 cm$^3$ in the MIDA model and 8.5 cm$^3$ in the Duke model and included areas of the WM and GM, such as
Caudate Nucleus, Accumbens Nucleus and Thalamus. Although these regions are not the preferred TMS targets, they are involved in cognitive and motor tasks and their malfunctioning is related to pathologies such as Parkinson’s disease and Huntington’s disease (Weber and Eisen 2002, Cincotta and Ziemann 2008, Lefaucheux et al 2014), attention deficit/hyperactivity disorder (Croarkin et al 2011, Rotenberg et al 2014) and obsessive-compulsive disorder (Carmi et al 2018). Therefore, an accurate prediction of the E-field induced in these regions could be of importance for improving the efficacy of new TMS applications while reducing side effects.

Significant SMAPE values, up to 20%, were also found in the skin and in correspondence of the carotid sinus in the neck (19.43% in the MIDA model) (see figure 4).

4. Discussion

For both head models, changes of σs determined variations on $E_{99}$ and $E_{\text{mean}}$, induced in the brain by tDCS, up to 40% and 30%, respectively, higher than those caused by the use of different anatomical models (12%). Local percentage variations, quantified by the SMAPE, which is a sensitive local observable, reached 70% in the frontal region beneath the cathode, when comparing the highest and lowest values assigned to $\sigma_s$ (0.0002 S m$^{-1}$ and 0.465 S m$^{-1}$). The E-field induced inside the brain was overestimated for $\sigma_s$ lower than the calculated equivalent $\sigma_s$ and vice versa.

These high differences were attributed to the capacitive coupling between the source (tDCS electrodes) and the tissues, so that an impedance variation of the outermost layer (skin) likely affected also the underlying layers (GM and WM). In fact, right below the electrodes, the E-field was almost orthogonal to the tissues interfaces and thus it was strongly sensitive to impedance discontinuity.

Conversely, for TMS, the effect of skin conductivity on the induced $E_{\text{mean}}$ and $E_{99}$ in the brain was negligible, much lower than the variability due to the different head models on the $E_{99}$ in GM (11%). This is expected since the induced E-field is dominated by the time derivative of B-field which is almost tangential to the interface between skin and subcutaneous tissues below the coil (Chen et al 2013, De Santis et al 2015). However, using the SMAPE, significant differences (higher than 10%) were found in the deep regions of the brain belonging to the basal ganglia. Due to the importance of such regions in cognitive, motor and sensorial functions, an accurate evaluation of the induced E-field is desirable for assessment of TMS effects. Other regions where the SMAPE assumed high values (up to 20%) where the skin and blood vessels, in correspondence of the carotid sinus.

Accounting for these differences may be relevant to control the onset of side effects, such as pain sensation due to stimulation of peripheral nerves in the epidermis. Such higher differences were related to the presence of the secondary E-field, proportional to $-\nabla V$ (being $V$ the electric scalar potential) generated by the charge accumulation at the tissue interfaces, which cannot be neglected.

This different behavior between TMS and tDCS was in line with results in Saturnino et al (2019), where the skin, together with other sub-cutaneous tissues, was included in a single layer (scalp) whose conductivity assumed a beta distribution between 0.2 and 0.5 S m$^{-1}$.

Our results, compared to those reported in the literature, suggested that the choice of skin conductivity to be used in dosimetric studies is subject to the degree of anatomical accuracy used for the skin representation in each head model.

Specifically, when considering models in which the skin is incorporated in a thick homogeneous scalp tissue, the average conductivity value that should be assigned to it would take into account all the included cutaneous and extra-cutaneous tissues (e.g. dermis, SAT, muscle).

For MIDA and Duke we suggest to use a value equal to 0.08 S m$^{-1}$ as in (Laakso et al 2018a) and confirmed by our slab modeling. This value can be applied to all the models that represent the skin as a separate tissue about 1.5 mm thick. It is lower with respect to the one estimated in Huang et al (2017) by means of intracranial measurements (0.29 S m$^{-1}$). This discrepancy is attributable to the different thickness associated to the skin layer in the used models. In MIDA and Duke the skin was about 1.5 mm thick and included only a thin layer of SAT as sub-cutaneous tissue, whereas the patient-specific models used in Huang et al (2017) considered the skin as a thick layer of scalp, that included the muscle, which is characterized by a higher conductivity value.

5. Conclusions

The accurate estimation of the E-field induced in the brain by transcranial stimulation techniques has assumed increasing importance in the optimization of these clinical applications. Therefore, realistic dosimetric models are needed. An open question is the attribution of appropriate skin conductivity values, due to their variability with internal and external environmental factors and to the scarcity of experimental data, especially at DC.

Results of our study on two different anatomical models, MIDA and Duke, showed that variability of skin conductivity in the range reported in literature determined non-negligible differences in the E-field induced in
the brain by tDCS (globally up to 40% and locally up to 70%), much higher than those attributable to anatomical differences between the two models (12%).

Conversely, the maximum and mean E-field induced inside the brain by TMS were sensitive to the anatomical differences between the two models (11%) and almost insensitive (<1%) to changes in $\sigma_a$ as expected. Nevertheless, SMAPE values up to 20% were found on the skin, in deep brain areas and at the level of the peripheral nerves.

In summary, the choice of a representative $\sigma_a$ value is fundamental to accurately predict the induced E-field correlated to the effects of tDCS observed experimentally.

Even in the TMS technique, a realistic skin model, separated from other extracutaneous tissues, should be considered to accurately simulate the induced E-field. In case it is not possible to obtain a realistic skin model, the error induced by the modeling approximation should be taken into account when estimating the E-field value induced to achieve the stimulation of target areas or that induced in non-target area.

For both techniques, the most representative skin conductivity value should be evaluated in each head model, considering the geometric and dielectric properties of the different layers that compose the skin. Therefore, this equivalent value will depend on the level of detail with which the skin of the considered head model is segmented. For MIDA and Duke models, it was estimated to be 0.08 S m$^{-1}$, calculated on the basis of experimental data (Tsai et al 2019) obtained from the forearm skin of healthy subjects at 1 kHz.

Further experimental studies are advisable to measure thicknesses and conductivities of the layers composing the human skin in correspondence of the head, especially at frequencies below 1 kHz. This would give a more accurate value to the skin conductivity and to its variability to be used in dosimetric studies that assess transcranial stimulation techniques.

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