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Inter-individual variations in electric fields induced in the brain by exposure to uniform magnetic fields at 50 Hz

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Abstract. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines and the Institute of Electrical and Electronics Engineers (IEEE) standard establish safety limits for human exposure to electromagnetic fields. At low frequencies, only a limited number of computational body models or simplified geometrical shapes are used to relate the internal induced electric fields and the external magnetic fields. As a consequence, both standard/guidelines derive the exposure reference levels for the external magnetic field without considering the variability between individuals. Here we provide quantitative data on the variation of the maximum electric field strengths induced in the brain of 118 individuals when exposed to uniform magnetic fields at 50 Hz. We found that individual characteristics, such as age and skull volume, as well as incident magnetic field direction, have a systematic effect on the peak electric field values. Older individuals show higher induced electric field strengths, possibly due to age-related anatomical changes in brain. Peak electric field strengths are found to increase for larger skull volumes, as well as for incident magnetic fields directed along the lateral direction. Moreover, the maximum electric fields provided by the anatomical models used by ICNIRP for deriving exposure limits are considerably higher than those obtained here. On the contrary, the IEEE elliptical exposure model produces a weaker peak electric field strength. Our findings are useful for the revision and harmonization of the current exposure standard and guidelines. The present investigation reduces the dosimetric uncertainty of the induced electric field among different anatomical induction models. The obtained results can be used as a basis for the selection of appropriate reduction factors when deriving exposure reference levels for human protection to low-frequency electromagnetic exposure.

1. Introduction

The International Commission on Non-Ionizing Radiation Protection (ICNIRP 2010) and the Institute of Electrical and Electronics Engineers International Committee on Electromagnetic Safety (IEEE ICES) (IEEE 2002, IEEE 2019), have established exposure criteria and associated limits for protection of people against adverse health effects provoked by electromagnetic field exposure. At extremely low frequencies (< 300 Hz), the dominant adverse effect regards alterations of synaptic activity in the central nervous system (CNS), which can lead to sensory alteration such as retinal phosphene induction or transient effects on brain function, and peripheral nerve stimulation (ICNIRP 2010, ICNIRP 2020, IEEE 2002, IEEE 2019). To avoid adverse health effects, the international standard/guidelines define two metrics for human protection: the basic restrictions (ICNIRP 2010) or dosimetric

reference limits (IEEE 2019), expressed in terms of induced electric field strength, and the reference levels (ICNIRP 2010) or exposure reference levels (IEEE 2019), which represent the maximum external electric/magnetic field strength that should induce electric fields that satisfy the basic restrictions. The ICNIRP guidelines consider two classes of people: general public and occupational exposure. On the other hand, the IEEE standard takes into account restricted or unrestricted environment scenarios. Exposure limits are more severe for general public exposure and people in unrestricted environment.

At mains frequency (50/60 Hz), the exposure limits for the CNS are considerably more restrictive than those for the peripheral nervous system (ICNIRP 2010, IEEE 2002, IEEE 2019). In the IEEE standard (IEEE 2002, IEEE 2019), the dosimetric reference limits in the brain have been derived based on thresholds data of magnetophosphenes (Lövsund *et al* 1980a, Lövsund *et al* 1980b). To account for variations across the population and protection of exceptionally sensitive individuals, additional reduction factors were applied to obtain the dosimetric reference limits. In the ICNIRP guidelines, the basic restrictions in the brain were also derived from estimated thresholds for retinal phosphenes (ICNIRP 2010, Bakker *et al* 2012). At 50 Hz, the basic restrictions defined by the ICNIRP guidelines are 20 mV m^{-1} (general public exposure) and 100 mV m^{-1} (occupational exposure). In the IEEE standard, the dosimetric reference limits are 14.7 mV m^{-1} and 44.2 mV m^{-1} for persons in unrestricted and restricted environments, respectively.

In both standard/guidelines, the (exposure) reference levels have been determined as the minimum external magnetic field that induced an electric field strength corresponding to the basic restrictions/dosimetric reference limits. There are important differences in how the (exposure) reference levels have been derived. In the IEEE standard (IEEE 2002, IEEE 2019), the exposure reference levels are obtained from the dosimetric reference limits by means of a homogeneous elliptical model, without additional reduction factors (the reduction factors are accounted for in the dosimetric reference limits). In the ICNIRP guidelines (ICNIRP 2010), the reference levels were obtained using published data based on dosimetry modelling in male and female body models (Dimbylow 2005a, Dimbylow 2006). To account for dosimetric uncertainty, an additional reduction factor of 3 was applied when deriving the reference levels from the basic restrictions.

Both the IEEE standard and the ICNIRP guidelines lacked data of the variability of the induced electric field between individuals when deriving the exposure reference levels. In this context, the ICNIRP knowledge gap document (ICNIRP 2020) addressed the importance of undertaking additional studies aimed at considering variations in the population and tissues. Quantitative data of variations within the population would be important for deriving reference levels that would not be overly conservative but would offer sufficient protection for a large majority of the population. In this study, we computationally investigated the variability of the electric fields induced in the brain of 118 subjects when exposed to uniform magnetic field at 50 Hz directed along three different orthogonal directions. The frequency of 50 Hz is commonly used in this kind of research (Dimbylow 2005b, Soldati *et al* 2018, Hirata *et al* 2011), as it corresponds to the European mains frequency and therefore represents a common scenario in daily life. The derived results could be scaled to the whole low-frequency range, since in this interval of frequencies the conductivity ratios of the brain tissues do not change considerably (Gabriel *et al* 2009). In addition, we explored how individual characteristics, such as skull volume, age, and gender, affected the electromagnetic exposure.

2. Materials and methods

2.1. Subjects and imaging methods

Ethical approval for the study was obtained from Aalto University Research Ethics Committee. A total number of 23 subjects were recruited (10 males, 13 females, aged 22–49 years), who gave written informed consent before participating in magnetic resonance imaging (MRI). For each of them, high resolution T1- and T2-weighted magnetic resonance (MR) images of the head were acquired using a 3 T scanner (Magnetom Skyra; Siemens, Ltd., Erlangen, Germany). Structural T1-weighted MRI were obtained using a Magnetization Prepared Rapid Acquisition in Gradient Echo (MPRAGE) sequence (TR/TE/TI/FA/voxel size/number of slices = 2530 ms/3.3 ms/1100 ms/7°/1.0 mm x 1.0 mm x 1.0 mm/176). T2-weighted MRI were also acquired (TR/TE/voxel size/number of slices = 3200 ms/412 ms/1.0 mm x 1.0 mm x 1.0 mm/176).

Structural T1- and T2-weighted images of additional 18 subjects were obtained from National Alliance for Medical Imaging Computing (NAMIC) Brain Multimodality database (<http://hdl.handle.net/1926/1687>). These subjects were all male and had a range of 21–55 years of age. To increase the power of the investigation, we further extended the sample size by considering 77 subjects (52 males, 25 females, aged 18–47 years) enrolled in our previous studies (Laakso *et al* 2016, Mikkonen *et al* 2018, Laakso *et al* 2018).

Overall, this research included a total number of 118 individuals (80 males, 38 females, mean age $\pm$ standard deviation: 28 ± 9 years).

2.2. Human models

Structural T1-weighted MR images were processed using FreeSurfer (Dale *et al* 1999, Fischl *et al* 1999) to segment the brain tissues (i.e., white and grey matter). The other non-brain tissues, such as the scalp, the skull and the cerebrospinal fluid (CSF), were segmented through an in-house procedure (Laakso *et al* 2015), which uses both T1- and T2-weighted MR images. Segmentation of subcortical structures (i.e., ventricles, brainstem, cerebellum and nuclei) produced by FreeSurfer was further improved through our semi-automatic pipeline. The final segmented head models, consisting of 24 tissues, were voxelized using cubic elements with a resolution of 0.5 mm. Volume conductor models were then generated by assigning electrical conductivities to each voxel based on the values determined by Dimbylow (Dimbylow 2005a). Table 1 shows some of the tissue conductivities employed in this investigation, which were assumed to be linear and isotropic. The same conductivities of the white and grey matters were assigned to the cerebellar white and grey matters, respectively.

2.3. Exposure scenarios

The head models were exposed to spatially uniform magnetic fields at 50 Hz in three different orthogonal directions: top-bottom (TOP), left-right (LAT), and antero-posterior (AP). The incident magnetic flux density was set to be equal to 1 mT, which is the reference level defined by ICNIRP guidelines in the case of occupational exposure at 50 Hz. For general public exposure, the reference level becomes 0.2 mT. Note that in the IEEE standard (IEEE 2002, IEEE 2019) the exposure reference levels for persons in unrestricted and restricted environments are 0.904 mT and 2.71 mT, respectively.

As the orientation of the coordinate axes could be different depending on the position of the subject's head in the MRI scanner, these directions were defined for each subject individually. This was achieved by first using BrainsFIT (Johnson *et al* 2007) to obtain an

Table 1: Electrical conductivities of the tissues at 50 Hz (Dimbylow 2005a).

Tissue	σ (S/m)
Grey matter	0.10
White matter	0.06
CSF	2.00
Brainstem	0.06
Compact bone	0.02
Spongy bone	0.08
Subcutaneous fat	0.04
Skin	0.10
Muscle	0.35
Dura	0.35
Blood	0.70

affine transformation matrix from the coordinates of each individual's MR images to those of the Montreal Neurological Institute (MNI) ICBM 2009a nonlinear asymmetric template (Fonov *et al* 2009, Fonov *et al* 2011, Laakso *et al* 2016). The MNI template consists of an average atlas of 152 adult human MRI scans. The incident magnetic field directions were then made to align with the anatomical directions (TOP, LAT and AP) using the coordinate transformation matrix.

2.4. Electric field modeling

Under the quasi-static assumption (Wang and Eisenberg 1994), the electric scalar potential ϕ can be expressed as:

$$\nabla \cdot \sigma \nabla \phi = j\omega \nabla \cdot \sigma \mathbf{A}, \quad (1)$$

where σ represents the electrical conductivity of the tissues, ω is the angular frequency, and $\mathbf{A}(\mathbf{r}) = \frac{1}{2} \mathbf{B}_0 \times \mathbf{r}$ is the magnetic vector potential of the incident magnetic flux density $\mathbf{B}_0$. In this study, the equation (1) was numerically solved using the finite-element method (FEM) with cubical first-order (trilinear) elements (Laakso and Hirata 2012). The FEM system equation was solved iteratively using the geometric multigrid method with successive over-relaxation (Laakso and Hirata 2012). The iteration was continued until the residual norm was lower than 10^{-6} . Finally, the induced electric field was calculated from the negative gradient of the scalar potential:

$$\mathbf{E} = -\nabla \phi + j\omega \mathbf{A}. \quad (2)$$

2.5. Post-processing of electric field data

The induced electric field calculated in a grid with an uniform resolution of 0.5 mm was averaged over $2 \times 2 \times 2$ mm³ cubes, as recommended by (ICNIRP 2010). The average was performed exclusively for the voxels having an averaging volume completely within the tissue of interest, without extending beyond the boundary of the tissues (ICNIRP 2010). Notice that in the IEEE standard, the electric field should be averaged over an arbitrarily oriented segment of 5 mm length (IEEE 2002, IEEE 2019). However, a recent study showed that both averaging schemes provide comparable results (Diao *et al* 2019).

After averaging, ICNIRP also recommends removing numerical artefacts by determining the 99th percentile for a specific tissue (ICNIRP 2010). Therefore, the 99th percentile value of the averaged electric field was calculated for each CNS tissue compartment. The

tissue compartments were: cerebral grey matter (GM), nuclei (including various deep grey matter structures), cerebral white matter (GM), cerebellar GM, cerebellar WM, brainstem and eyes (approximating the retina). Finally, the highest value was taken over all these tissue compartments, which will be referred from now on as the maximum electric field strength (max EF) induced in the brain and eye tissues. This approach followed the one used in a previous investigation (Dimbylow 2005a). For completeness, the same method was used in each subject to calculate the highest 99.9th and 100th (maximum value) percentile values of the ICNIRP-averaged electric field over all the CNS tissues. However, only data derived from the 99th percentile values will be considered in the following analysis.

2.6. Statistical analysis

The open-source programming language R (version 3.6.2) was employed for the statistical analysis. More specifically, the R package `lme4` (Bates *et al* 2015) was used to fit the data with an approach based on the linear mixed effects model. The aim was to investigate the effect of different predictors on the maximum electric field strength (E_{max}). As fixed effects, we considered the incident magnetic field direction (D) for the TOP, LAT and AP exposures, as well as the age (A), the gender (G), and the skull volume (V) of the participants. All the two-way interaction terms were included in the model, i.e., volume $\times$ direction, age $\times$ direction and age $\times$ volume. As random effects, we entered slopes and intercepts depending on the relationship between subjects (S) and the incident magnetic field directions. Our hypothesis was that each subject had not only different intercepts, but also different slopes for the effect of the incident directions. The preceding model can be written as follows:

$$\log(E_{max}) \sim V + A + D + V \times D + A \times D + A \times V + G + (D|S), \quad (3)$$

where in round brackets we indicate the random effects and with the symbol $\times$ the interaction terms. To remove the effect of meaningless intercepts and reduce multicollinearity among the predictors, the numerical variables age and volume were centered by subtracting their respective average values (mean skull volume $\pm$ standard deviation: 1.5 ± 0.13 litres). The maximum electric field strengths in (3) were log-transformed to make the residuals conform more closely to the normal distribution assumption. The parameters of the linear mixed effects model were computed by means of the maximum likelihood estimation. For the fixed effects, the significance of each predictor was studied using F-tests with the `anova` function included in the R package `lme4`. This function employs the Satterthwaite's method of approximation to calculate the denominator degrees of freedom and the p-values with a level of statistical significance of 0.05 (Kuznetsova *et al* 2017).

3. Results

3.1. Variability of the induced electric fields

Figure 1 shows the magnitude of the electric field induced in five representative subjects when exposed to uniform magnetic field (1 mT) at 50 Hz along AP, LAT and TOP directions, respectively. Similar calculations were performed for each of the head models considered in this investigation.

As mentioned in section 2.5, the maximum electric field strength in each brain was chosen as the highest 99th percentile of the ICNIRP-averaged induced electric field over all the different CNS tissues. For each exposure scenario, the variability of the obtained maximum electric field strengths among the individuals was well described by a normal distribution

Figure 1: Electric fields induced in five voxelized brain models exposed to an uniform magnetic field at 50 Hz along AP, LAT and TOP directions. The magnetic flux density was set to be equal to the reference level for ICNIRP occupational exposure (1 mT). Only some of the different tissue compartments generated from the segmentation process, such as the cerebellum, the brainstem and the grey matter, are shown.

(figure 2) according to Kolmogorov–Smirnov normality test ($p > 0.05$). From the histograms of the computed data, we calculated the mean values and standard deviations (SD) with their

corresponding 95% confidence intervals (CI), as well as the 80%/0.95 tolerance intervals (TI). The latter provides the range of the maximum electric field strength within which the 80% of the population lies with 95% confidence. Results are shown in table 2, where we also reported the minimum and maximum values of the distributions, together with the analogous statistical data derived from the 99.9th and 100th percentiles.

Figure 2 includes the pie charts indicating the proportion of CNS tissues in which the electric field was found to be the maximum. Results are in good agreement with those of the figure 1, LAT exposure producing high electric field strengths on the sides of the longitudinal fissure and in particular posteriorly to the brain. As a consequence, both the GM and the WM in the cerebellum were found to be the regions where the induced electric field was the maximum most of the times. High intensity electric field deposition in the posterior regions of the brain was marginally observed in the case of AP exposure, for which GM and WM tissues at the level of the temporal lobe and partially the occipital lobe were mainly involved by high electric field strengths. Regarding the TOP direction, GM and WM also resulted to be the tissues in which the induced electric field was the highest, considering its distribution mainly involved the lateral and frontal areas of the brain. In terms of magnitude, LAT exposure gave the highest electric field strengths, whereas the TOP direction produced the lowest ones (figure 2 (d)).

Figure 2: Histograms with normal distribution overlay of the maximum electric field strengths induced by uniform exposure to 1 mT magnetic flux density at 50 Hz along the (a) AP, (b) LAT, and (c) TOP directions. Mean value $\pm$ SD, and tolerance interval are reported. Pie charts provide the percentage of CNS tissue that exhibited the maximum electric field strength. (d) Boxplot of the maximum electric field strengths for each exposure scenario.

Table 2: Statistical data of the maximum electric field strengths (mV m^{-1}) for each exposure scenario. Mean value and standard deviation with their corresponding 95% confidence intervals in brackets extracted from the normal distributions. The minimum and maximum values are also reported, together with the upper (UTI) and lower (LTI) 80%/0.95 tolerance intervals. In addition, statistical data derived from the 99.9th and 100th percentile electric field values are listed.

	99th percentile electric field		
	AP	LAT	TOP
Minimum	15.5	18.3	14.0
LTI	16.0	19.1	15.0
Mean [CI]	18.0 [17.7, 18.2]	22.1 [21.7, 22.5]	16.8 [16.6, 17.1]
SD [CI]	1.4 [1.2, 1.6]	2.1 [1.9, 2.4]	1.3 [1.1, 1.5]
UTI	20.0	25.2	18.7
Maximum	21.2	28.3	20.4

	99.9th percentile electric field		
	AP	LAT	TOP
Minimum	18.4	21.2	16.1
LTI	19.0	22.3	17.4
Mean [CI]	21.7 [21.4, 22.1]	29.5 [28.6, 30.4]	20.0 [19.7, 20.4]
SD [CI]	1.9 [1.7, 2.2]	5.0 [4.4, 5.7]	1.8 [1.6, 2.1]
UTI	24.5	36.7	22.7
Maximum	26.3	43.6	25.3

	100th percentile electric field		
	AP	LAT	TOP
Minimum	23.8	26.4	22.0
LTI	25.0	29.4	22.8
Mean [CI]	29.8 [29.2, 30.4]	40.5 [39.1, 41.9]	29.0 [28.2, 29.8]
SD [CI]	3.3 [2.9, 3.8]	7.7 [6.8, 8.8]	4.3 [3.8, 4.9]
UTI	34.6	51.6	35.2
Maximum	39.1	60.6	46.9

3.2. Statistical analysis

Linear mixed effects model (3) fitted to the data showed a statistically significant effect of age on the maximum induced electric field [$F(1, 118.5) = 52.5$, $p = 5 \times 10^{-11}$], older subjects having higher electric strengths. Skull volume also had a significant positive effect [$F(1, 124.9) = 46.5$, $p = 3 \times 10^{-10}$]. The differences between field directions were significant [$F(2, 118) = 731.6$, $p = 2 \times 10^{-16}$], the LAT direction inducing higher fields than those in the TOP or AP directions. The only predictor not having a statistically significant effect on the maximum induced electric field strength was gender [$F(1, 118.0) = 0.07$, $p = 0.8$]. The interaction between skull volume and direction had a significant effect [$F(2, 118.0) = 3.5$, $p = 0.03$], the AP exposure having a slightly more pronounced increase in the maximum electric field strength as skull volume increased. However, neither the interaction term direction $\times$ age [$F(2, 118.0) = 3$, $p = 0.053$] nor the interaction term volume $\times$ age [$F(1, 118.0) = 0.003$, $p = 0.9$] were significant. No pattern/trend was observed when plotting the residuals against the predicted values, indicating the validity of the assumption of residuals' equal variances (homoscedasticity). The normality assumption of the residuals was also verified according to the Kolmogorov–Smirnov normality test ($p > 0.05$) and graphical diagnostics. The results of the fitted linear mixed model for the average subject (i.e., without including random effects in the predictions) are visualized in figure 3.

Figure 3: (a) Linear mixed effects model's estimated relationship between the maximum electric field strength and age for each exposure direction (AP, LAT and TOP). (b) Results showing the estimated relationship between the maximum electric field strength and skull volume. Lines represent the expected values for the average subject (i.e., without including random effects in the predictions), shadowed areas are the 95% confidence intervals, and the dots are the partial residuals.

4. Discussion

This investigation represents the first attempt to quantify how both individual characteristics and anatomical differences affect the maximum electric field strengths induced in the brain by uniform magnetic field exposure at 50 Hz. Earlier studies investigated the variability in the induced electric field between anatomical human models (Aga *et al* 2018, Bakker *et al* 2012). However, the statistical power of these researches was limited by a rather small number of subjects involved (6 in Aga *et al* (2018) and 8 in Bakker *et al* (2012)). Here, a total number of 118 individuals were recruited, leading to stronger conclusive results. Furthermore, in addition to anatomical differences, we included other factors for evaluating the variability of the induced electric fields, such as age, gender, skull volume and incident magnetic field directions. The characterization of these effects assumes particular interest for the development of human exposure guidelines of electromagnetic fields at low frequencies, considering that both the IEEE standard and ICNIRP guidelines lack quantitative data about the variability of the induced electric field between individuals.

Skull volume and magnetic field directions had a systematic effect on the maximum induced electric field strength despite individual variations, as shown in figure 3(b). The higher induced field strengths for larger heads and for the exposure in the LAT direction follow from a larger cross-sectional area in the sagittal plane, which leads to an increased field strength due to Faraday's law of induction. Those results are consistent with previous studies showing that the LAT direction produces higher electric field strengths compared to TOP and AP directions (Soldati and Laakso 2020, Dimbylow 2005a, Hirata *et al* 2010, Chen *et al* 2013). Depending on the direction of the incident uniform magnetic field, different CNS tissues exhibited the highest electric field strength, as reported in the pie charts of figure 1. This might also partially explain the effect of direction on the highest electric fields.

Higher maximum induced electric fields were found in older individuals, as reported in figure 3(a). This effect can be explained by the age-related changes in the brain (Good *et al* 2001, Sowell *et al* 2003). Ageing decreases the volume of the grey matter, whereas it

increases the volume of the CSF (Good *et al* 2001, Sowell *et al* 2003). This trend has also been observed in the present study (see Appendix A). As the conductivity of the CSF is higher than the one of the grey matter, the total induced current, and therefore the peak induced electric field strength, tends to increase with age. A similar effect was observed in a previous study (Janssen *et al* 2013), where higher electric fields induced by transcranial magnetic stimulation were found in the GM and WM tissues when the thickness of the cortical layer was reduced, and correspondingly the CSF volume increased. Our investigation did not include infants and children, as well as people above 55 years old. However, for the former we expect the induced electric field strengths to be weaker compared to the adult population given the smaller skull and CSF volumes. For the elderly population, the peak electric fields are expected to increase since the CSF volume was found to keep expanding over the age of 55 years old (Good *et al* 2001, Sowell *et al* 2003).

Despite the statistical significance of skull volume and age, their effect on the highest electric fields was modest. For instance, considering the AP exposure, the average difference in terms of maximum electric field strength between the smallest (1.22 L) and largest (1.86 L) skull volumes is expected to be 3.9 mV m^{-1} . In the case of LAT and TOP directions, this difference is foreseen to be around 3.0 mV m^{-1} . Likewise, the expected value of the difference between subjects of minimum (18) and maximum ages (55) is 3.0 mV m^{-1} for LAT exposure, whereas it is equal to 2.2 mV m^{-1} and 2.7 mV m^{-1} for AP and TOP directions, respectively.

For the uniform magnetic field exposure at the occupational reference level of 1 mT (ICNIRP 2010), the maximum electric field strength across the subjects was always in compliance with the respective basic restrictions of 100 mV m^{-1} . Our results can be compared to those used as the basis for the ICNIRP guidelines (ICNIRP 2010) and the IEEE standard (IEEE 2002, IEEE 2019). The ICNIRP guidelines refer to the study of Dimbylow (Dimbylow 2005a), who found a maximum induced electric field strength in the brain equal to 33.0 mV m^{-1} and 31.4 mV m^{-1} for LAT exposure of the adult male NORMAN and female NAOMI models, respectively. Those values are 5.1 and 4.3 standard deviations above the average value (22.1 mV m^{-1}) calculated herein. The higher electric fields in NORMAN and NAOMI can be partly explained by their lower resolution (approximately 2 mm), which tends to produce overestimation compared to finer resolutions (Soldati and Laakso 2020). For comparison with the IEEE standard (IEEE 2002, IEEE 2019), the elliptical LAT exposure model would produce an induced electric field of 16.3 mV m^{-1} , which is 2.7 standard deviations below the mean value obtained in this study. The lower value is due to the fact that the homogeneous ellipsoid cannot model enhancement of the electric field strength due to anatomical features. The use of Grubbs test indicates that all the induction models, namely NORMAN, NAOMI and the homogeneous ellipse, would be considered as outliers in our data.

We focused our investigation on the 99th percentile value of the spatially-averaged electric field, which is the post-processing method required in the ICNIRP (2010) guidelines as a practical trade-off between computational accuracy and underestimation of the maximum electric field strength. In addition, we used a voxel resolution of 0.5 mm. In a previous investigation (Soldati and Laakso 2020), we found that the computational error of the induced electric field calculated using this approach was minor, between 0.3% and 1.1% depending on the exposure direction. Furthermore, we found that also the 99.9th and 100th percentile values of the electric field produced acceptably small computational error (0.4–1.2% and 0.2–1.5%, respectively), as long as the electric field was spatially averaged (Soldati and Laakso 2020). However, the computational error of the 100th percentile value might be considerably higher if a voxel resolution lower than 0.5 mm is employed (Soldati and Laakso 2020). Therefore, percentile values higher than the 99th percentile could also be used in defining numerically

reliable basic restrictions. Higher percentile values would reduce the underestimation of the highest electric field strengths, especially for localized exposure (Soldati and Laakso 2020). The differences between the percentile values should be considered when establishing the value of the basic restriction. For instance, the basic restrictions defined for the 100th percentile value would have to be in the order of 1.8 higher than the basic restrictions for the 99th percentile value to provide an equivalent level of protection for exposure to uniform magnetic fields (see table 2).

This study has some limitations that are listed as follows. Firstly, one of the most important source of uncertainty is the estimation of the electrical conductivity of the tissues, which plays a crucial role in computational dosimetry. At low frequencies, widely-used tissue electrical conductivity values were derived by Gabriel (Gabriel *et al* 1996, Gabriel *et al* 2009), who extensively reviewed literature data based on *in vivo* and *in vitro* measurements on animals. However, the electrical conductivities might vary considerably between different studies (Schmidt *et al* 2013). Furthermore, new advanced measurements in electrical impedance tomography, which allow reliable estimation of *in vivo* human tissue conductivities, showed that the electrical conductivity of brain tissues may be significantly higher than those commonly used (McCann *et al* 2019). For example, in the case of LAT exposure, the higher brain conductivity values (grey matter: 0.47 S m^{-1} , white matter: 0.22 S m^{-1}) tabulated in McCann *et al* (2019) would produce an average maximum electric field strength of $15.6 \pm 0.8 \text{ mV m}^{-1}$, which is considerably weaker than the one obtained here ($22.1 \pm 2.1 \text{ mV m}^{-1}$). Induction models are employed by both standard/guidelines to derive basic restrictions, and they are affected by variation in electrical conductivity values. In this context, ICNIRP called for more studies aimed at characterizing how the uncertainty in tissue properties affect the induced electric field (ICNIRP 2020). Secondly, we assumed the electrical conductivities to be isotropic. However, white matter has been reported to have increase conductivity components along and across the fibers (Gabriel *et al* 2009, Wu *et al* 2018). The effect of anisotropic properties should also be investigated more extensively in future researches (ICNIRP 2020, Reilly and Hirata 2016). Thirdly, both IEEE standard (IEEE 2002, IEEE 2019) and ICNIRP guidelines (ICNIRP 2010) define basic restriction for the CNS and peripheral nervous system (PNS). As our anatomical conductors models were cut at the neck level, we could solely derive data for the tissues of the CNS, without considering the tissues extending below the head. Lastly, the induced electric field strengths are derived for uniform magnetic field exposure at 50 Hz. However, our findings can be scaled to other frequencies within the whole low-frequency range, where a similar variability can be expected. For instance, the results will be still valid at 60 Hz if multiplying the induced electric field by a factor of 1.2. Notice that at frequencies above 400 Hz, the ICNIRP basic restrictions are the same in all parts of the body, and therefore, the exposure of the PNS should also be considered.

5. Conclusion

We exposed the anatomical head models of 118 individuals to uniform magnetic fields at the ICNIRP occupational reference level. Different directions of the incident magnetic field at 50 Hz were considered (LAT, TOP and AP). The peak induced electric fields were always in compliance with the ICNIRP occupational basic restrictions for the CNS tissues.

Our computational results indicate a certain variation of the maximum induced electric field strengths among the population, which followed a normal distribution. As expected from Faraday's law, LAT exposure gave the highest induced electric field strengths. In this context, the ICNIRP occupational basic restriction for the brain (100 mV m^{-1}) was

found to be 36.6 standard deviations above the average value derived here for LAT exposure ($22.1 \pm 2.1 \text{ mV m}^{-1}$). This large difference is mainly due to the additional reduction factor of 3 that ICNIRP applies to account for dosimetric uncertainty when deriving the reference levels from the basic restrictions. Additionally, the anatomical models used as basis for deriving the ICNIRP reference levels produced considerably higher peak electric fields than the average LAT value, to such an extent that they would be considered as outliers compared to our data. Regarding the IEEE standard, however, the elliptical LAT induction model provided such a low peak value that resulted to be an outlier as well. However, uncertainty in tissue properties may have a major impact on the induced electric field strengths. This uncertainty needs to be further characterized in future investigations, and reduced by either performing additional conductivity measurements and/or reviewing current literature.

Our investigation is the first of its kind to explore the effects of anatomical variability and individual characteristics on the induced electric fields. Statistical analysis showed that skull volume, age, and incident magnetic field direction had a significant effect on the induced electric field strengths. Despite statistical significance, these effects on the peak induced electric fields were modest.

We believe that the present investigation will be useful for the future revision and harmonization of human exposure international guidelines and standard. The derived results are intended to reduce the uncertainties on the variability of the peak electric field strengths induced by uniform magnetic field exposure among different individuals. These quantitative data can be used for deriving appropriate reduction factors when evaluating exposure reference levels for human protection to electromagnetic field at low frequencies.

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Appendix A: Age-related changes in the brain.

Multiple linear regression analysis revealed significant effect of age and gender on both CSF and GM volumes. Results showed a significant increase in CSF volume with age [$R^2 = 0.44$, $F(1, 114) = 71.0$, $p = 1 \times 10^{-13}$] and gender [higher for men, $F(1, 114) = 12.3$, $p = 6 \times 10^{-4}$]. There was also a significant interaction between gender and age [$F(1, 114) = 4.5$, $p = 0.03$], indicating a more pronounced increase for older men than women. Those results, shown in figure 4(a), are in accordance with previous findings (Coffey *et al* 1998, Gur *et al* 1991). A statistical significant decline of GM volume with age was observed [$R^2 = 0.32$, $F(1, 114) = 20.1$, $p = 2 \times 10^{-5}$], male having a greater GM volume [$F(1, 114) = 32.1$, $p = 1 \times 10^{-7}$]. The interaction between age and gender was not significant [$F(1, 114) = 0.4$, $p = 0.5$]. Therefore, the age-related decline did not differ between males and females significantly (figure 4(b)).

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Figure 4: Multiple regression model's estimated relationship between CSF volume and age (a), as well as the relationship between GM volume and age (b). Black color represents males while red stands for females. Lines show the expected values of the model, shadowed areas are the 95% confidence intervals, and the dots are the partial residuals.

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