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Abstract

Transcranial Magnetic Stimulation (TMS) is a non-invasive technique approved by the US Food and Drug Administration (FDA) to treat certain neurological disorders. When comparing TMS to techniques with similar desired outcomes, such as conventional brain surgery, TMS has far fewer risks due to its non-invasive nature. TMS works by inducing an electric field (E-field) that polarizes or depolarizes brain tissues depending on treatment mode. The human brain reaches 90 % of its adult volume at about age six and does not reach full maturity until approximately 25 years. The differences in the brain volume from adolescents to adults could alter the effectiveness of TMS, primarily because the coils have been designed for use on adult patients. Therefore, comparing the efficacy of TMS coils across age groups to determine if the difference in brain volume is enough to warrant specific TMS treatment protocols for adolescents is of the essence in advancing TMS research. In this research, the authors compare the use of a novel TMS coil design, quadruple butterfly coil (QBC), across different age groups to test the effectiveness of the coil on various stages of brain development. Simulations were run using a finite element analysis software, Sim4Life. Besides age and brain (grey matter) volume, the authors also considered other factors such as the brain-scalp distance (BSD), cerebrospinal fluid (CSF) thickness, scalp thickness, skull thickness, and skull volume of the human models in the analysis. This study provides an understanding of the various factors contributing to the response from TMS. The maximum E-field intensity on the scalp (E-Max scalp), maximum E-field intensity on the brain (E-Max brain), and the proportion of the E-Max brain to E-Max scalp were parameters considered in this analysis.

Keywords

Age Group, Brain Development, Transcranial Magnetic Stimulation (TMS), Quadruple Butterfly Coil (QBC)

Disciplines

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Transcranial Magnetic Stimulation: the effect of age and other factors on the intensity of the Quadruple Butterfly Coil

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Transcranial Magnetic Stimulation (TMS) is a non-invasive technique approved by the US Food and Drug Administration (FDA) to treat certain neurological disorders. When comparing TMS to techniques with similar desired outcomes, such as conventional brain surgery, TMS has far fewer risks due to its non-invasive nature. TMS works by inducing an electric field (E-field) that polarizes or depolarizes brain tissues depending on treatment mode. The human brain reaches 90 % of its adult volume at about age six and does not reach full maturity until approximately 25 years. The differences in the brain volume from adolescents to adults could alter the effectiveness of TMS, primarily because the coils have been designed for use on adult patients. Therefore, comparing the efficacy of TMS coils across age groups to determine if the difference in brain volume is enough to warrant specific TMS treatment protocols for adolescents is of the essence in advancing TMS research. In this research, the authors compare the use of a novel TMS coil design, quadruple butterfly coil (QBC), across different age groups to test the effectiveness of the coil on various stages of brain development. Simulations were run using a finite element analysis software, Sim4Life. Besides age and brain (grey matter) volume, the authors also considered other factors such as the brain-scalp distance (BSD), cerebrospinal fluid (CSF) thickness, scalp thickness, skull thickness, and skull volume of the human models in the analysis. This study provides an understanding of the various factors contributing to the response from TMS. The maximum E-field intensity on the scalp (E-Max scalp), maximum E-field intensity on the brain (E-Max brain), and the proportion of the E-Max brain to E-Max scalp were parameters considered in this analysis.

Index Terms— Age Group, Brain Development, Transcranial Magnetic Stimulation (TMS), Quadruple Butterfly Coil (QBC).

I. INTRODUCTION

Transcranial Magnetic Stimulation (TMS) is a United States Food and Drug Administration (FDA) approved treatment for select neurological and psychiatric disorders [1]. TMS is a non-invasive technique used for determining motor evoked potentials (MEP), mapping the brain, and determining the function of selected regions of the brain. It is also commonly used as a tool for studying neuronal connectivity. Compared to similar neurological research tools such as Deep Brain Stimulation (DBS), TMS is considered safe, with minimal risk to the patient [2].

During TMS, electromagnetic coils are positioned on the scalp, generating a transient magnetic field (H-field), which induces an electric field (E-field) in the affected brain's tissues. The E-field hyperpolarizes or depolarizes the neurons causing the synapses to alter their action accordingly [3]. There are several TMS coil configurations, and they all exhibit different stimulation effects with respect to the penetration depth and focality of the induced E-field [4]. The quadruple butterfly coil (QBC) is a novel coil designed with an emphasis on increased focality [5]. When determining the effectiveness of TMS, two measurement parameters are generally considered; the maximum induced E-field intensity within the brain (E-Max) and the volume of the brain stimulated by half of the E-Max (V-half). The V-Half is commonly used to determine the focality of the coil.

Until approximately 25 years of age, the human brain is not fully developed, and from newborn until 25, the brain goes through structural and developmental changes [6]. As humans develop throughout their adolescence, their brain size and structure change. The most visible changes occur leading up to

and during the elementary age. During this time frame, the brain will quadruple in size and reach 90 % of its adult volume at age six. This change produces an exuberant neural network, and children in this age range have a higher gray matter volume than adults. With TMS, the anatomy of the cortex affects the response to stimulation [8]. A linear relationship between brain volume and TMS effectiveness has been reported in the literature [9], [10]. For instance, studying the effect of brain size on the efficacy of the commercially available figure-of-eight (FOE) coil, Crowther et al. compared the induced E-field across age groups and reported a significant variation between the adult and pediatric models [11].

With advancing TMS technology for treating neuropsychiatric disorders in pediatric patients, researching how the performance of existing TMS coils varies with different brain sizes becomes crucial. Since pediatric patients have differing brain anatomy and physiology from adults, it is important to assess the risk pediatric patients are exposed to during TMS and ascertain TMS's effectiveness. One other important reason to study how TMS performance varies with age and differing brain size will be to determine if TMS can be considered an effective tool for mapping brain development, as it has been used as a tool for determining MEP in adults [7].

The brain-scalp distance (BSD) is also considered an anatomical feature that affects TMS response. In addition to the changes occurring during adolescence, one change over 55 years is the BSD. The brain begins to shrink, increasing the BSD and cerebrospinal fluid (CSF) thickness. The effect of the BSD on response during TMS has been shown to impact the effectiveness of TMS no matter the coil used [12]–[14].

The BSD closely relates to the coil-to-cortex distance (CCD): the greater the BSD, the greater the reach of the coil from the cortex, and the lower the intensity of the E-field reaching the cortex. Another study that examined the BSD's impact on the effectiveness of TMS found that for every additional millimeter between the vertex where the coil is placed and the targeted neural tissue, an additional 3 % of the TMS stimulator's output is needed to have the desired treatment effect [15]. In addition, studying the effect of CSF thickness on TMS responses is also crucial. This is because it contributes to the patients' BSD and negatively correlates with the intensity of the induced E-field during TMS [16].

The cranial vault (skull volume) also increases dramatically [7] as humans develop throughout their adolescence until the age of ten, after which there are very minimal changes in size in the cranial vault [17]. In addition, skull thickness has been confirmed to increase with age in pediatric patients aged 0 to 18 years [18] and decrease in female adults from 20 to 100 years [19]. Studying the effect of the changing skull volume and thickness across the age groups on TMS effectiveness becomes very important also.

This study investigated the effect of age and brain size on models' responses during TMS. Besides age and brain size (grey matter volume), other factors such as the BSD, CSF thickness, scalp thickness, skull thickness, and skull volume of the models were also investigated to determine TMS effectiveness. Studying the effect these factors have on the intensity of the E-field is important in understanding the individual responses exhibited by patients from different age groups during TMS treatment. In addition, this study will help assess the risk (if any) that pediatric patients get exposed to during TMS.

II. METHOD

A. Human Models

i. Virtual Population (ViP) Models

The models (Fig. 1) used in this study were sourced from the Computable Virtual Population Models from the Information Technologies in Society (IT²S) foundation database [20]. The models have well-defined anatomy and were selected to each represent a different age group. The adult models used as the control are 34 years old male (34M) and 26 years old female (26F), as they both fall in the typical age range of models (25 to 35 years) used for TMS studies. The models used to represent the pediatric population are 14 years old male (14M), 11 years old female (11F), 8 years old female (8F), 8 years old male (8M), 6 years old male (6M), and 5 years old female (5F) [8]. Heterogeneity of the various tissues' electrical properties was introduced in the estimation of the induced E-field of the human models [21]. This is because tissue heterogeneity has been confirmed to contribute to the intensity of the E-field [22], [23]. The tissue properties were sourced from the IT²S foundation database.

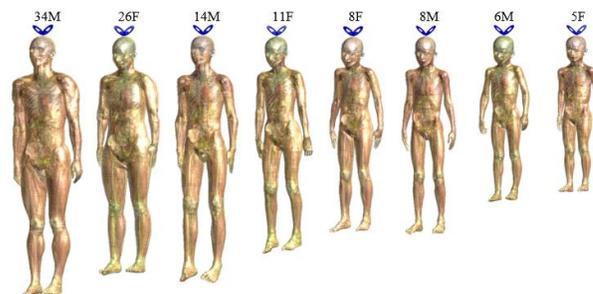


Fig. 1. ViP Model

ii. Human Connectome Project (HCP) Models

Due to the small sample size from the ViP Models, 50 head models generated from magnetic resonance imaging (MRI) scans were used to assess the effect of brain-scalp distance (BSD), cerebrospinal fluid (CSF) thickness, scalp thickness, grey matter (GM) volume, skull thickness and skull volume on the intensity of the induced E-field. The head models sourced from the HCP Library [24] and developed by [14] are healthy subjects with age range of 25 to 35 years.

B. Simulations

The QBC is a new patented coil design with two large sets and two small sets of coils. The large coils are the same dimension as a conventional FOE coil, while the small coils have dimensions about 40 % of the large coil. Both sets of coils are designed to make an angle of 90° with each other. The coils were modeled, and finite element analysis (FEA) was conducted using a low-frequency electromagnetic field solver software, Sim4Life [24]. A current amplitude of 5 kA was allowed to flow through the QBC at a frequency of 2.5 kHz to simulate the TMS pulses. The output from this simulation is comparable to a conventional TMS stimulator used in clinical applications. The QBC was positioned over the vertex of the head of each of the models, and the intensity of the induced E-field was computed. Insulation of the coil was also accounted for in the FEA study.

C. Data Interpretation and Statistical Analysis

Results from Sim4Life were exported to MATLAB for postprocessing and interpretation of data. The maximum E-field intensity on the scalp (E-Max scalp), maximum E-field intensity on the brain (E-Max brain), and the proportion of the E-Max brain to E-Max scalp were calculated for each of the models. The maximum induced E-field on the scalp (E-Max scalp) and the maximum induced E-field on the brain (E-Max brain) were calculated using Matlab scripts written for this purpose. The proportion of the E-Max brain to the E-Max scalp was calculated using MS-Excel. For the statistical analysis, scripts written in R programming language were developed to analyze the data and determine the correlation coefficient for the three parameters and the different anatomical factors.

III. RESULTS AND DISCUSSION

a) Virtual Population (ViP) Models

i. Variability in E-Max intensity

The distribution of the induced E-field on the scalp and grey matter is shown in Fig. 2. The ViP models exhibited unique responses to the stimulation effect. Model 6M exhibited the highest E-Max intensity (324 V/m) on the scalp, while model 14M exhibited the highest E-Max intensity (213 V/m) in the brain. One observation with the pediatric models in Fig. 2 is that the induced E-field has a greater spread on both the scalp and brain than the adult models. This confirms that a specialized protocol might be necessary for pediatric patients receiving TMS treatment, especially as focality is required for a successful TMS protocol.

Model 11F exhibited the highest magnitude of the proportion of E-Max; this implies that the model 11F had a high proportion of the E-field from the scalp reaching the brain. This is highly desirable since to achieve increased effectiveness with TMS, a high percentage of the induced E-field must reach the brain for required cortical activation. On the other hand, model 34M exhibited the lowest magnitude of the proportion of E-Max. This is expected since we also observed that model 34M had the highest BSD, which increased the distance between the scalp and the brain, hence, impacting the E-field intensity reaching the brain.

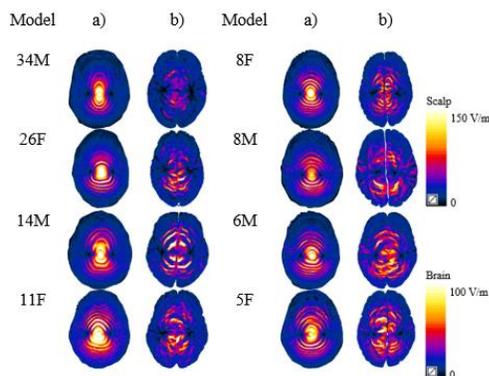


Fig. 2. Induced E-field distribution on the a) scalp and b) brain of the ViP Model. For all models, the intensity of the E-field on the scalp was normalized to 150 V/m, and the E-field on the brain was normalized to 100 V/m for a good comparison.

ii. Variability in E-Max intensity with penetration depth

Fig. 3 presents the distribution of the induced E-field intensity with depth across the ViP models. One common feature of all the models is that their E-Max intensity decreased with depth, as expected from Biot-Savart law. We also observed that each model exhibited a unique penetration depth profile irrespective of their age. Model 6M exhibited the highest E-Max intensity on the scalp. At a 30 mm depth, model 11F exhibited the highest E-Max intensity. Beyond the 30 mm depth, model 34M exhibited a sudden increase and then a decline. The reason for the sudden increase is not apparent, but we assume that the anatomical layer at this depth might be contributing to this response.

iii. Variation of E-Max with Age

No significant statistical relationship (Fig. 4) was observed between age and the three parameters (R -square = 0.071, P -

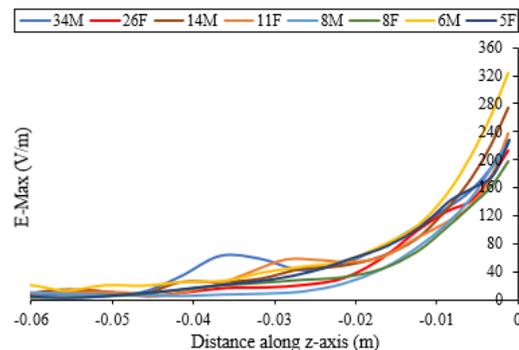


Fig. 3. Variation of the Induced E-field (V/m) with depth across the ViP Model.

value = 0.525 and t -score = -0.675) for the E-Max scalp, (R -square = 0.139, P -Value = 0.364 and t -score = -0.983) for the E-Max brain, (R -square = 0.063, P -Value = 0.548 and t -score = -0.636) for the proportion of E-Max brain to E-Max scalp.

iv. Variation of E-Max with the Brain size

The brain size in this study represents the volume of the grey matter (GM). With differences in the GM volume between adults and pediatric patients, the effect of varying GM volume on TMS was also analyzed. The statistical relationship between the GM volume and E-Max scalp was calculated as (R -square = 0.233, P -Value = .226 and t -score = 1.351). This showed a very low correlation. For the E-Max brain, the statistical relationship was computed as (R -square = 0.596, P -Value = 0.025 and t -score = 2.976). This relationship is quite significant, and further investigation is required with a larger sample size. A statistical relation of (R -square = 0.316, P -Value = 0.147 and t -score = 1.663) was computed for the proportion of E-Max brain to E-Max scalp.

v. Variation of E-Max with the BSD

The BSD was taken as the perpendicular vertical distance from the vertex to the line connecting the highest point on each hemisphere of the brain of each human model. There was no significant statistical relationship between the BSD and E-Max scalp (R -square = 0.089, P -Value = 0.473 and t -score = -0.765). For the E-Max brain, the statistical relationship was computed as (R -square = 0.185, P -Value = 0.287 and t -score = -1.169). Compared with previous work, the statistical relationship between the BSD and the E-Max brain is low; hence, this requires further investigation with larger sample size. For the proportion of E-Max brain to E-Max scalp, a statistical relationship of (R -square = 0.113, P -Value = 0.416 and t -score = -0.874) was computed.

vi. Variation of E-Max with the CSF thickness

CSF thickness was measured as the distance between the skull and the grey matter. This was measured for each model, and a low statistical relationship was observed between the CSF thickness and the E-Max scalp (R -square = 0.105, P -Value = 0.435 and t -score = -0.837). For the other two parameters, no statistical relationship was observed, as shown in Fig. 4.

vii. Variation of E-Max with the Scalp thickness

The scalp thickness is the layer covering the cranial vault or the skull, and it consists of the skin layer and other tissues. The scalp thickness was measured as the distance from the vertex to the top of the skull. No statistical relationship was observed between the scalp thickness and the three

parameters. (R -square = 0.003, P -Value = 0.905 and t -score = -0.125) for the E-Max scalp, (R -square = 0.005, P -Value = 0.871 and t -score = -0.170) for the E-Max brain, (R -square = 0.015, P -Value = 0.771 and t -score = -0.305) for the proportion of E-Max brain to E-Max scalp.

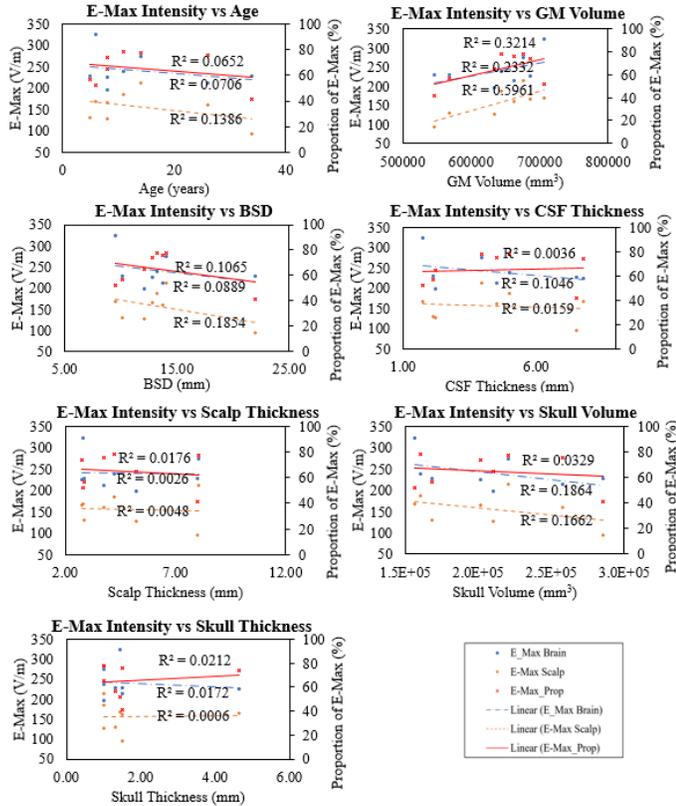


Fig. 4. Correlation plots for the different anatomical features and the three parameters (ViP Model).

viii. *Variation of E-Max with the Skull Volume*

The skull volume, also referred to as the cranial vault, is the spatial distribution (dimension) of the skull. The statistical relationship between the skull volume and E-Max scalp was calculated as (R -square = 0.186, P -Value = 0.285 and t -score = -1.173). This showed a very low correlation between the E-Max scalp and the skull volume, although with a higher value than some of the other factors). The statistical relationship between the skull volume and E-Max brain was calculated as (R -square = 0.166, P -Value = 0.316 and t -score = -1.094) and (R -square = 0.034, P -Value = 0.664 and t -score = -0.457) for the proportion of E-Max brain to E-Max scalp. More study is required with a larger sample size to confirm the relationship between the E-Max parameters and the skull volume.

ix. *Variation of E-Max with the Skull thickness*

The skull thickness is the region between the scalp and the CSF. It consists of the cancellous and cortical skull bone. The statistical relationship between the skull thickness and E-Max scalp was calculated as (R -square = 0.017, P -Value = 0.757 and a t -score = -0.324). This showed no correlation between the E-Max scalp and the skull thickness. The statistical relationship between the skull thickness and E-Max brain was calculated as (R -square = 0.0006, P -Value = 0.956 and t -score = 0.058) and (R -square = 0.0098, P -Value = 0.815 and t -score = 0.244) for the proportion of E-Max brain to E-Max scalp.

No statistical relationship was observed between the three parameters and the skull thickness.

b) *Human Connectome Project (HCP) Models*

With the limited sample size of the ViP Model, the HCP models were also analyzed to confirm the effect of selected factors on the TMS effectiveness (Fig. 5). Here, the E-Max scalp and E-Max brain were the only parameters computed. The effect of age and brain size was not analyzed since the HCP models' age range was within a close range.

i. *Variation of E-Max with the BSD*

The relationship between the E-Max brain and BSD was observed to be statistically significant (R -square = 0.459, P -Value = 6.671e-08 and t -score = -6.376). This supports the results of previous studies that conclude that E-Max intensity decreases with increasing BSD. We also observe that there was no correlation between the E-Max scalp and the BSD (R -square = -0.065, P -Value = 0.909 and t -score = -0.115). This seems reasonable since the BSD is an inherent property of the model and not a superficial one.

ii. *Variation of E-Max with the CSF thickness*

There was no significant statistical relationship observed between the E-Max scalp and CSF thickness (R -square = 0.057, P -Value = 0.095 and t -score = -1.702). The relationship with the E-Max brain was however observed to be statistically significant (R -square = 0.453, P -Value = 8.609e-08 and t -score = -6.303). We observe that the E-Max intensity decreases with increasing CSF thickness, and just like the BSD, this is expected since the CSF thickness is an inherent property of the model.

iii. *Variation of E-Max with the Scalp thickness*

For both of the E-Max parameters, no significant statistical relationship was observed with the scalp thickness. For the E-Max scalp, (R -square = 3.037e-06, P -Value = 0.990 and t -score = -0.012) was observed. For the E-Max brain, (R -square = 0.0295, P -Value = 0.233 and t -score = -1.208).

iv. *Variation of E-Max with the Skull Volume*

Just as observed with the ViP models, the skull volume showed no significant relationship with the E-Max scalp (R -square = 0.033, P -Value = 0.205 and t -score = 1.284) was observed. For the E-Max brain, an (R -square = 0.012, P -Value = 0.444 and t -score = -0.772) values were observed.

v. *Variation of E-Max with the Skull thickness*

The relationship between the E-Max scalp and the skull thickness was observed to be statistically insignificant. The (R -square = 0.004, P -Value = 0.653 and t -score = -0.452). For the E-Max brain, the statistical relationship was observed as (R -square = 0.128, P -Value = 0.011 and t -score = -2.652). Although quite low, the relationship between the E-Max brain and skull thickness should be further investigated.

IV. CONCLUSION

This study showed that the human models from the different age groups all exhibited unique responses to activation from TMS. In addition, all age-dependent anatomical features, like the grey matter volume, CSF thickness, and BSD showed significant relationships with the induced E-field intensity. We

confirm that special treatment protocol will be necessary for TMS treatment of pediatric patients from this study. Future work will include coil design for pediatric patients to avoid overstimulation from the conventional adult TMS coils.

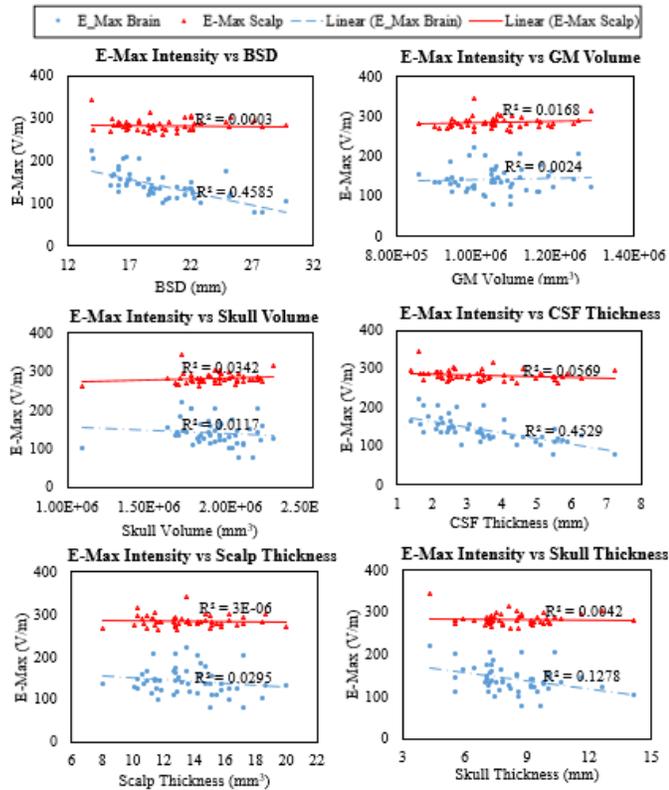


Fig. 5. Correlation Plots for the different anatomical features and the two parameters (HCP Model).

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