Supplementary Materials

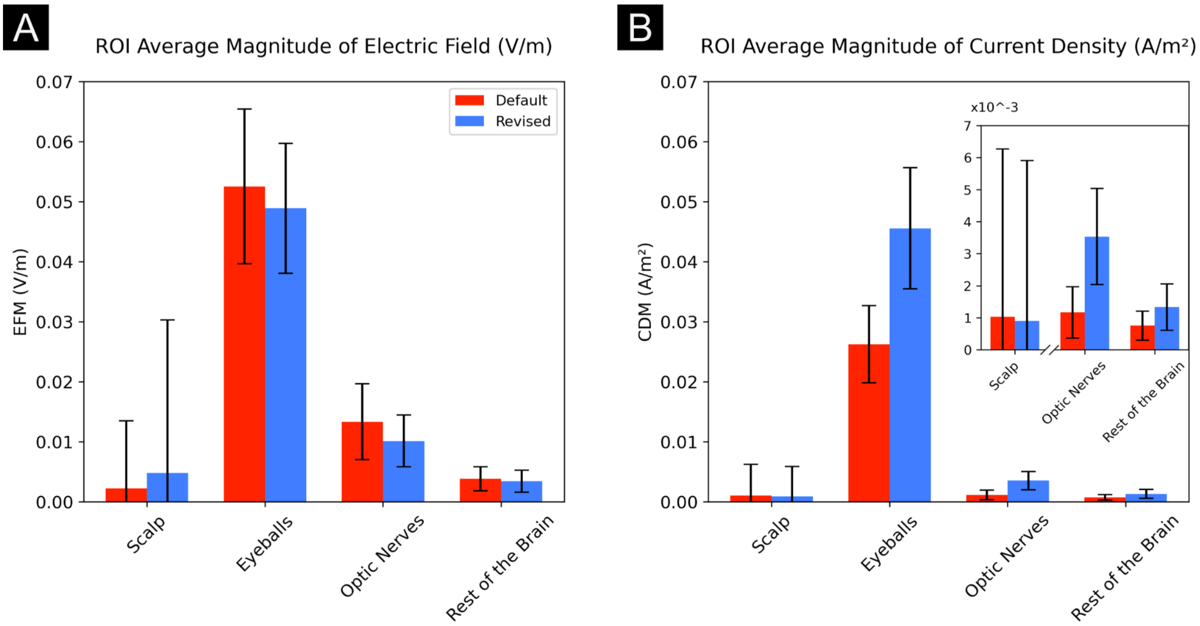
Differences in Electric Field Based on Conductivity Values (SimNIBS Default vs. Swiss IT'IS Foundation)

In this section dedicated to computer-based IEF simulations, we focus on comparing the results obtained using the default conductivity values provided by SimNIBS with those derived from our revised conductivity values, as detailed in the Discussion section. The volumetric results are illustrated in Supplementary Figure 1 and summarized in Supplementary Table 1 and Supplementary Table 2, while the surface results are depicted in Supplementary Figure 2 and Supplementary Figure 3.

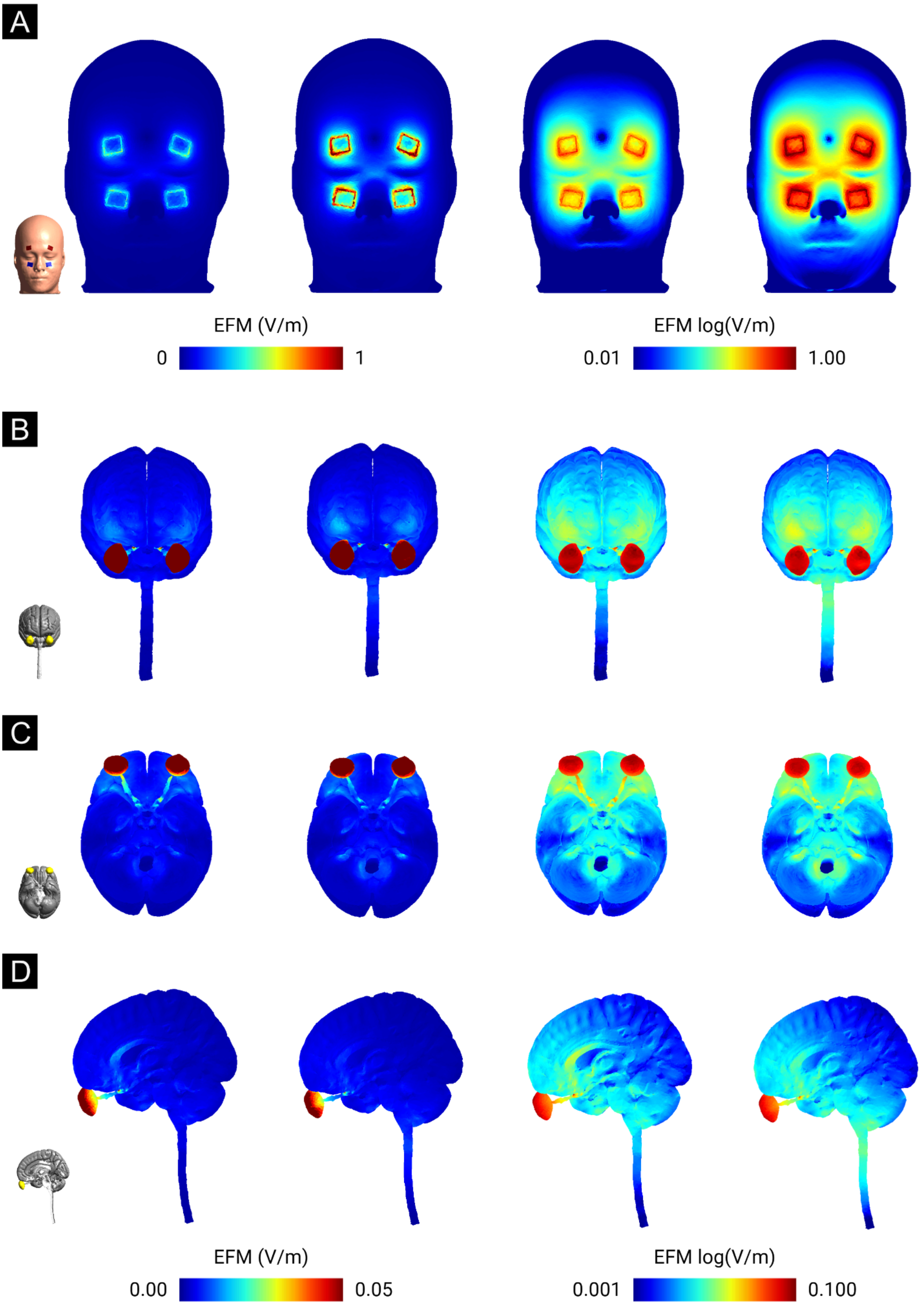
The revised conductivity values, characterized by a lower value for the scalp and higher for nerve tissue (see Table 2-1), led to notable changes in the EFM and CDM across various ROIs. Specifically, the revised values produced a higher EFM on the skin surface below the electrodes, with a mean increase from 0.0022 V/m to 0.0048 V/m for the scalp, accompanied by a rise in the maximum EFM from 0.4457 V/m to 1.1187 V/m. In contrast, the EFM for nerve tissue, such as the optic nerve, decreased, with the mean value dropping from 0.0134 V/m to 0.0102 V/m and the maximum declining from 0.0394 V/m to 0.0375 V/m. Similarly, the eyeballs exhibited a decrease in mean EFM from 0.0526 V/m to 0.0489 V/m.

For the CDM values, the revised conductivity settings led to slightly higher values in nerve tissues. For example, the mean CDM in the optic nerve increased from 0.0017 A/m² to 0.0035 A/m², while the maximum rose from 0.0047 A/m² to 0.0130 A/m². The eyeballs also saw an increase in mean CDM from 0.0263 A/m² to 0.0458 A/m², and the maximum CDM increased from 0.0438 A/m² to 0.0726 A/m². In contrast, the scalp exhibited a slight decrease in mean CDM from 0.0010 A/m² to 0.0009 A/m², with a small increase in the maximum from 0.2072 A/m² to 0.2182 A/m². These changes reflect the altered distribution of the electric and current density magnitudes due to adjustments in the conductivity values, demonstrating more focused and intense stimulation in nerve tissues while reducing the EFM on deeper neural structures.

The comparison between default and revised conductivity values in computer-based IEF simulations revealed distinct changes in the distribution of EFM and CDM. The revised values, with lower conductivity for the scalp and higher for nerve tissues, resulted in a higher EFM on the skin surface under the electrodes but a lower EFM in nerve tissues such as the eyeballs, optic nerves, and the rest of the brain. Conversely, CDM values were slightly elevated in nerve tissues with the revised settings, indicating a more focused stimulation effect. These findings underscore the complex interplay between conductivity, electric field distribution, and current density, emphasizing the need for precise parameter adjustments in neuromodulation strategies to optimize efficacy and safety. Understanding these nuanced interactions is essential for tailoring stimulation protocols to individual anatomical variations and achieving desired therapeutic outcomes in neuromodulation.



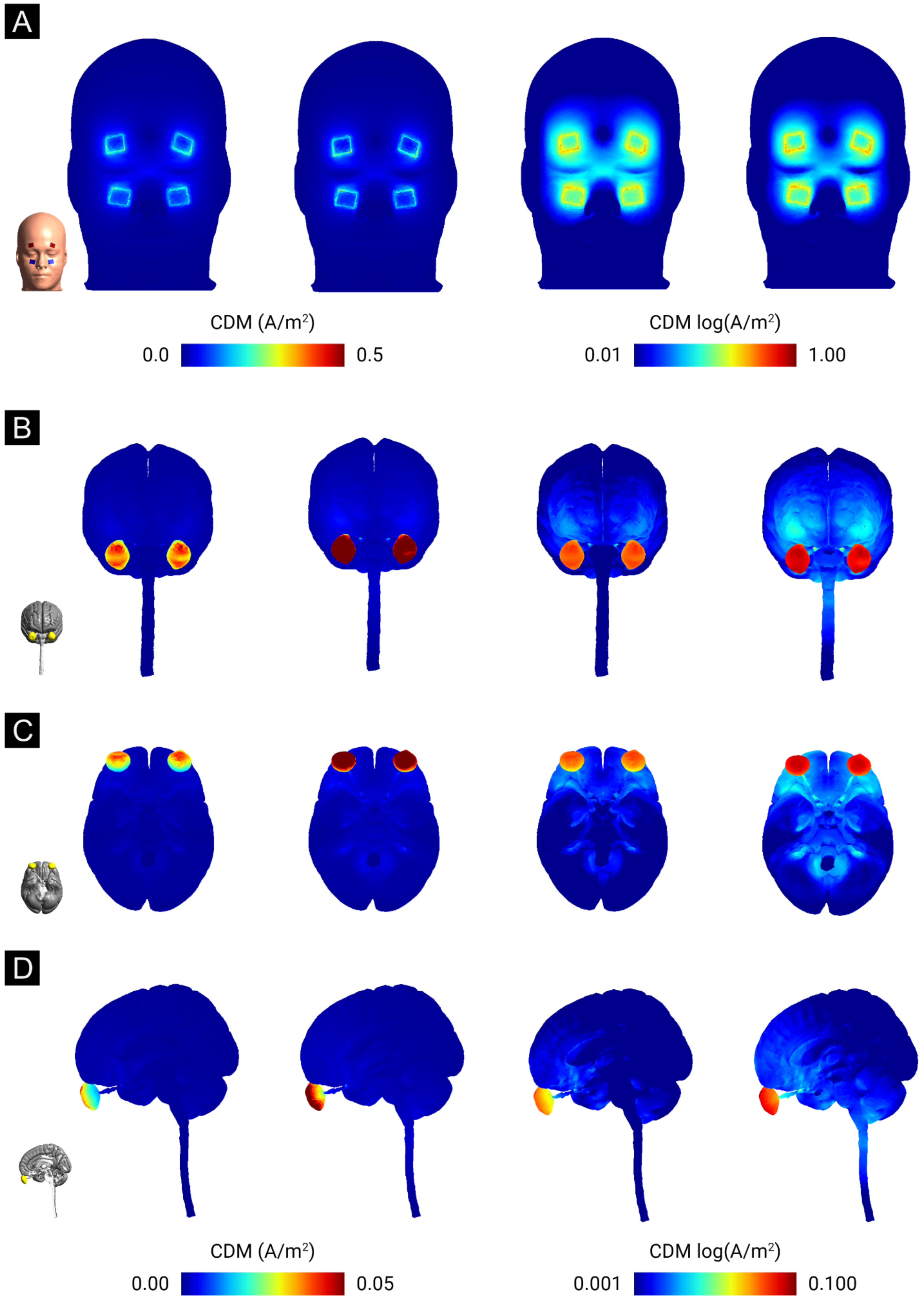
Supplementary Figure 1. *Mean electric field magnitudes (EFMs, V/m) (**A**) and current density magnitudes (CDMs, A/m^2) (**B**) for volumes and ROIs representing the scalp, eyeballs, optic nerves, and the rest of the brain, based on computer simulation results for the revised (blue) and default (red) conductivity values in SimNIBS. The inset provides an expanded view of regions with smaller magnitude differences. Error bars represent one standard deviation.*



Supplementary Figure 2. *Comparison of electric field magnitudes (EFM, V/m) for default and revised conductivity parameters (S/m) used in computer simulations conducted with SimNIBS software. The results for* *the default parameters are shown in the first and third columns, while those for the revised parameters are presented in the second and fourth columns. Additionally, the results in the first and second columns are expressed on a linear scale, whereas those in the third and fourth columns are expressed on a logarithmic scale.*

Supplementary Table 1. *Electric field magnitude (EFM, V/m) volumetric statistics for different regions of interest (ROIs), comparing results from default and revised conductivity values. The table shows the mean, sum, standard deviation (SD), maximum (Max), and minimum (Min) EFM values for the scalp, eyeballs, optic nerve, and rest of the brain. Differences between the revised and default values are provided, highlighting changes in the distribution and intensity of the EFM across these regions.*

Volume	**Conductivity**	**Mean**	**Sum**	**SD**	**Max**	**Min**
Scalp	Default	0.0022	27,121.3	0.0113	0.4457	0.000
	Revised	0.0048	58,016.5	0.0255	1.1187	0.000
	Difference	-0.0026	-30,895.2	-0.0142	-0.6730	0.000
Eyeballs	Default	0.0526	921.8	0.0129	0.0877	0.0267
	Revised	0.0489	857.8	0.0108	0.0779	0.0256
	Difference	0.0037	64.0	0.0021	0.0098	0.0010
Optic Nerve	Default	0.0134	21.9	0.0063	0.0394	0.0051
	Revised	0.0102	16.6	0.0043	0.0375	0.0048
	Difference	0.0032	5.2	0.0020	0.0018	0.0003
Rest of the Brain	Default	0.0038	6,311.6	0.0020	0.0313	0.0000
	Revised	0.0034	5,652.2	0.0018	0.0244	0.0000
	Difference	0.0004	659.4	0.0002	0.0069	0.0000



Supplementary Figure 3. *Comparison of current density magnitudes (CDM, A/m²) for default and revised conductivity parameters (S/m) used in computer simulations conducted with SimNIBS software. The results for* *the default parameters are shown in the first and third columns, while those for the revised parameters are presented in the second and fourth columns. Additionally, the results in the first and second columns are expressed on a linear scale, whereas those in the third and fourth columns are expressed on a logarithmic scale.*

Supplementary Table 2. *Current density magnitude (CDM, A/m^2) volumetric statistics for different regions of interest (ROIs), comparing results from default and revised conductivity values. The table shows the mean, sum, standard deviation (SD), maximum (Max), and minimum (Min) EFM values for the scalp, eyeballs, optic nerve, and rest of the brain. Differences between the revised and default values are provided, highlighting changes in the distribution and intensity of the CDM across these regions.*

Volume	Conductivity	Mean	Sum	SD	Max	Min
Scalp	Default	0.0010	12,611.4	0.0052	0.2072	0.0000
	Revised	0.0009	11,313.0	0.0050	0.2182	0.0000
	Difference	0.0001	1298.4	0.0002	-0.011	0.0000
Eyeballs	Default	0.0263	460.9	0.0064	0.0438	0.0038
	Revised	0.0456	799.5	0.0101	0.0726	0.0089
	Difference	-0.0193	-338.6	-0.0036	-0.0287	-0.0051
Optic Nerve	Default	0.0017	2.8	0.0008	0.0050	0.0006
	Revised	0.0035	5.8	0.0015	0.0130	0.0017
	Difference	-0.0018	-3.0	-0.0007	-0.0081	-0.001
Rest of the Brain	Default	0.0008	1,230.5	0.00045	0.0040	0.0000
	Revised	0.0013	2,174.7	0.00072	0.0085	0.0000
	Difference	-0.0006	-944.2	-0.0003	-0.0046	0.0000

Key takeaways:

1. Revised conductivity effects: Adjusting conductivity values (lower for the scalp, higher for nerve tissues) significantly altered the distribution of EFM and CDM.
2. Increased scalp EFM and decreased nerve tissue EFM: The revised values led to a marked increase in EFM on the scalp beneath the electrodes, while showing a notable decrease in the eyeballs, optic nerve, and other neural tissues.
3. Higher CDM in nerve tissue: The revised settings resulted in increased CDM values in the eyeballs, optic nerve, and other brain regions.

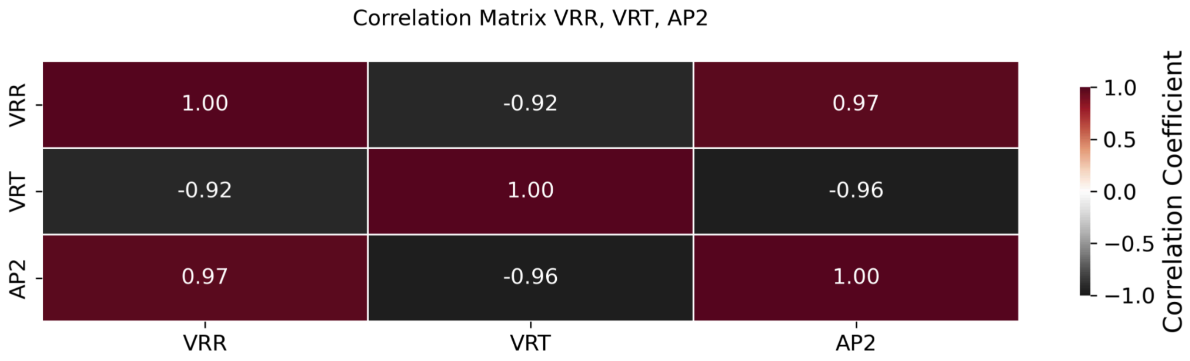
4. Refined stimulation targeting: The revised values produced greater effects on the scalp in terms of EFM and enhanced the targeted stimulation effect on nerve tissues in terms of CDM.

Behavioral and Electrophysiological Correlations in Study 1

It is worth highlighting that we observed nonlinear responses to pCS depending on its parameters in study 1. This nonlinearity was evident both at the behavioral level, as reflected in valid response rate (VRR, %) and valid response time (VRT, ms), and at the electrophysiological level, as demonstrated by the averaged late P2 component in the 150-300 ms time window (A2P, μV). These findings align with research on the intensity-specific effects of tACS, which similarly demonstrate distinctly nonlinear patterns (Zhao et al., 2023). This nonlinear behavior can be further understood through the Naka-Rushton equation (Naka and Rushton, 1966), which effectively models the relationship between stimulus intensity and neural response. The Naka-Rushton framework describes how neural responses increase with stimulus strength but eventually saturate, resulting in diminishing returns beyond a certain intensity threshold. This model has been widely applied to various physiological responses in the visual system, where it captures the nonlinear dynamics of retinal and cortical responses to increasing light intensity (Anastasi et al., 1993; Binns et al., 2011). Similarly, in the context of pCS, the observed saturation effect in all three levels, i.e. VRR, VRT, and A2P, suggests that further increases in stimulation strength may yield minimal improvements in response outcomes.

This saturation and nonlinearity observed at both the behavioral and electrophysiological levels seem to be highly related, as evidenced by the strong correlations between VRR, VRT, and the A2P. The correlation analysis, illustrated in Supplementary Figure 4, reveals a positive relationship ($r = 0.97$) between VRR and A2P, indicating that higher response rates are closely associated with greater neural activation, as reflected by increased P2 amplitudes. Conversely, VRT shows a strong negative correlation with both VRR ($r = -0.92$) and A2P ($r = -0.96$), suggesting that faster responses are linked to higher response rates and more robust neural activity.

These findings suggest that the observed behavioral and electrophysiological responses reflect the perception of phosphenes induced by pCS, given their strong correlation and inverse logarithmic relationship to the responses elicited by visual stimuli, such as LED flashes. The tight coupling between VRR, VRT, and the A2P mirrors the dynamics of visual stimulus processing, further supporting the conclusion that pCS effectively generates a visual percept. This interconnectedness between behavioral and neural responses highlights the shared mechanisms underlying phosphene perception and responses to direct visual stimuli, underscoring the nonlinear nature of these processes.



Supplementary Figure 4. *Correlation matrix heatmap of behavioral and electrophysiological responses. The heatmap displays the correlation matrix for VRR (Valid Response Rate, %), VRT (Valid Response Time, ms), and AP2 (Averaged Potential in the 150-300 ms range within the occipital cluster, representing the P2 late component). Correlations were computed using Pearson's correlation coefficient. The matrix integrates three response dimensions - behavioral (VRR and VRT) and electrophysiological (AP2) - across visual stimulation and nine current pulse types. The results highlight the relationships and interplay between behavioral and electrophysiological responses under varying stimulation conditions.*

Key takeaways:

1. Nonlinear effects of pCS were observed in both behavior and electrophysiology.
2. The Naka-Rushton custom model explains the saturation effect, where increasing current pulse duration yields diminishing returns.
3. Strong correlations exist between behavioral and electrophysiological factors.

References

1. Anastasi, M., Brai, M., Lauricella, M., & Geracitano, R. (1993). Methodological aspects of the application of the Naka-Rushton equation to clinical electroretinogram. Ophthalmic research, 25(3), 145–156. https://doi.org/10.1159/000267283

2. Binns, A. M., Mortlock, K. E., & North, R. V. (2011). The relationship between stimulus intensity and response amplitude for the photopic negative response of the flash electroretinogram. Documenta ophthalmologica. Advances in ophthalmology, 122(1), 39–52. https://doi.org/10.1007/s10633-010-9257-7

3. Naka, K. I., & Rushton, W. A. (1966). S-potentials from luminosity units in the retina of fish (Cyprinidae). The Journal of physiology, 185(3), 587–599. https://doi.org/10.1113/jphysiol.1966.sp008003

4. Zhao, Z., Shirinpour, S., Tran, H., Wischnewski, M., & Opitz, A. (2023). Intensity- and frequency-specific effects of transcranial alternating current stimulation are explained by network dynamics. bioRxiv : the preprint server for biology, 2023.05.19.541493. https://doi.org/10.1101/2023.05.19.541493