

MEG Reveals Vaccination Protection from Dengue-Related Reductions in Global Resting State Brain Activity in Nonhuman Primates



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INTRODUCTION

Navy Medicine Research and Development is critical to the force generation of a ready and deployable U.S. Navy by providing evidence-based approaches to define health guidelines that maximize force strength. Understanding the evolving health concerns in the context of viral infections is critical to service member readiness, fitness and mission completion. Dengue virus (DENV) infection affects over 400 million people annually worldwide, with severe cases potentially leading to neurological complications including encephalitis and cognitive impairment. The potential for DENV to cause neurological sequelae underscores the need to evaluate not only immunological protection but also neuroprotective benefits of candidate vaccines. This study was designed to evaluate the immunogenicity and neuroprotective efficacy of a novel psoralen-inactivated dengue vaccine in nonhuman primates (NHPs), utilizing magnetoencephalography (MEG) to assess neurological outcomes and comparing the properties of two proprietary adjuvants.

METHODS

- This randomized controlled trial was approved by WFUSM IACUC and U.S. Navy BUMED.
- Male African green monkeys were divided into four groups: (1) unvaccinated controls, (2) psoralen-inactivated DENV vaccine (PsIV), (3) PsIV with proprietary adjuvant-1, and (4) PsIV with proprietary adjuvant-2. Psoralen inactivation was employed to maintain viral antigenicity while ensuring complete viral inactivation.
- Immunogenicity was assessed through neutralizing antibody titers, T-cell responses, and cytokine profiles.
- MEG was recorded following vaccination or no vaccination and post-infection challenge with DENV-1. Sedated NHPs were scanned in a 275-channel CTF Systems MEG. 5 min. of resting-state (RS) activity (sampling rate 2400 Hz) were recorded post-infection. T1-weighted 3D MPRAGE MRIs were acquired on a 3T Siemens Skyra with a 32-channel head coil.
- RS MEG data were co-registered with each NHP's MRI, preprocessed, and beamformed with SAM (DC–80 Hz) to generate Z-deviate SPMs.
- Source series (equivalent to local field potentials) were constructed for 33 regions of interest (ROIs) for each NHP and divided into 15 epochs (20 s each). Power spectral densities (PSDs) were computed via Welch's method and split into bands: δ (DC–4 Hz), θ (4–8 Hz), α (8–13 Hz), β (13–30 Hz), γ (30–80 Hz), and full (DC-80 Hz). Linear models for spectral power were constructed in R: power per band ~ vaccine group (1–4) * ROI (n=33). All factors were indicators; band power was continuous. Tukey HSD post hoc tests determined group differences (FWER 0.05). Simple effects contrasts per band assessed ROI-specific differences with Holm correction.

RESULTS

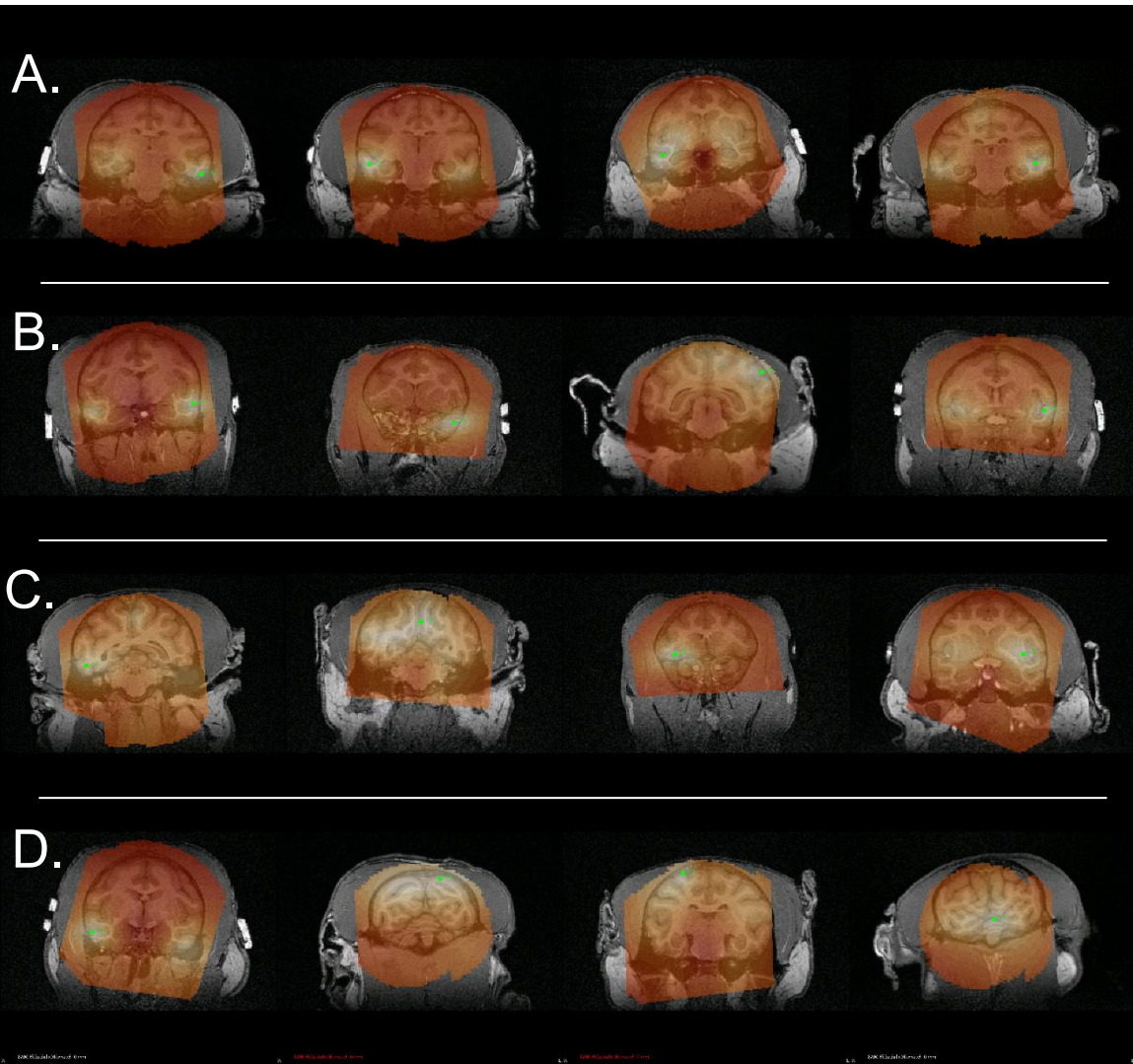


Figure 1. RS SAM SPMs (DC-80 Hz) for A) PsIV+Adj2, Group 4; B) PsIV+Adj1, Gr 3; C) PsIV, Gr 2; and D) controls, Gr 1. One map/subject; SAM peaks = brain generators.

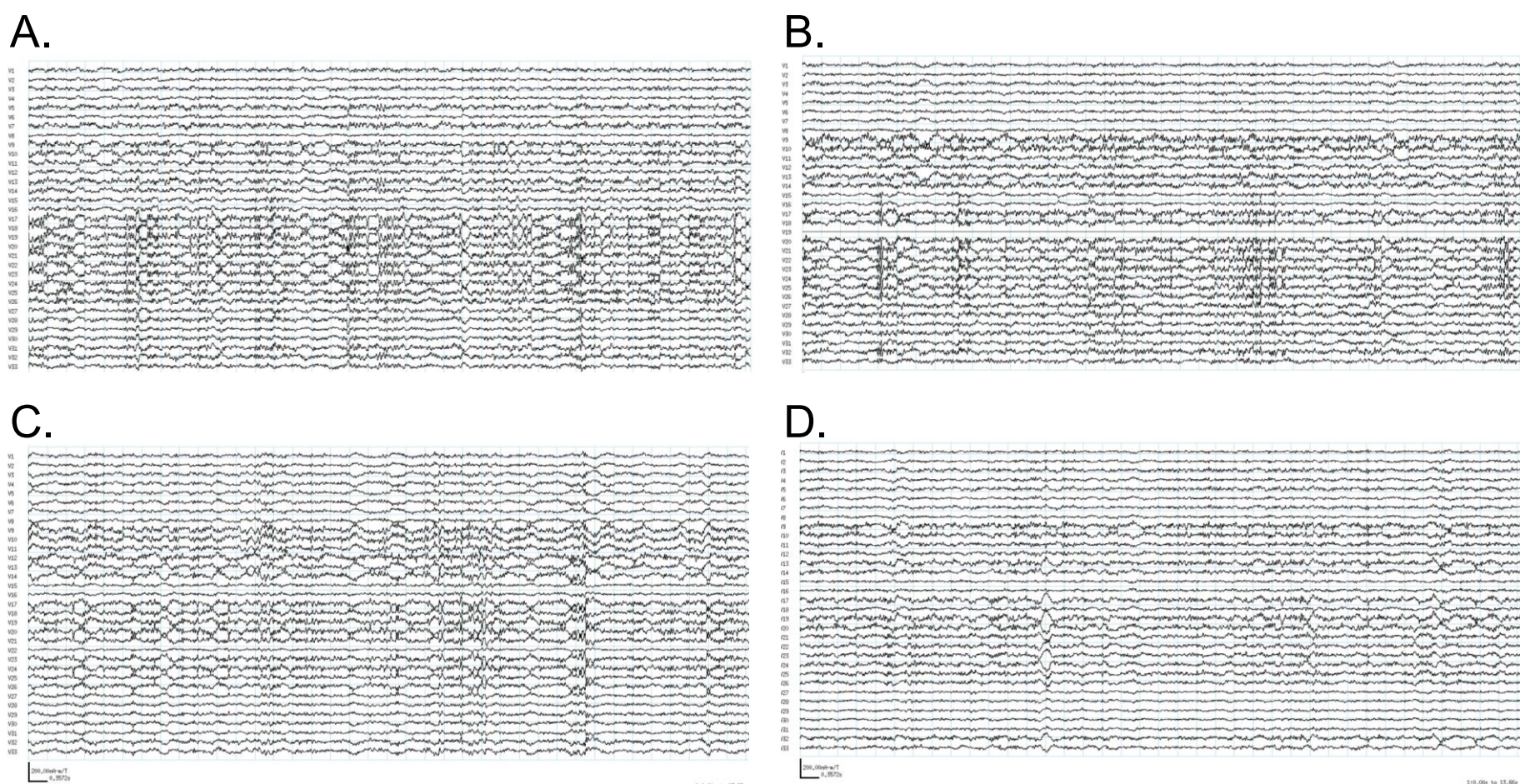


Figure 2. Virtual electrodes for one example subject per group. A) PsIV+Adj2, Group 4; B) PsIV+Adj1, Gr 3; C) PsIV, Gr 2; and D) control, Gr 1.

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Animal Care: Animal study protocol was reviewed and approved by the Wake Forest University Institutional Animal Care and Use Committee (IACUC). All experiments were conducted in compliance with the Animal Welfare Act and in accordance with the principles set forth in the *Guide for the Care and Use of Laboratory Animals*.

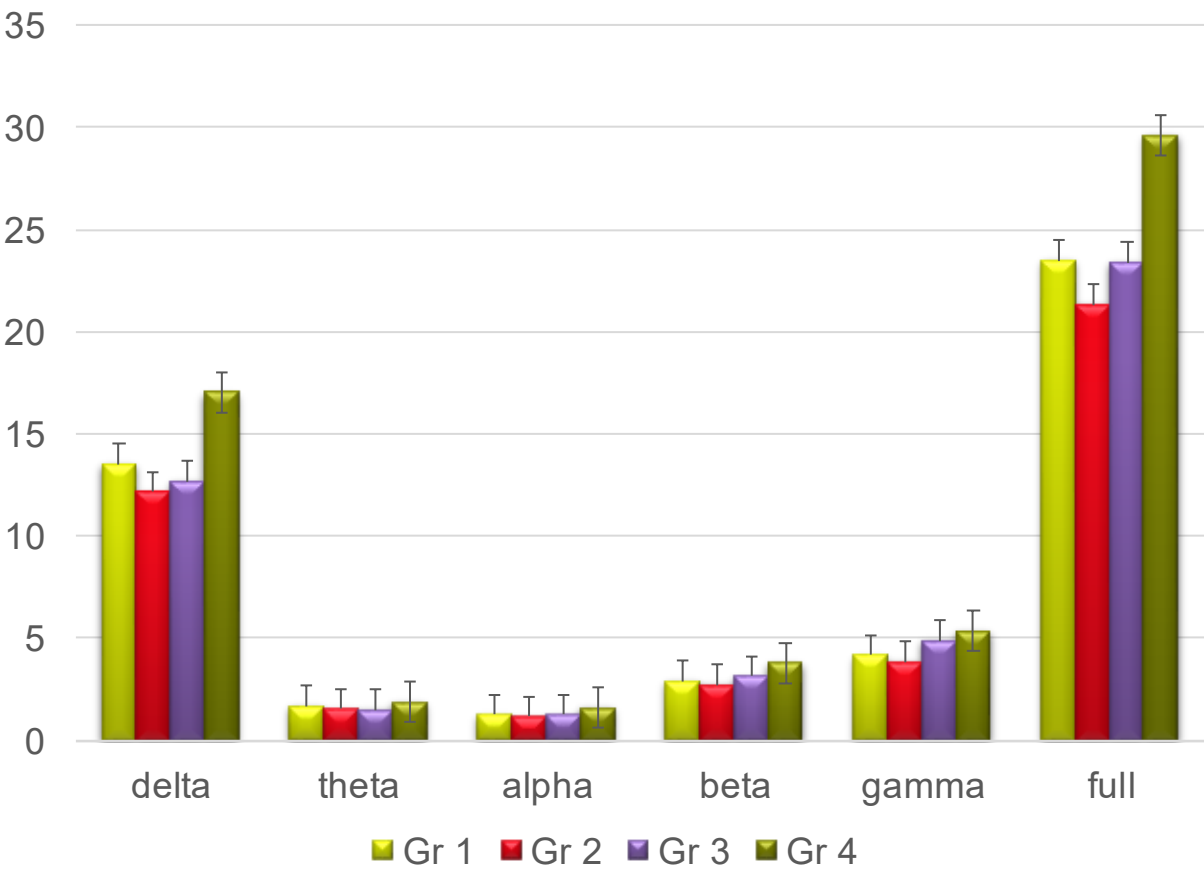


Figure 3. Estimated marginal means for spectral power per frequency band, pooled across ROIs. The y-axis is in units of $10^{-17} T^2$.

Comparison	MeanDiff	SE	df	Sum of Sq	F	Pr(>F)
1-2	2.1814	0.3	1	4606	39.3592	3.62E-10
1-3	0.1251	0.3	1	15	0.1295	0.7189
1-4	-6.105	0.3	1	36078	308.2848	< 2.2e-16
2-3	-2.0562	0.4	1	3837	32.7872	1.05E-08
2-4	-8.2864	0.4	1	62313	532.4545	< 2.2e-16
3-4	-6.2301	0.3	1	38426	328.3491	< 2.2e-16

Table 1. Simple effects comparisons between groups for the full bandwidth, pooled across ROIs. The main effect for group was significant ($p < 2.2 \times 10^{-16}$).

CONCLUSIONS

- Band power demonstrated substantial preservation of neural activity across multiple brain regions in subjects vaccinated with PsIV and proprietary adjuvant-2 compared to all other groups following viral challenge. These findings were consistent with the immunology results.
- These results establish MEG as a powerful tool for detecting subtle yet significant changes in brain function that may be overlooked by other imaging modalities and highlight vaccination's role in mitigating neurological outcomes.
- This study advances our understanding of vaccine-induced neuroprotection and demonstrates MEG's value for monitoring brain function in the context of viral infections.