

A vagal pathway from fMRI Neurofeedback-induced reward activity to peripheral immunity

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Introduction

The brain's reward system has been linked to peripheral immune function in humans. We previously demonstrated that fMRI-neurofeedback-driven upregulation of the ventral tegmental area (VTA) – a key dopaminergic node of the reward system – is followed by a stronger antibody response to Hepatitis B Virus (HBV) vaccination, suggesting that volitional engagement of the reward system can modulate peripheral immunity (Lubianiker, Koren et al. 2026). Work in mice has established a causal reward-to-immune pathway mediated by the autonomic nervous system (ANS): stimulation of VTA dopaminergic neurons enhances both innate antibacterial and anti-tumor adaptive immunity, effects that are abolished by peripheral sympathetic ANS ablation. A complementary line of work shows that hypothalamic activity, which has bidirectional functional links with mesolimbic reward circuitry, signals to peripheral lymphoid tissue via the splenic nerve and increases antibody production after vaccination. Together, this work outlines a plausible process model: reward-circuit engagement → autonomic outflow → peripheral immune activity. Yet, how this pathway operates in humans, and through which neural and physiological signals it is carried, remains unknown. We therefore tested whether autonomic activity, indexed by cardiac vagal tone, mediates the previously reported association between neurofeedback-induced VTA upregulation and antibody response to HBV vaccination in humans.

Methods

In a double-blind RCT in which participants completed four fMRI-neurofeedback training sessions upregulating the mesolimbic system or control networks, followed by HBV vaccination. We tested whether cardiac vagal tone mediates the previously reported association between VTA upregulation and post-vaccination antibody response. VTA upregulation was quantified as the change in VTA percent signal BOLD change during “upregulate>rest” contrasts across neurofeedback runs. Parasympathetic vagal tone was indexed as the root mean square of successive differences (RMSSD) of inter-beat intervals, computed from an electrocardiogram acquired during the final neurofeedback session (session 4), immediately prior to vaccination. The immune outcome was the change in HBV antibody titer measured two weeks to one month post-vaccination.

Of the sixty healthy participants included in the original correlational analysis, Forty-nine participants had complete data on all three measures and were entered into a mediation analysis testing whether session-4 RMSSD accounted for the VTA–antibody association. To establish temporal specificity, we repeated the mediation using RMSSD from the first neurofeedback session. We further tested whether mean heart rate, a general cardiovascular metric, accounted for the mediation when entered as a covariate. Finally, we used a GLM with subject-wise z-scored session-4 RMSSD as a covariate on regulate>rest BOLD activity to test whether the lateral

hypothalamus (LH) and paraventricular nucleus (PVN), both implicated in mediating brain-immune connections, were coactivated during neurofeedback regulation prior to vaccination.

Results

Mediation analysis revealed a significant indirect effect of VTA upregulation on HBV antibody response through session-4 RMSSD ($\beta=3.294$, $SE=1.37$, 95% $CI=[1.27, 7.074]$, $p=0.016$), alongside a non-significant direct effect once RMSSD was included as a mediator ($\beta=4.025$, $SE=4.147$, 95% $CI=[-4.34, 12.40]$, $p=0.337$), indicating full mediation. This mediation was temporally specific: RMSSD measured at the first neurofeedback session did not mediate the VTA–antibody association. The session-4 mediation effect remained significant after controlling for mean heart rate ($\beta=3.136$, $SE=1.681$, 95% $CI=[0.887, 7.783]$, $p=0.032$), indicating that the effect reflects vagal control specifically rather than general cardiovascular activity. ROI analyses showed that regulate>rest activity covaried positively with RMSSD in bilateral PVN ($r=0.305$, $p=0.032$) and right LH ($r=0.346$, $p=0.016$), while the left LH did not survive correction.

Conclusions

These results identify parasympathetic vagal tone as a full mediator of the association between reward-related VTA upregulation and antibody response to vaccination in humans, with hypothalamic nuclei (PVN, right LH) emerging as candidate central hubs linking reward engagement to autonomic and immune outcomes. This non-invasive evidence in humans complements prior rodent work showing that VTA-driven immune effects depend on an intact ANS. Notably, those studies implicated peripheral sympathetic (splenic) pathways, whereas our findings point to a more general autonomic vagal route – a discrepancy that merits further investigation and may reflect species or measurement differences. Future work using vagal neuromodulation, stimulation or pharmacological manipulations could test this pathway causally. Altogether, these findings offer a candidate neuroimmune pathway linking reward circuitry to peripheral immune function via autonomic, vagally-mediated signaling, motivating further research into neurofeedback- and vagal-based interventions for immune-related conditions.

References:

Lubianiker, N., Koren, T., Djerasi, M. *et al.* Upregulation of reward mesolimbic activity and immune response to vaccination: a randomized controlled trial. *Nat Med* **32**, 572–581 (2026). <https://doi.org/10.1038/s41591-025-04140-5>