nature medicine

Supplementary information

https://doi.org/10.1038/s41591-025-04140-5

Upregulation of reward mesolimbic activity and immune response to vaccination: a randomized controlled trial

In the format provided by the authors and unedited

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Figure S1

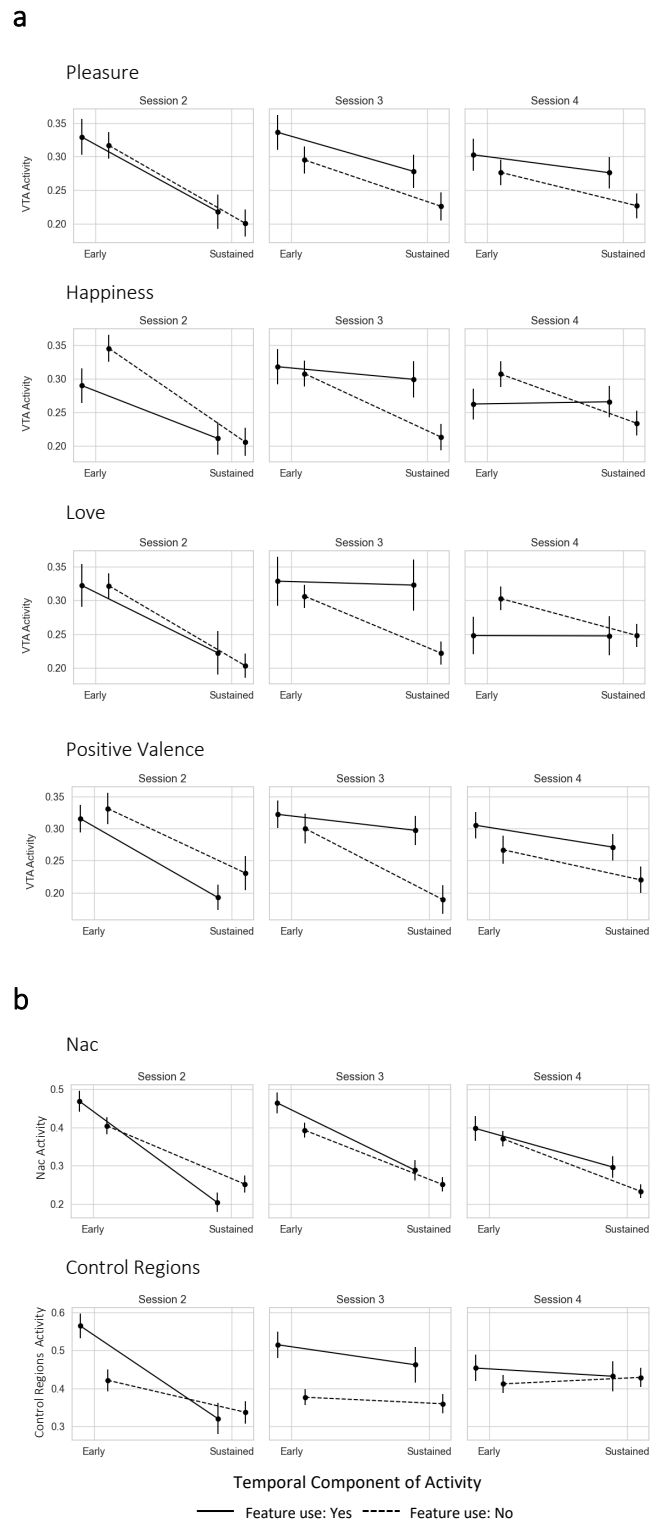

Figure S1: ROI activity and reward-related mental features use across sessions. a. VTA activity and reward-related features. Neural activity in the VTA (Mean±SEM) across sessions 2 to 4 for different within-trial temporal activity components (early: first quartile lasting 10 seconds; sustained: the remaining 30 seconds of a regulation epoch), in strategies with (solid lines) and without (dashed lines) four reward-related features:

'pleasure', 'happiness', 'love', and 'positive valence'. N=5626 trials. Effects were estimated using mixed linear effects regression analysis. Full results are reported in **Table S1**. **b. Positive expectation and Nac and control regions activity.** Positive expectation use (solid vs dahsed) and neural activity in the Nac (upper panels; N=5004 trials) and non-mesolimbic control regions (lower panels; N=2634 trials) across sessions and temporal activity components.. Results are reported in the main text, in **Table 2**.

Figure S2

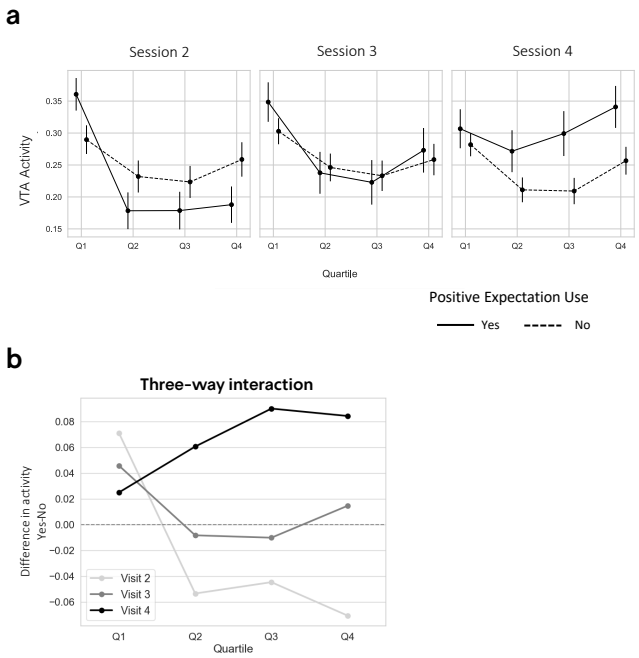

Figure S2: VTA activity and Positive expectation use across sessions and temporal quartiles. a. VTA activity across temporal quartiles of the regulation epoch and sessions, for strategies with (solid lines) and without (dashed lines) positive expectation. Results are reported in the supplementary information. b. added benefit of invoking positive expectations for VTA activity across sessions, depicting a three-way-interaction. N=5004 trials.

Associations between positive expectation, within-trial temporal components and NF regulation - complementary analyses

To ensure that our simplified modelling of within-trial temporal quartiles as early (Q1) vs sustained (Q2 to Q4) did not lead to misrepresentation of temporal dynamics, we ran a complementary mixed-linear effects regression analysis, similar to the one reported in the main text except for the within-trial time variable that contained four levels (Q1 to Q4) instead of two (Early/Sustained). This more elaborate model enables a fine-grained description of within-trial dynamics. Analysis revealed a significant main effect of positive expectation ($\beta = 0.112$, $p = .002$), indicating that at the onset of training (during session 2), trials involving positive expectation were associated with higher immediate (i.e., Q1) VTA upregulation. As for the more compact model reported in the main text, this effect was complemented by a significant negative interaction between positive expectation and Q1 vs Q3 ($\beta = -0.115$, , $p = .019$) and Q1 vs Q4 ($\beta = -0.142$, $p = .004$), suggesting that the immediate effect weakened or flipped towards the second half of the epoch (**Fig. S2a, left panel**). Moreover, a three-way interaction reflecting how the quartile-by-expectation relationship changes across sessions was found for session 2 vs 4, both from Q1 to Q3 ($\beta = 0.181$, $p = 0.01$) and to Q4 ($\beta = 0.201$, $p = 0.005$). These interactions replicate the learning effect captured by the compact model, and extend them by pointing to Q3 and Q4 (i.e. the second half of the epoch) as the time points that contribute to this effect: while at the beginning of training positive expectation shows added benefit only for transient activity that weakens quickly (**Fig. S2b, light grey line**), at the last session before vaccination this trend flips, with added benefit of positive expectation for sustained VTA activity (throughout the third and forth quartiles of the regulation epoch; **Fig. S2a, right panel, and Fig. S2b, black line**).

Lack of correlations between trait motivational measures and post-vaccination immune response

The VTA-Immune correlation could result from individual differences in motivational traits. Specifically, it could be that regardless of the temporal contingency between fMRI-NF training and the HBV vaccination, participants with strong neural and/or behavioural motivational tendencies would exhibit both higher reward-ML upregulation effects during fMRI-NF training, and an enhanced post-vaccination HBVab change compared with those with weak motivational tendencies.

To test this possibility, we examined whether post-vaccination HBVab change and reward-ML regulation effects were correlated with gold-standard metrics capturing individual variability in motivational traits.

During session 1, participants from all study groups performed the Effort Expenditure for Rewards Task (EEfRT) before and the Monetary Incentive Delay (MID) task during fMRI scanning. In addition, participants filled out three questionnaires capturing motivational tendencies: Tri-Personality Questionnaire (TPQ)[8], Neuroticism - Extraversion - Openness Five-Factor-Inventory (NEO-FFI)[9]n, and Sensitivity to Reward and Sensitivity to Punishment Questionnaire (SPSRQ)[10]. Individual neural measures of reward anticipation were extracted from the MID task from the Nac and the VTA via ROI analyses. For reward consumption, we extracted MID activation from the ventromedial prefrontal cortex (vmpfc) (see 'Online Methods'). In addition to group-level analysis of reward anticipation (reported in **Extended data Fig. 1**) we conducted a group-level GLM constructing a z-scored map for reward consumption. Analyses revealed a distinct network that has been previously associated with reward consumption during MID task[1,11], including the medial prefrontal cortex, bilateral Nac and ventral pallidum, as well as visual regions. Then, we constructed a spherical ROI with a 5 mm radius around the peak activation of the medial pfc cluster (MNI coordinates: X=-4, Y=59, Z=-1), and conducted an ROI analysis to extract individual neural responses to reward consumption.

We calculated Pearson's correlations between neural responses to reward consumption and anticipation, with post-vaccination HBVab change (N=81 from all groups) and with individual VTA upregulation effects (N=67 from NF groups). Analyses did not reveal significant correlations between reward anticipation and consumption and HBVab change (Nac reward anticipation and HBVab change: r=0.13, p=0.268; VTA reward anticipation and HBVab change: r=0.08, p=0.472; vmpfc reward consumption and HBVab change: r = 0.06, p=0.582) nor between VTA reward anticipation and VTA upregulation effects (r=0.175, p=0.155).

Next, we examined whether effort expenditure as measured in EEfRT relates to HBVab change or VTA upregulation effects. The individual probability to select a hard task across varying levels of reward was extracted per subject from EEfRT performance (see 'Online Methods'). It was correlated with VTA regulation and peripheral immune functions. Similar to the MID metrics, we did not find significant correlations between effort expenditure levels and HBV change (r=-0.05, p=0.661) or VTA upregulation (r=-0.05, p=0.680).

Moreover, to capture participants' behavioural motivational tendencies, we conducted a 2-step K-means cluster analysis, conducted on 70 subjects with qualified questionnaire data (see 'Online Methods'). This analysis revealed two clusters of participants that significantly differed in various subscales relating to reward and

motivation as quantified by TPQ, SPSRQ and NEO-FFI questionnaires, with 43 subjects classified as exhibiting approach tendencies, and 27 subjects classified as exhibiting avoidance tendencies. Following classification, we first sought to examine the convergent validity of the clustering procedure. In a previous work that used a similar approach, clusters were associated with differing Nac responses to reward anticipation in a motivational task[12]. Similarly, we examined whether clusters differed in Nac response to reward anticipation during MID task. Independent t-test revealed a marginal difference between clusters ($t(66) = 1.56$, $p(\text{one-sided})=0.058$).

To assess whether approachers exhibited stronger HBVab change or regulation effects compared to avoiders, we conducted two independent t-tests between groups with post-vaccination HBVab change, and VTA upregulation effects, as dependent variables. Analyses did not find significant differences between groups (HBVab change: $t(66)=-0.38$, $p=0.701$; VTA upregulation effects: $t(55)=0.47$, $p=0.637$).

Finally, we used our mental strategies data to assess whether the general propensity to invoke positive expectations (which could reflect an a-priori psychological positivity trait) was associated with the immune outcome. For each individual, we calculated the mean frequency of positive expectation use across all sessions, and correlated it with HBV change. However, these measures were not significantly correlated ($r=0.1$, $p=0.452$).

Overall, these analyses show that neither the specific VTA upregulation effect, nor the post-vaccination HBVab change, and thus the correlation between them, can be attributed to differences in neurobehavioural motivational tendencies and capacities as measured by these designated tasks and questionnaires.

Associations between the Immune response, VTA functional connectivity and Insula activity during the neurofeedback task

To examine whether additional regions were involved in or confounded the link between VTA activity and the immune response, we conducted two analyses. First, we inspected whether VTA connectivity patterns during NF regulation were connected to the immune response. Specifically, the VTA has neuroanatomical connections to regions outside the mesolimbic tract that may participate in brain-immune links, such as connections between VTA and the amygdala[13,14] and the mPFC[15,16]. Accordingly, longitudinal changes in VTA functional connectivity with pre-defined ROIs, including the bilateral Nac, right and left amygdala, and left vmpfc were assessed for the 'Regulate>Rest' contrast (see 'online methods' section for ROIs definitions and

additional details). As for the brain-immune analysis, data from both groups were analyzed together. Correlational analyses were conducted to examine the relationship between changes in VTA functional connectivity (estimated similarly to NF regulation effects, i.e., via linear slopes across runs) and post-vaccination HBV antibody levels. However, none of the VTA functional connectivity measures were significantly correlated with HBVab post-vaccination change (VTA to Nac: r = -0.2, p = 0.126; VTA to right amygdala: r = -0.13, p = 0.34; VTA to left amygdala: r = 0.03, p = 0.82; VTA to left vmpfc: r = -0.05, p = 0.705).

Second, previous studies implicated the Insula in monitoring immune processes[17], as well as in causally triggering a peripheral inflammatory response in mice[18]. Hence, we inspected whether changes in Insula activity during NF training were correlated with the immune response. We defined a 5 mm sphere ROI around right Insula coordinates taken from a meta-analysis of neuroanatomical correlates of peripheral immunity[19] and conducted an ROI analysis using similar methods to those applied on the mesolimbic ROIs (See 'fMRI-NF ROI analysis: characterization of regulation effects' in online methods section). Specifically, we quantified the change in BOLD psc during 'Regulate>Rest' contrast across runs by calculating individuals' linear slopes, and correlated them with the immune outcome scores (change in HBV antibody levels). However, the correlation was not significant (r = 0.07, p = n.s.).

fMRI-Neurofeedback training Instructions

Before each fMRI-NF training session, participants learned about (or were remined of) the goals for each screen (see **Fig. 1b**, main text), and then read the following instructions:

"*In order to modulate (increase or decrease) brain activity during neurofeedback practice, a wide variety of strategies can be used. Each brain region is activated during different mental processes: for example, one region may be active when we sense (see or hear). Another region, when we imagine ourselves or others in various types of situations. An additional region will be active when we anticipate something, or when we experience some intense emotion. And yet another region will be active when we concentrate on a complex mental task. Therefore, different mental strategies are appropriate for each region, related to the role that the region plays in our brain. Furthermore, Each participant can find their own suitable strategies.*

During neurofeedback training, you are asked to find the most effective strategy/strategies for increasing brain activity in your target region.

General Guidelines for Finding a Strategy:

Continuous Application of a Strategy: *A successful strategy is one that can be* ***consistently applied*** *throughout the entire activation screen, for about 40 seconds. A strategy that you cannot maintain this way may not be successful for you.*

Specificity and Vividness: *Use your imagination to create a* ***rich and dynamic image*** *suitable for the mental state you have chosen. Alternatively, focus on a specific feature of the experience that can optimally* ***induce the state of mind*** *you wish to maintain.*

Relaxation During the Rest Screen: *Adhering to the instructions for the rest screen is* ***no less important*** *than executing the strategy during the activation screen. A successful strategy will be useless if it "spills over" into the 'Rest' screen. Note that even thoughts during about strategies in general, about success or failure, and so on, may interfere with the measurement of activity during the rest period.*

Script for communicating with Participants Between Neurofeedback Runs:

Between NF runs, the researcher instructed the participants with the following script:

Sustained Activation: *"Were you able to execute the strategies for the entire duration of the activation screen?"*

Specificity and Vividness: *"Were the strategies vivid and rich enough, or were you able to accurately achieve the mental state you were aiming for?"*

Rest Screen: *"Were you able to follow the instructions during the rest screens (not to apply or consider strategies and not to think about the scores; to focus on the interface)?"*

> **For experimenter:** *If the participant is bothered by a lack of success, or is excited and unable to follow the instructions for the rest screen, try to reassure them by explaining that the task is challenging and it's okay if they are not succeeding, and that during the rest screen they must disconnect as much as possible from preoccupation with success and with the mental strategies.*

Strategy Switching: *If the scores were not successful – did the participant switch strategies after two or three cycles (as opposed to switching every cycle, or sticking to the same strategy without switching despite low scores)?*

Readiness for the Next Run: *Based on the feedback they have received so far, does the participant know how they wish to proceed (stick with a successful strategy / switch to different strategies)? If they plan to switch, instruct the participant to take half a minute to a minute to formulate new optional strategies for themselves.*

Update the Choice screen for the next run.

Immunological and fMRI-NF pilot studies

Between January and December 2019 (prior to the initiation of the main trial), we conducted pilot studies to characterize the nature of the immune response to HBV vaccination in our target population, and to test the efficacy of our NF protocol in yielding robust reward-ML activations.

Thirteen participants were recruited for the pilot studies. To characterize the immunological response to HBV vaccination regardless of NF training, three participants underwent blood tests and were vaccinated in similar time intervals to those of the no-NF study group in our main trial (two baseline measurements before vaccination, and three blood tests collected three, fourteen, and twenty-eight days following vaccination). Four additional participants underwent reward-ML fMRI-NF training, HBV vaccination, and immunological assessments to compare the former effects with the downstream immunological effects of reward-ML NF. Group allocation was not randomized, blinded, or pre-registered prospectively like the main trial. In addition to the four reward-ML NF participants, six additional subjects participated in reward-ML fMRI-NF training sessions without HBV vaccination and immunological assessments, resulting in a total of 10 participants for the estimation of reward-ML activations during NF.

Immunological analyses (**Fig. S3a**) demonstrated our ability to detect the increase in HBV antibody levels 14 and 28 days following vaccination (pre and post-vaccination measures were calculated like in the main trial). We also detected a large variability in the post-vaccination response, which supported our decision to collect a relatively large number of participants per group to reveal potential immunological effects. Critically, we found that participants who were vaccinated against HBV approximately 10 years prior to their recruitment can show high baseline HBV antibody levels, which led us to apply a more strict exclusion criterion than the pre-registered one with respect to previous vaccination history, i.e., to exclude subjects that received any prior HBV vaccination other than during infancy (which applied to most of our cohort; described in the main text).

Our fMRI analysis (**Fig. S3b**) validated our four-session NF training length, demonstrating increasingly better regulation effects that peaked at the fourth NF session (In **Fig. S3b** we plot the "Rest" and "Regulate" conditions separately to provide more information about the nature of the regulation effects, which are proportional to the differences in reward-ML activity (y axis) between the two conditions.

Figure S3

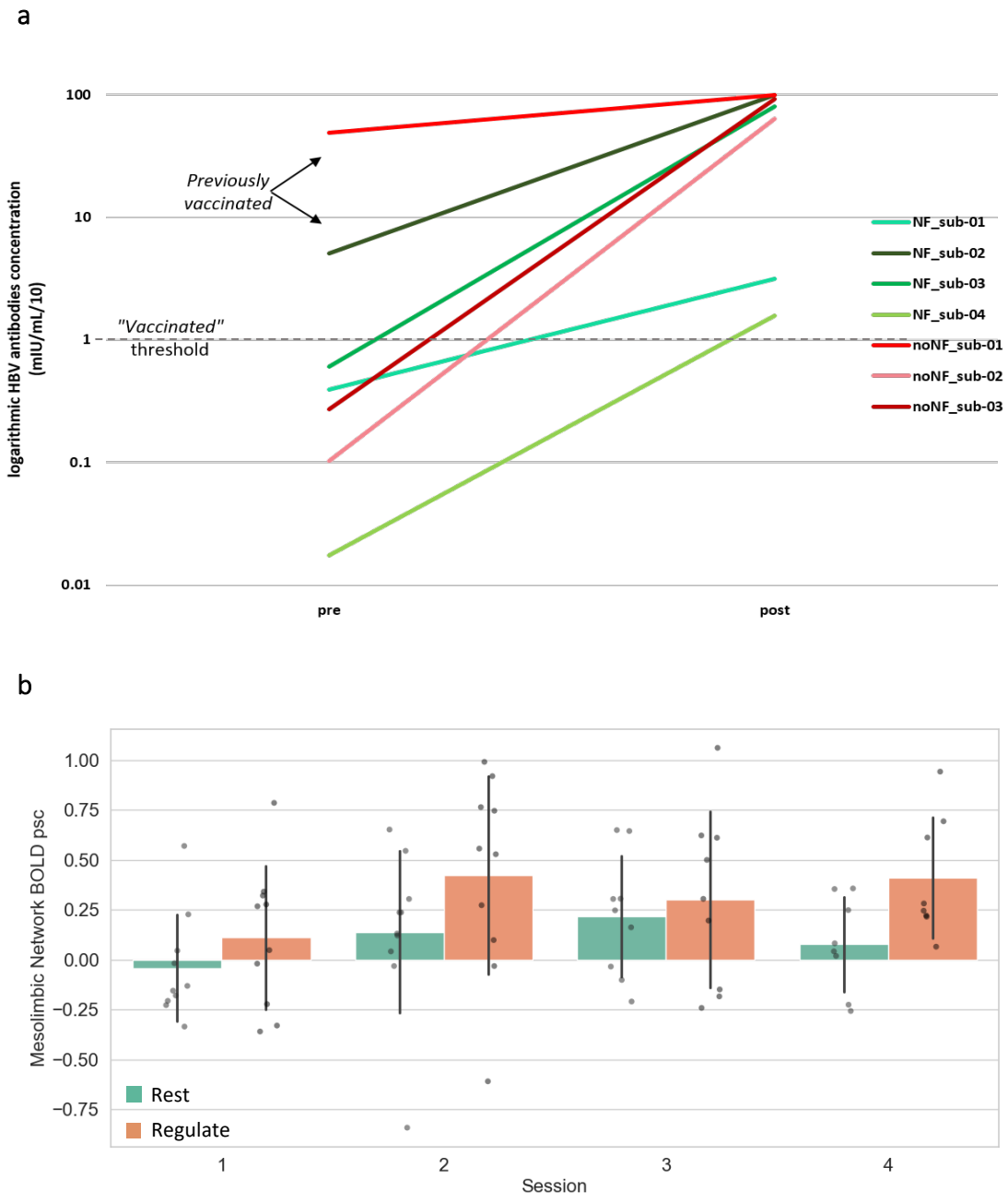

Figure S3: Pilot Study Results. a. Immunological assessments. Seven pilot subjects (four performing reward-ML NF (green shades) and three not performing NF (red shades)) received HBV vaccine and underwent immunological assessments according to the protocol described in the main text for reward-ML NF groups and no-NF group, respectively. Log-transformed HBVab levels are shown on the y-axis for pre (mean session 1 and 4) and post (mean session 5 and 6). Analysis revealed a large variability between subjects and previously vaccinated individuals, characteristics that were used to determine the experimental protocol (described in the main text). **b. reward-ML activations during fMRI-NF training.** Ten pilot subjects performed 4 fMRI-NF training sessions in line with the experimental protocol described in the main text (**Figure 1a and b**). Our goal was to determine the ideal training length being a substantial difference between 'Rest' and 'Regulate' conditions. Two-tailed paired t-tests per session revealed a significant difference between conditions for session 2 (t=2.55, p=0.031, N=10) and session 4 (t=2.625, p=0.034, N=8; 2 pilot subjects did not finish the full 4 session training). Based on these results and other considerations, a four-session training length was determined.

Table S1

Effect	Estimate	2.5 CI	97.5 CI	SE	DF	T-stat	P-val	Sig
VTA activity and Pleasure								
Intercept	**0.288**	**0.235**	**0.341**	**0.027**	**163.749**	**10.612**	**0.0**	***
Session (session 3)	0.009	-0.028	0.047	0.019	5583.292	0.493	0.622	
Session (Session 4)	-0.006	-0.044	0.033	0.02	5590.718	-0.296	0.767	
Activity Component (Early/Sustained)	**-0.082**	**-0.119**	**-0.045**	**0.019**	**5547.254**	**-4.333**	**0.0**	***
Positive Expectation	0.02	-0.023	0.064	0.022	5612.942	0.91	0.363	
Cycle number	**-0.004**	**-0.007**	**-0.002**	**0.001**	**5562.584**	**-3.148**	**0.002**	**
Session (session 3) : Activity Component	0.033	-0.019	0.085	0.027	5547.254	1.248	0.212	
Session (session 4) : Activity Component	0.047	-0.006	0.1	0.027	5547.254	1.731	0.083	
Session (session 3) : Positive Expectation	0.018	-0.042	0.078	0.031	5601.744	0.588	0.557	
Session (session 4) : Positive Expectation	0.012	-0.049	0.072	0.031	5607.424	0.373	0.709	
Activity Component : Positive Expectation	0.003	-0.055	0.061	0.03	5547.254	0.111	0.912	
Session (session 3) : Activity Component: Positive Expectation	0.004	-0.077	0.086	0.042	5547.254	0.102	0.919	
Session (session 4) : Activity Component: Positive Expectation	0.013	-0.069	0.095	0.042	5547.254	0.308	0.758	
VTA activity and Love								
Intercept	**0.287**	**0.236**	**0.339**	**0.026**	**143.351**	**10.886**	**0.0**	***
Session (session 3)	0.014	-0.02	0.047	0.017	5574.47	0.793	0.428	
Session (Session 4)	-0.002	-0.036	0.032	0.017	5583.065	-0.116	0.907	
Activity Component (Early/Sustained)	**-0.084**	**-0.117**	**-0.051**	**0.017**	**5547.133**	**-4.972**	**0.0**	***
Positive Expectation	0.039	-0.01	0.088	0.025	5612.742	1.563	0.118	
Cycle number	**-0.004**	**-0.007**	**-0.002**	**0.001**	**5564.722**	**-3.281**	**0.001**	**
Session (session 3) : Activity Component	0.024	-0.022	0.071	0.024	5547.133	1.018	0.309	
Session (session 4) : Activity Component	0.045	-0.002	0.092	0.024	5547.133	1.87	0.062	
Session (session 3) : Positive Expectation	0.013	-0.054	0.081	0.034	5596.315	0.391	0.696	

Session (session 4) : Positive Expectation	0.001	-0.066	0.068	0.034	5598.199	0.035	0.972	
Activity Component : Positive Expectation	0.013	-0.052	0.078	0.033	5547.133	0.394	0.694	
Session (session 3) : Activity Component: Positive Expectation	0.043	-0.049	0.134	0.047	5547.133	0.907	0.364	
Session (session 4) : Activity Component: Positive Expectation	0.025	-0.066	0.117	0.047	5547.133	0.544	0.587	
VTA activity and Happiness								
Intercept	**0.303**	**0.25**	**0.356**	**0.027**	**161.506**	**11.172**	**0.0**	***
Session (session 3)	-0.012	-0.049	0.026	0.019	5578.546	-0.609	0.543	
Session (Session 4)	-0.013	-0.052	0.026	0.02	5595.596	-0.666	0.506	
Activity Component (Early/Sustained)	**-0.099**	**-0.137**	**-0.061**	**0.019**	**5547.214**	**-5.147**	**0.0**	***
Positive Expectation	-0.017	-0.06	0.026	0.022	5612.939	-0.79	0.43	
Cycle number	**-0.004**	**-0.007**	**-0.002**	**0.001**	**5566.516**	**-3.11**	**0.002**	**
Session (session 3) : Activity Component	0.032	-0.02	0.084	0.027	5547.214	1.197	0.231	
Session (session 4) : Activity Component	0.047	-0.007	0.101	0.027	5547.214	1.712	0.087	
Session (session 3) : Positive Expectation	**0.071**	**0.012**	**0.131**	**0.03**	**5596.693**	**2.345**	**0.019**	*
Session (session 4) : Positive Expectation	0.029	-0.031	0.089	0.031	5602.326	0.947	0.344	
Activity Component : Positive Expectation	0.043	-0.015	0.101	0.029	5547.214	1.46	0.144	
Session (session 3) : Activity Component: Positive Expectation	0.011	-0.071	0.092	0.042	5547.214	0.256	0.798	
Session (session 4) : Quartile : Positive Expectation	0.011	-0.07	0.093	0.042	5547.214	0.275	0.783	
VTA activity and Positive Valence								
Intercept	**0.295**	**0.239**	**0.352**	**0.029**	**202.196**	**10.252**	**0.0**	***
Session (session 3)	-0.018	-0.062	0.027	0.023	5583.7	-0.786	0.432	
Session (Session 4)	-0.036	-0.081	0.008	0.023	5586.236	-1.596	0.111	
Activity Component (Early/Sustained)	**-0.071**	**-0.116**	**-0.026**	**0.023**	**5547.178**	**-3.089**	**0.002**	**
Positive Expectation	0.005	-0.038	0.048	0.022	5607.198	0.219	0.827	
Cycle number	**-0.004**	**-0.007**	**-0.002**	**0.001**	**5563.853**	**-3.363**	**0.001**	***
Session (session 3) : Activity Component	-0.007	-0.068	0.054	0.031	5547.178	-0.232	0.816	
Session (session 4) : Activity Component	0.038	-0.024	0.1	0.032	5547.178	1.199	0.231	
Session (session 3) : Positive Expectation	**0.065**	**0.005**	**0.124**	**0.03**	**5596.075**	**2.137**	**0.033**	*
Session (session 4) : Positive Expectation	**0.066**	**0.007**	**0.126**	**0.031**	**5596.024**	**2.174**	**0.03**	*
Activity Component : Positive Expectation	-0.016	-0.074	0.042	0.03	5547.178	-0.536	0.592	
Session (session 3) : Activity Component: Positive Expectation	0.077	-0.005	0.158	0.041	5547.178	1.85	0.064	
Session (session 4) : Activity Component: Positive Expectation	0.025	-0.057	0.107	0.042	5547.178	0.597	0.551	

Table S1: Results of mixed linear effects regression analysis assessing how neural activity in the VTA during NF is associated with within-trial neural dynamics, training sessions, and four reward and positive affect features ('Happiness', 'Love', 'Pleasure' and 'Positive Valence'). N=5626 trials. The effect of each feature on VTA activity was tested in a separate model. Significant effects are bolded.

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