Blink-related arousal network surges are shaped by cortical vigilance states

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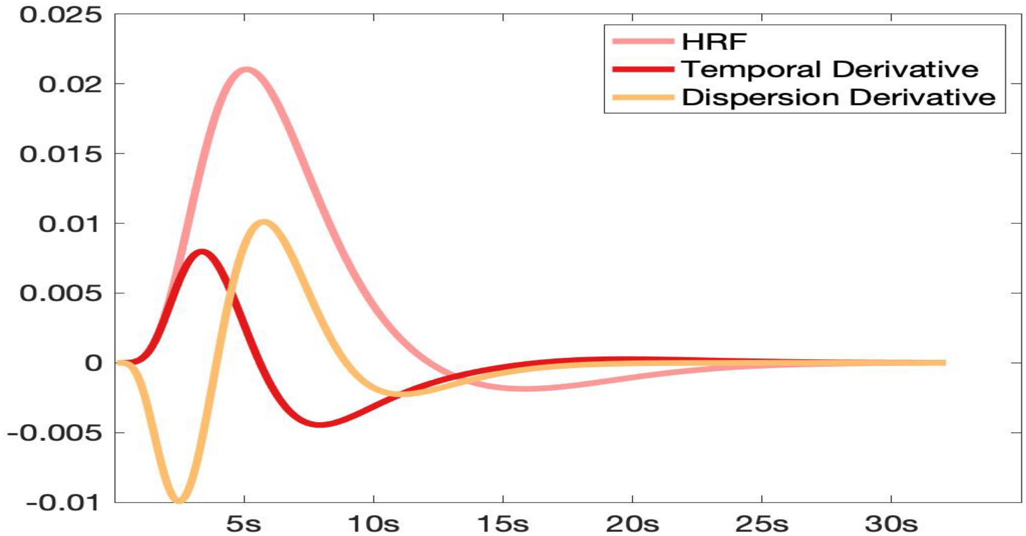
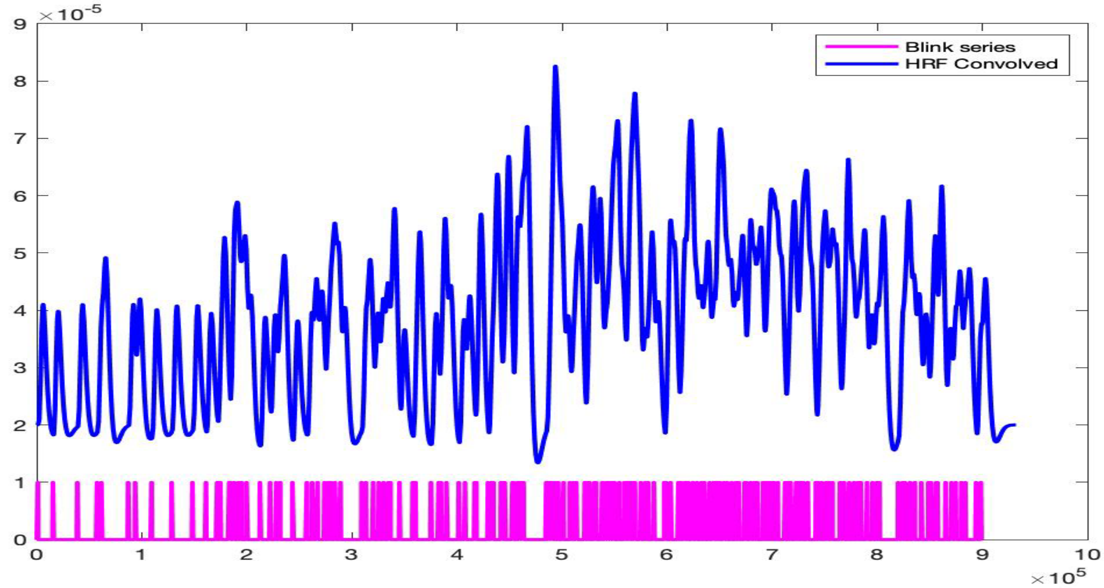
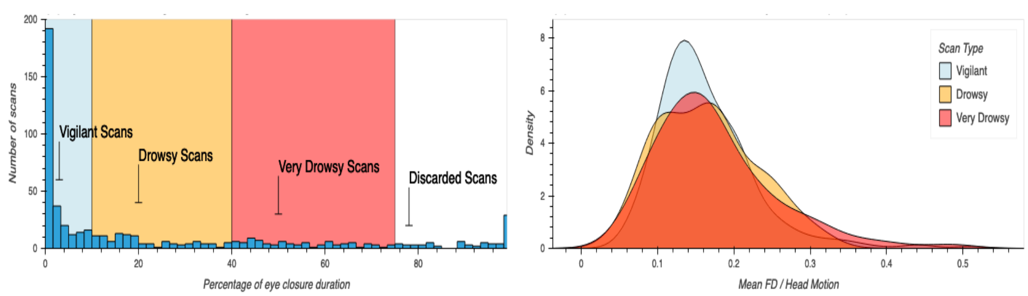
Supplementary Material



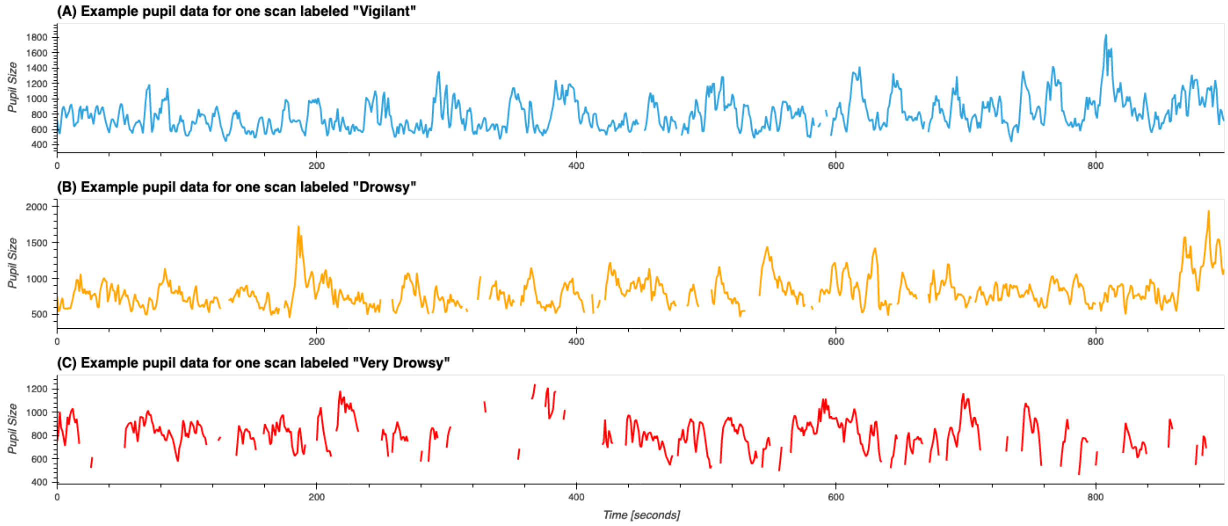
Sup. Fig. 1. Hemodynamic Response Function (HRF) model. Canonical HRF (pink line) has been used in the study.



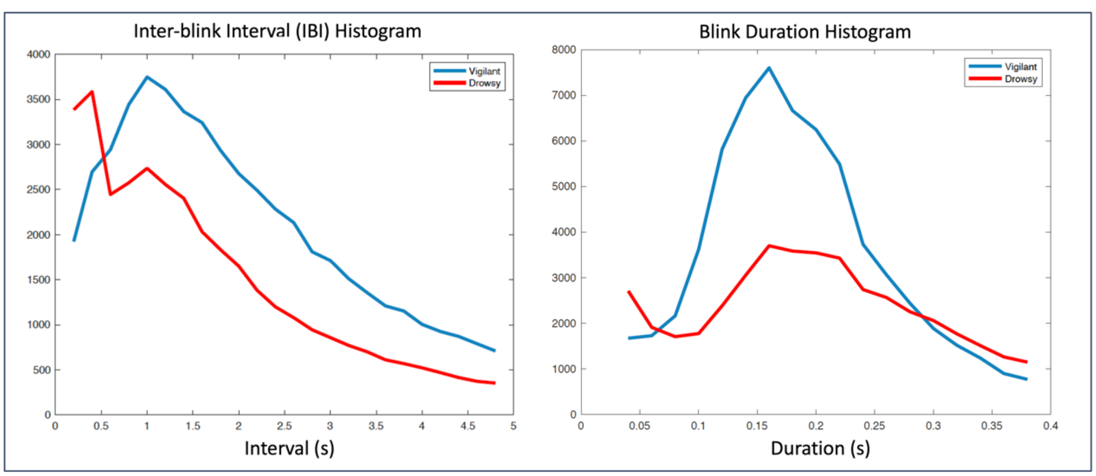
Sup. Fig. 2. Example of the convolution of the blink time series with the HRF canonical function.



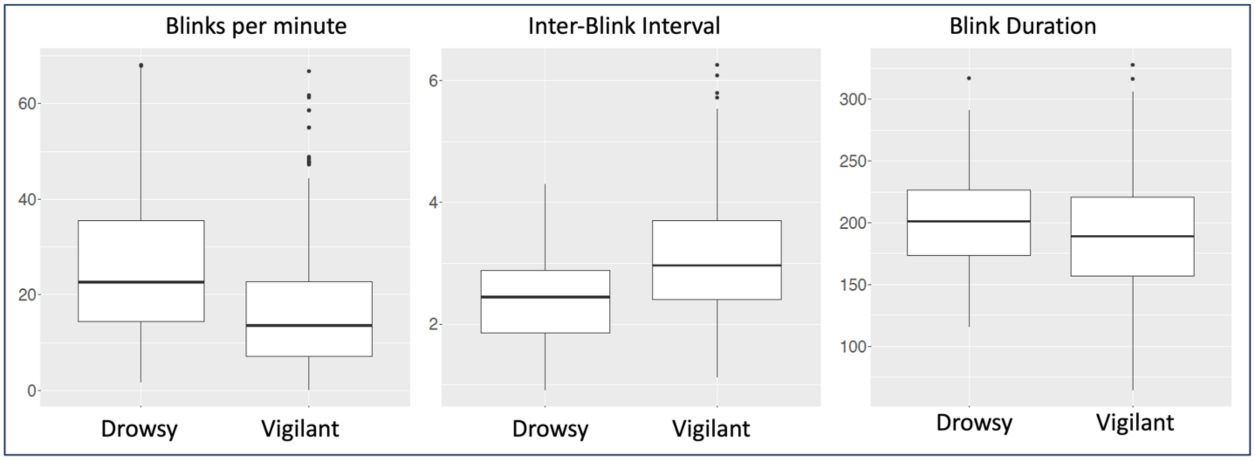
Sup. Fig. 3. Histogram of the runs with different vigilance states (left) and framewise displacement of the fMRI runs classified per vigilance state (right).



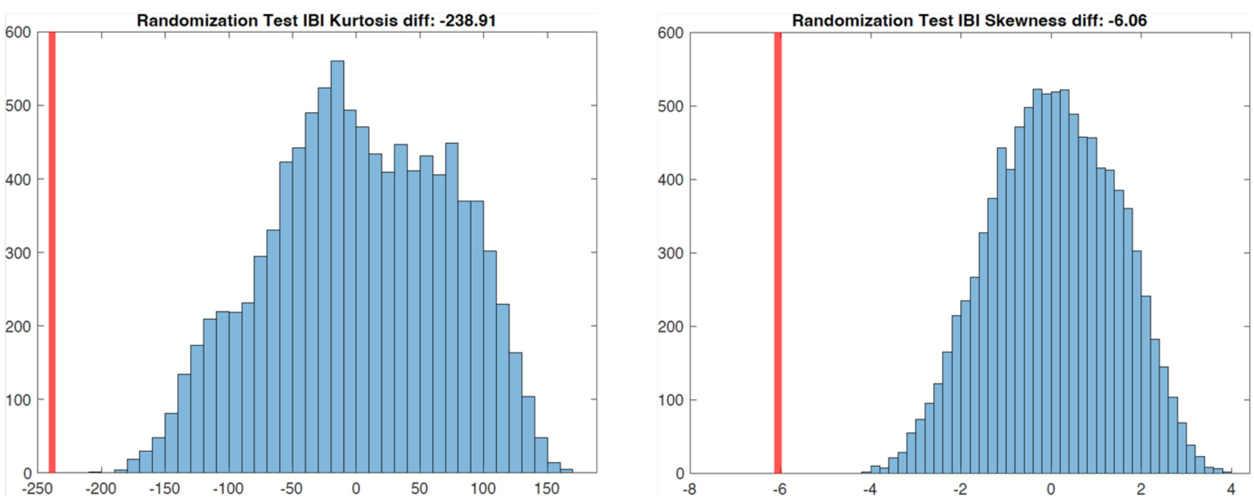
Sup. Fig. 4. Eye-closure probability in time per each vigilance state.



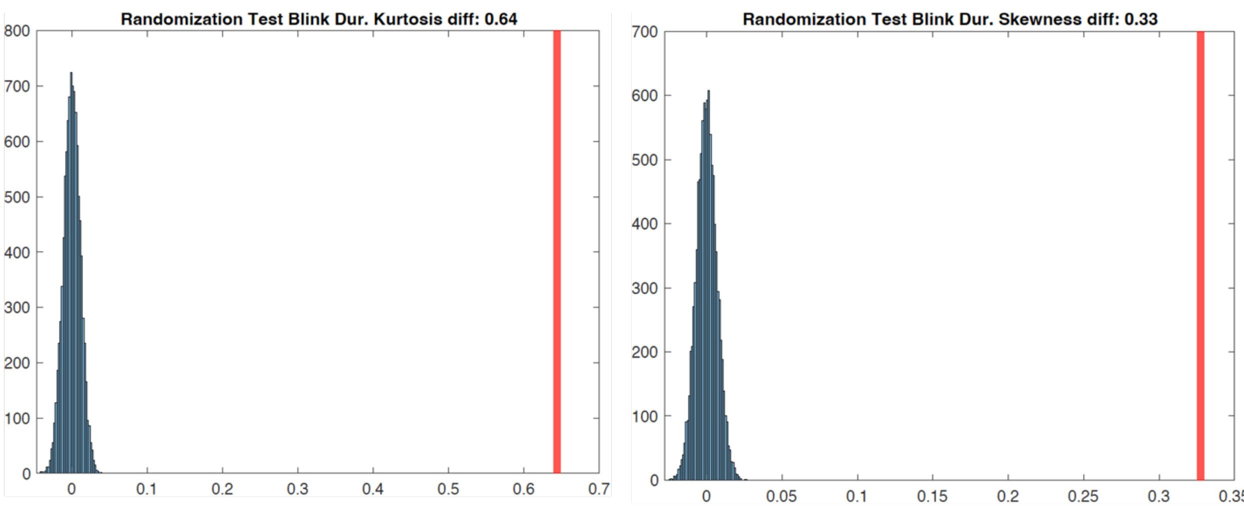
Sup. Fig. 5. Inter-blink interval (IBI) and blink duration histograms shown per vigilance state across all the blinks used in the experiment. Y-axis shows the counts, x-axis IBI and blink durations in seconds.



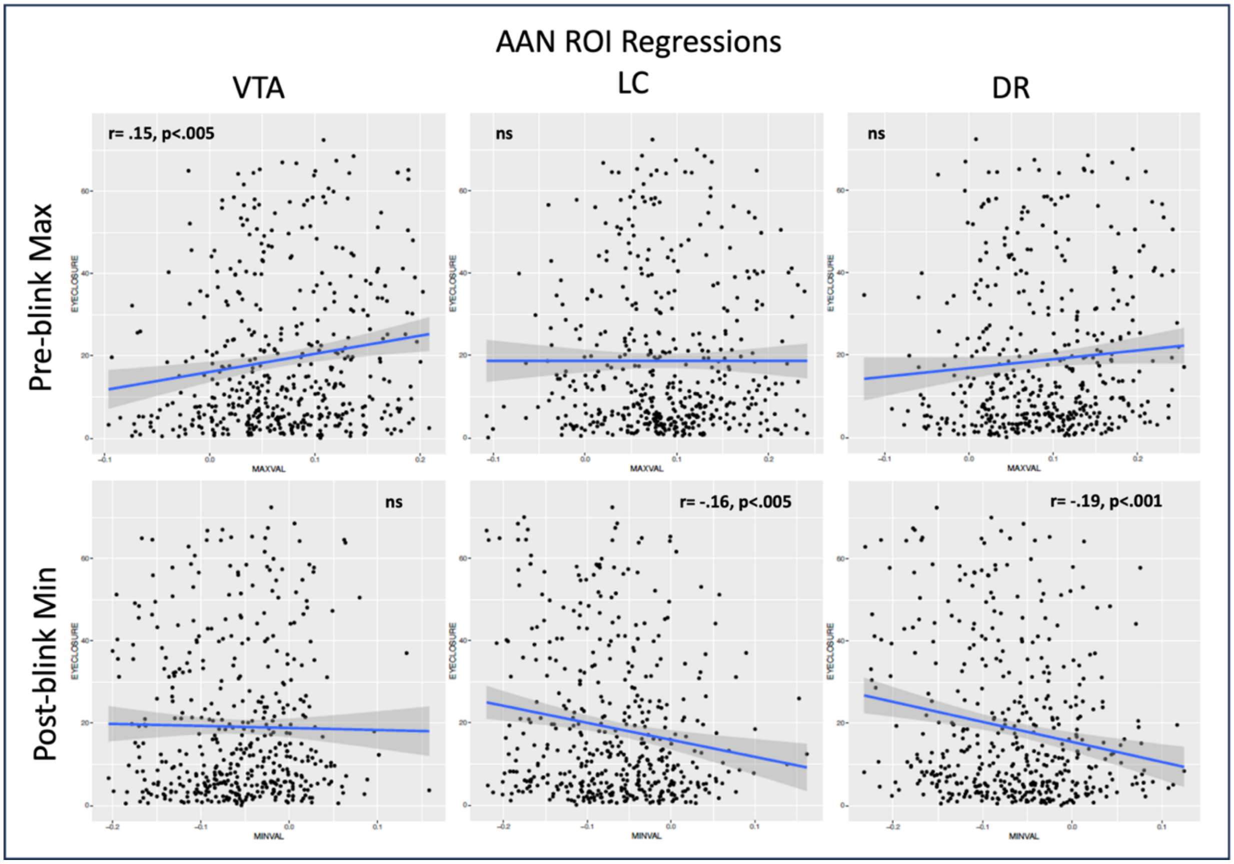
Sup. Fig. 6. Box-plots comparing vigilance states on eye blink measures.



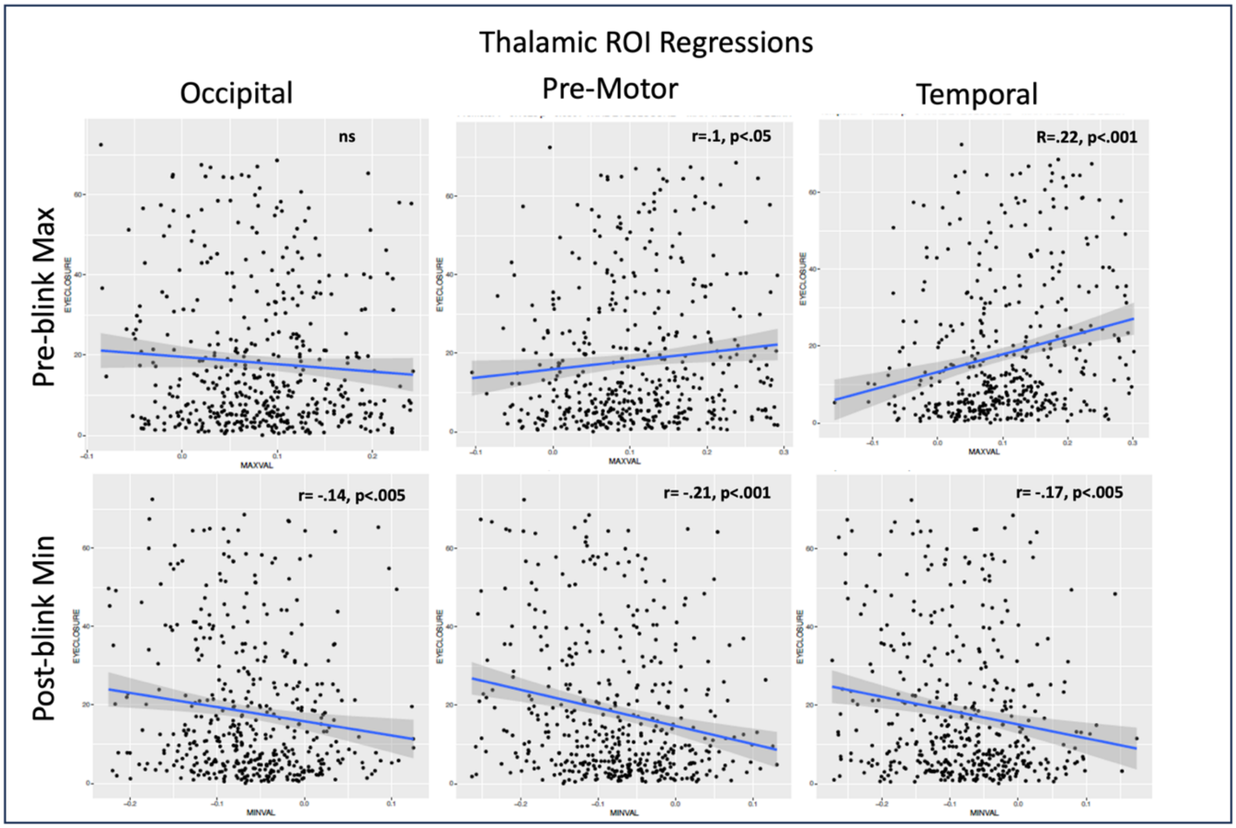
Sup. Fig. 7 IBI randomization-based testing plots. Random sampling of values from all the runs and the differences between the Vigilant and Drowsy states show normal-like distribution. Red line marks the difference observed in the actual population of values (Vigilant-Drowsy).



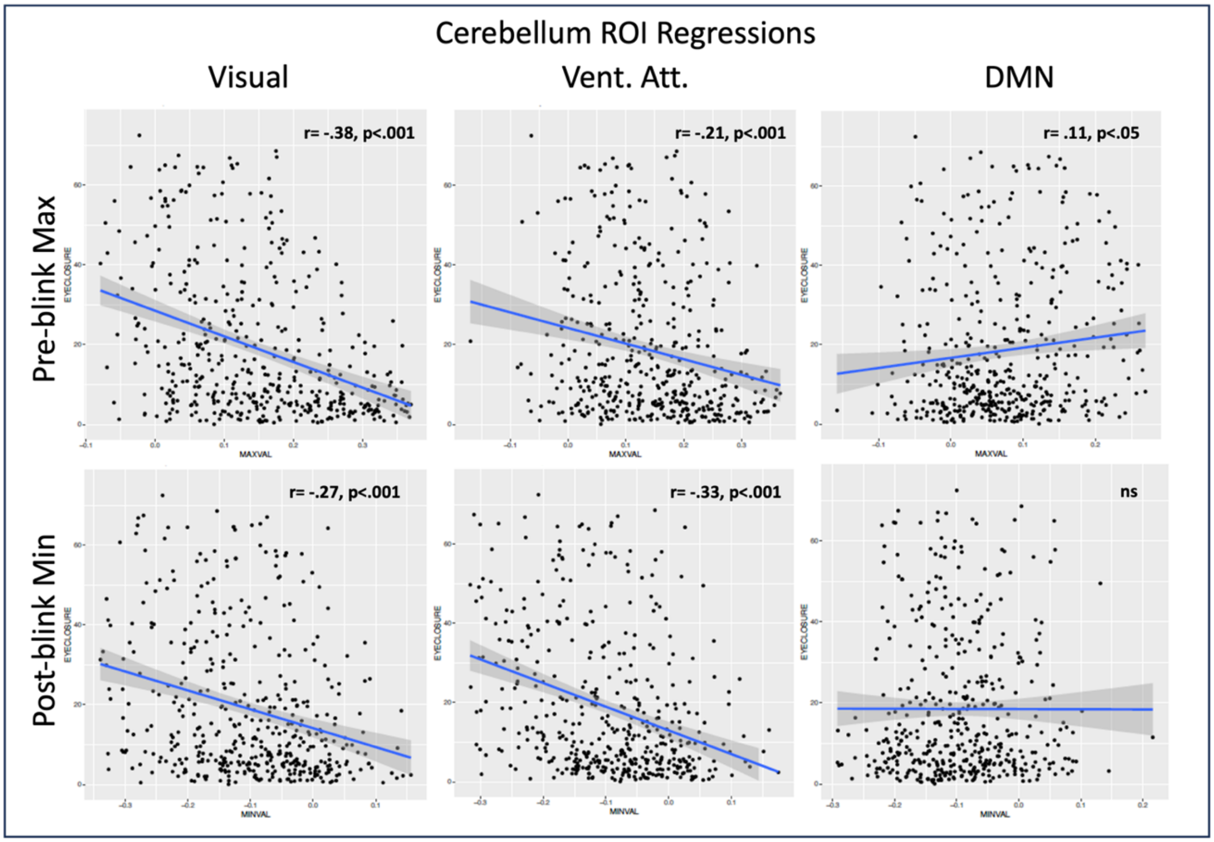
Sup. Fig. 8 Blink Duration randomization-based testing plots. Random sampling of values from all the runs and the differences between the Vigilant and Drowsy states show normal-like distribution. Red line marks the difference observed in the actual population of values (Vigilant-Drowsy).



Sup. Fig. 9. Pre-blink maximum and post-blink minimum values and vigilance regression analysis plots for canonical HRF based analysis for AAN (results reported in the main manuscript). Regression analysis showing pre- blink max and post-blink min amplitudes (x-axis) with drowsiness (y-axis) shown for AAN ROIs VTA, LC and DR.



Sup. Fig. 10. Pre-blink maximum and post-blink minimum values and vigilance regression analysis plots for canonical HRF based analysis for thalamus (results reported in the main manuscript). Regression analysis plots showing pre-blink max and post-blink min amplitudes (x-axis) with drowsiness (y-axis) for Thalamic Occipital, Pre. Motor and Temporal ROIs.



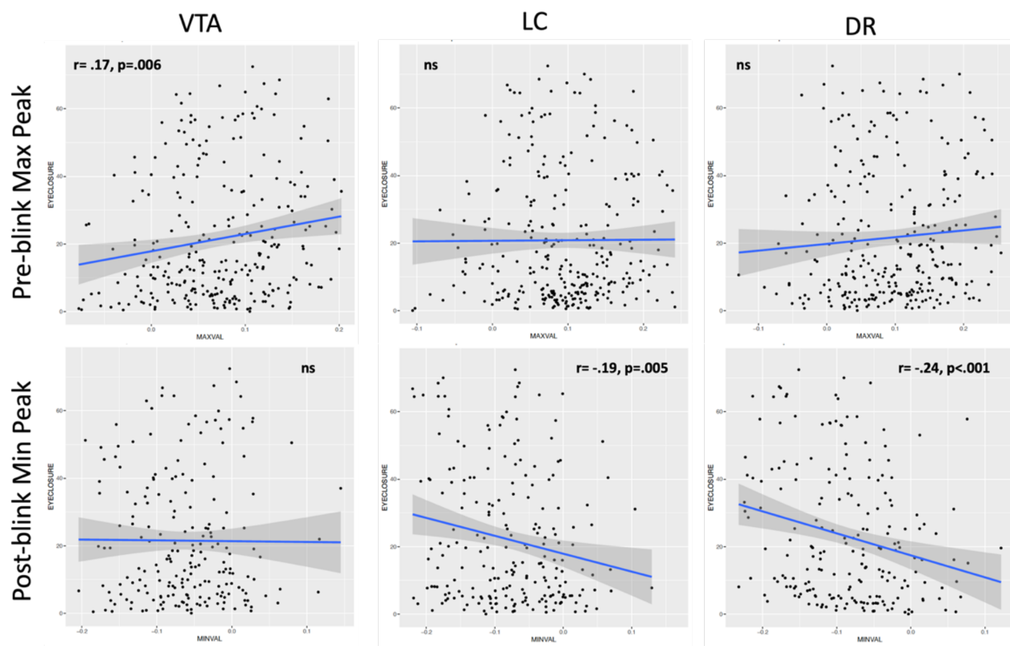
Sup. Fig. 11. Pre-blink maximum and post-blink minimum values and vigilance regression analysis plots for canonical HRF based analysis for cerebellum (results reported in the main manuscript). Regression analysis plots showing pre-blink max and post-blink min amplitudes (x-axis) and drowsiness (y-axis) for Cerebellum Visual, Vent. Attention and DMN ROIs.

Supplementary Report Part I

Pre-blink maximum and post-blink minimum 'peaks' and vigilance regression analysis of the canonical HRF blink-BOLD correlations (additional analysis):

We extracted pre-blink maximum and post-blink minimum peak values at corresponding peak lags. Then we investigated the linear correlation between vigilance (continuous eye closure ratio in y-axis) and the peak correlation values and peak time lags (x-axis) obtained from the cross—correlation analysis reported above across runs. In the regression analysis, for peak value assessment, pre-blink positive correlations mean higher drowsy (more eye closure) values with higher peak correlation values before blinks. On the other hand, post-blink negative correlations mean larger negative peak correlation values (negative values on x-axis) with higher drowsiness values. For peak lag analysis, positive correlation simply means that the peak lag emerged earlier in time (earlier lag value) when the drowsiness was lower.

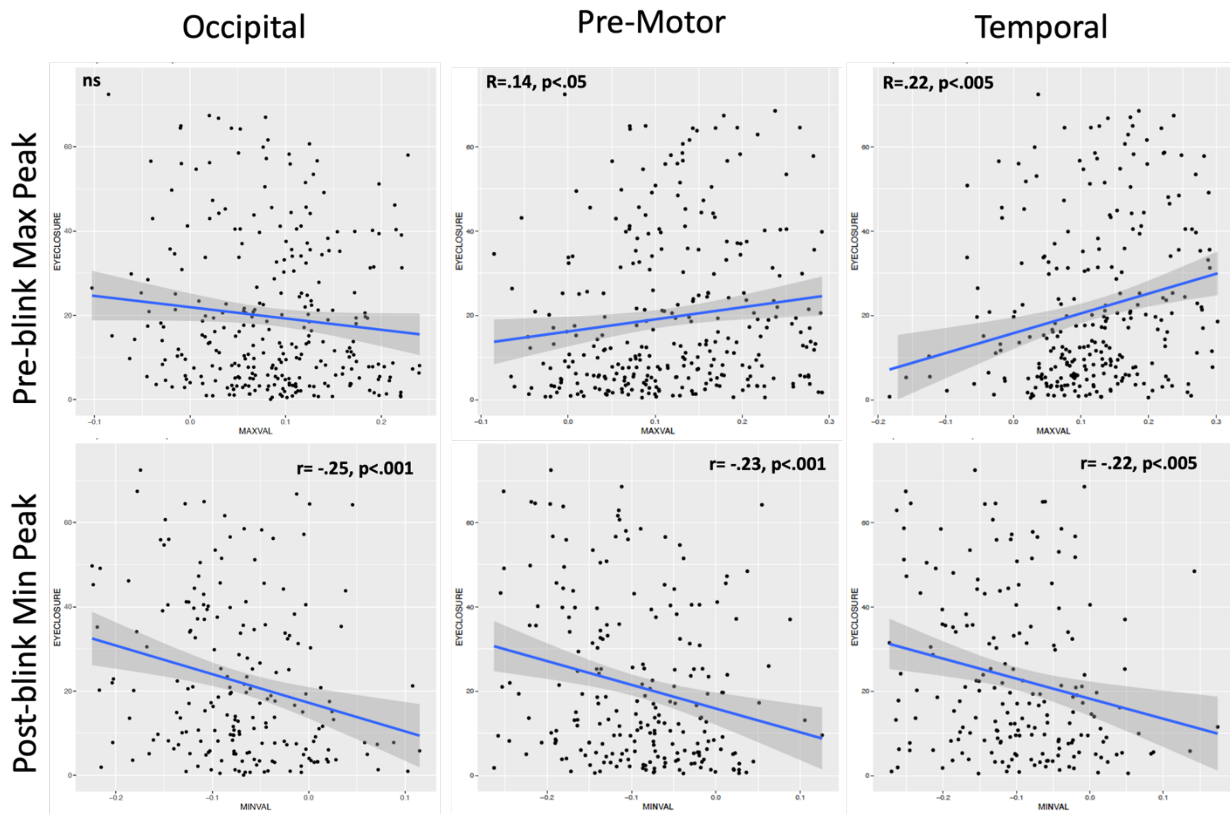
AAN
(Below '*' indicates multiple comparison corrected alpha = .05/10 = .005).
Max pre-blink peak amplitudes: Positively correlated only for VTA (r=.17, p=.006).
Min post-blink peak amplitude: Correlations were found for DR (r=-.24, p<.001*), LC (r=-.19, p=.005*), MR (r=-.21, p=.0016*), PBC (r=-.2, p=.004*), PO (r=-.25, p<.001*), PPN (r=-.14, p<.05), and SNpc (r=-.18, p<.05).
Max pre-blink peak latency and min post-blink peak latency: None of the ROIs were significant.
Summary: We found that peak latencies were highly variable and not significant across vigilance states, but peak amplitudes were more reliable. For VTA there was a marginal effect of drowsiness where pre-blink max peak value increased as drowsiness increased. For post-blink min peaks, DR, LC, MR, PBC, PO showed very significant effect of drowsiness (higher the drowsiness, more negative the peak values) while the similar effects on PPN and SNpc were weak. See figure below for VTA, LC and DR peak amplitude regression analysis.



Sup. Fig. 12. Pre-blink maximum and post-blink minimum peak values and vigilance regression analysis plots for canonical HRF based analysis for AAN. Regression analysis showing pre-blink max and post-blink min peak value (x-axis) with drowsiness (y-axis) shown for AAN ROIs VTA, LC and DR.

Thalamus

(Below * indicates multiple comparison corrected alpha = .05/7 = .007).
Max pre-blink peak amplitudes: Positively correlated only for Pre-Motor (r=.14, p<.05), Temporal (r=.22, p=.004*), and Parietal; (r=-.11,p=.06).
Min post-blink peak amplitude: *Negative* correlations were found for Sensory (r=-.16, p<.05), Occipital (r=-.25, p<.001*), Frontal (r=-.2, p=.002*), PreMotor (r=-.23, p<.001*), Parietal (r=-.33, p<.001*), and Temporal (r=-.22, p<.005*).
Max pre-blink peak latency: Negative correlations (higher the drowsiness earlier the peak) found for Motor (r=-.16, p=.006*) and Parietal (r=-.27, p<.001*) ROIs, while positive correlation was found (higher the drowsiness, peak is closer to the blink) for Temporal (r=.16, p=.006*) ROI.
Min post-blink peak latency: Post-blink maximum peak lag times were negatively correlated (higher the drowsiness earlier the peak – closer to the blink) for Motor (r=-.2, p<.005*), Sensory (r=-.15, p<.05), and Parietal (r=-.33, p<.001*) ROIs, and positively correlated (higher the drowsiness later the peak) for Temporal (r=.15, p<.05).
Summary: We observed reliable peak amplitude and peak lag correlations in Thalamus ROIs. Temporal ROI region showed significant pre-blink and post-blink peak amplitude changes due to vigilance (Higher the drowsiness more positive pre-blink and more negative post-blink amplitudes). Post-blink vigilance effects were also observed for Occipital, Frontal, PreMotor, and Parietal ROIs. While correlation plots suggested that Parietal ROI to show larger pre-blink peak correlations for Vigilant state -contrary to the other ROIs-, this did not reach significance. In the lag analysis, interestingly, Temporal ROI was distinct in that peak latency showed positive correlations indicating that the rise and fall of the peaks in Vigilant state emerged earlier than the Drowsy state in this ROI opposite to the other two ROIs, Motor and Parietal, wherein Vigilant state showed closer-to-blink pre-blink max lag and later post-blink min lag.



Sup. Fig. 13. Pre-blink maximum and post-blink minimum peak values and vigilance regression analysis plots for canonical HRF based analysis for thalamus. Regression analysis showing pre-blink max and post-blink min peak value (x-axis) with drowsiness (y-axis) for Thalamic Occipital, Pre. Motor and Temporal ROIs.

Cerebellum

(Below '*' indicates multiple comparison corrected alpha = .05/7 = .007).

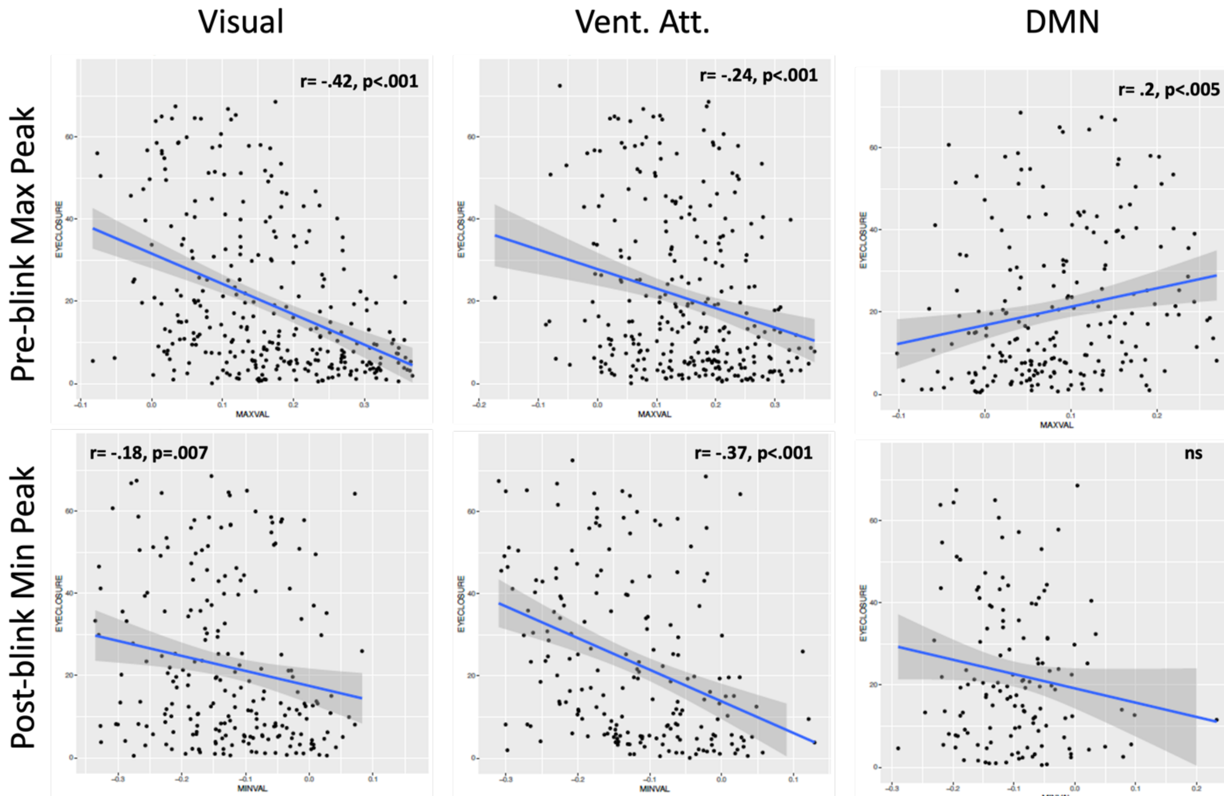
<u>Max pre-blink peak amplitudes:</u> Contrary to the patterns in AAN and Thalamus, most pre-blink maximum peak values were 'negatively' correlated for Visual (r=-.42, p<.001*), Sen. Motor (r=-.013, p<.05), Dor. Att. (r=-.2, p<.001*), and Vent. Att. (r=-.24, p<.001*), Orb. Frontal (r=.15, p<.05), but 'positively' correlated for DMN (r=.2, p<.005*).

<u>Min post-blink peak amplitude:</u> *Negative* correlations were found for Visual (r=-.18, p=.007*), Sen. Motor (r=-.013, p<.05), Dor. Att. (r=-.32, p<.001*), and Vent. Att. (r=-.37, p<.001*), Orb. Frontal (r=.31, p<.001*), Fron. Par. Control ROI (r=-.28, p<.001*).

<u>Max pre-blink peak latency:</u> Negative correlations (higher the drowsiness earlier the peak) found for Visual (r=-.38, p<.001*), Dor. Att. (r=-.19, p<.005*), Vent. Att. (r=-.27, p<.001*), and positive correlation for DMN (r=.23, p<.001*).

<u>Min post-blink peak latency:</u> Post-blink maximum peak lag times were negatively correlated (higher the drowsiness earlier the peak – closer to the blink) for Visual (r=-.37, p<.001*), Dor. Att. (r=-.27, p<.001*), Vent. Att. (r=-.22, p<.005*), and positive correlation for DMN (r=.23, p=.007*).

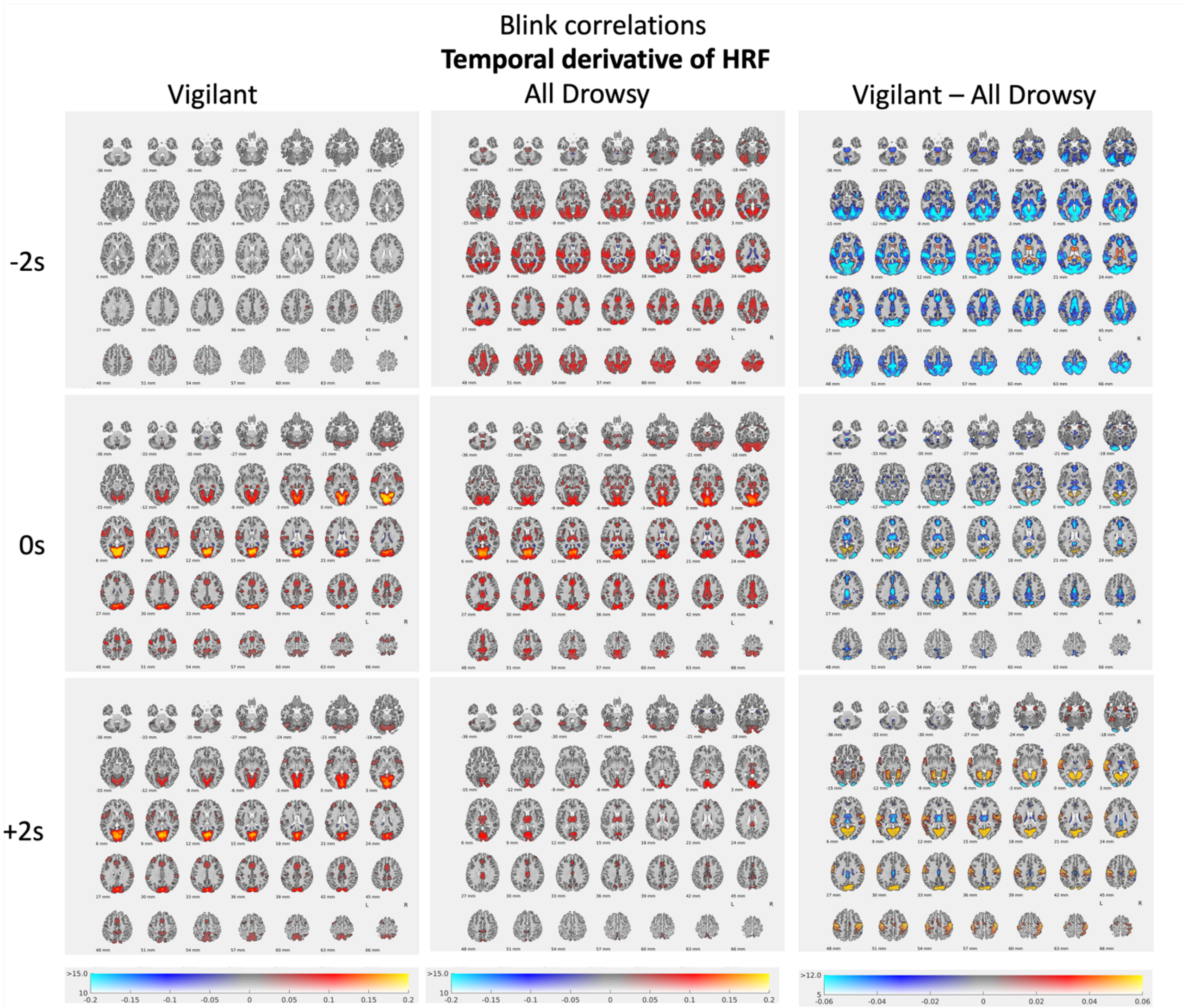
Summary: We observed reliable peak amplitude and peak lag correlations in Cerebellum ROIs like Thalamus ROIs. Visual, Sen. Dor. Att. and Vent. Att. Showed negative correlations in pre and post blink peak amplitudes and lags (i.e., higher the drowsiness less positive pre-blink max and more negative post-blink min amplitudes), while DMN showed opposite effects; significant pre-blink peak amplitude positive correlation (Higher the drowsiness more positive pre-blink amplitude). Peaks in the drowsy state emerged earlier in the pre-blink and post-blink windows for the Drowsy state compared to Vigilant state Visual, Dor. Att. and Vent. Att. ROIs except DMN ROI.



Sup. Fig. 14. Pre-blink maximum and post-blink minimum peak values and vigilance regression analysis plots for canonical HRF based analysis for cerebellum. Regression analysis showing pre-blink max and post-blink min peak value (x-axis) and drowsiness (y-axis) for Cerebellum Visual, Vent. Attention and DMN ROIs.

Supplementary Report Part II

Results with the blink time series convolved with temporal derivative of HRF



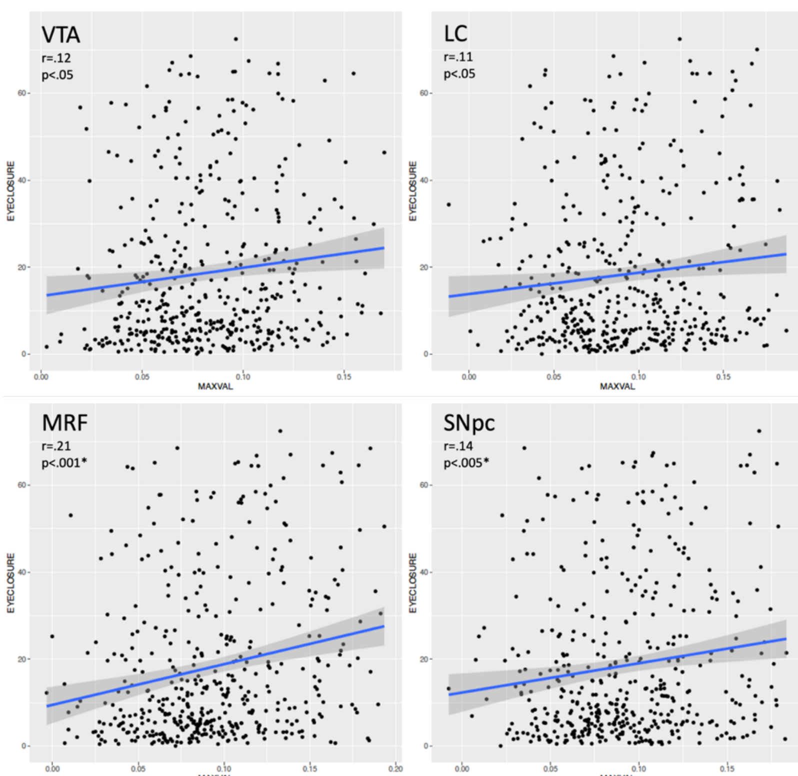
Sup. Fig. 15. BOLD - blink (convolved with the temporal derivative of HRF) cross-correlations across the brain. Blink cross-correlations (for the blink activity convolved with temporal derivative of HRF) across the brain in time lags of -2s, 0s, and 2s where negative values indicate BOLD preceding and positive values indicate BOLD following the blink. Blink time series are convolved with the temporal derivative of HRF. Correlation values (r) are shown in the x-axis of the color bar (from -.2 to .2) with t>10 for the main effects and (from -.06 to .06) with t>5 for difference.

Regression analysis between maximum correlation and vigilance for the blink activity convolved with temporal derivative of HRF

We first extracted maximum value at the corresponding lag per run. We then investigated the linear correlation between vigilance (continuous eye closure ratio in y-axis) and the correlation values and time lags (x-axis) obtained from the cross—correlation analysis reported above across runs.

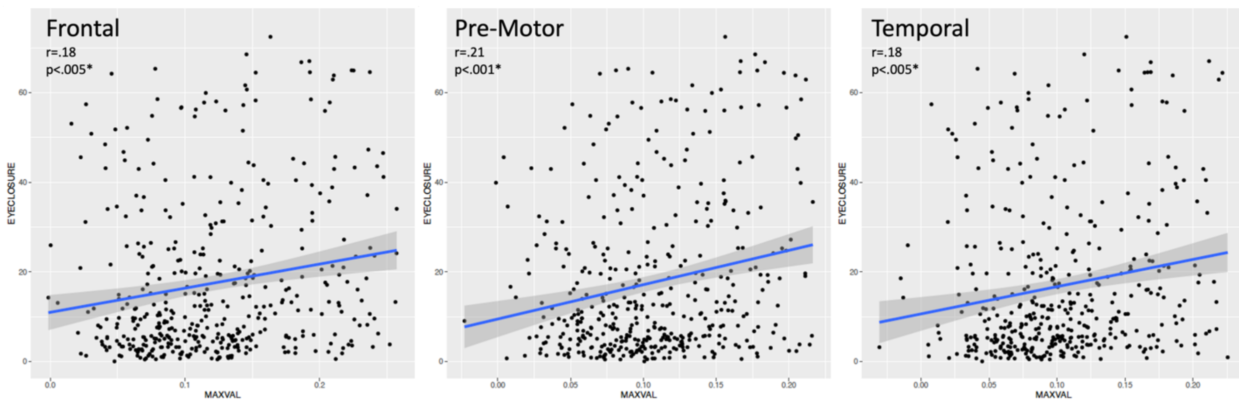
In the regression analysis, for amplitude assessment, positive correlations mean higher drowsy (more eye closure) values with higher correlation values before blinks. For the lag analysis, positive correlations indicate that the lag emerged earlier in time (earlier lag value) when the drowsiness was lower.

AAN
(Below '*' indicates multiple comparison corrected alpha = .05/10 = .005).
Analyses for the correlation with maximal amplitudes were positive and significant for DR ($r=.12$, $p<.05$), LC ($r=.11$, $p<.05$), MR ($r=.18$, $p<.001$*), MRF ($r=.21$, $p<.001$*), PAG ($r=.1$, $p<.05$), PPN ($r=.12$, $p<.05$), VTA ($r=.12$, $p<.05$),
SNpc ($r=.14$, $p<.005$*)
Max correlation lags in AAN ROIs did not reach significance in the regression analysis.
Summary: For the blink activity convolved with temporal derivative of HRF, We found that max amplitudes were positively associated with drowsiness (max correlation value increased as drowsiness increased) significantly in MR, MRF, and SNpc (and marginally (not-corrected) in DR, LC, PAG, PPN and VTA .) See **Sup. Fig. 16** for VTA, LC and SNpc amplitude regression analysis:



Sup. Fig. 16 Regression analysis (for the blink activity convolved with temporal derivative of HRF) showing max amplitudes (x-axis) with drowsiness (y-axis) shown for AAN ROIs VTA, LC MRF, and SNpc.

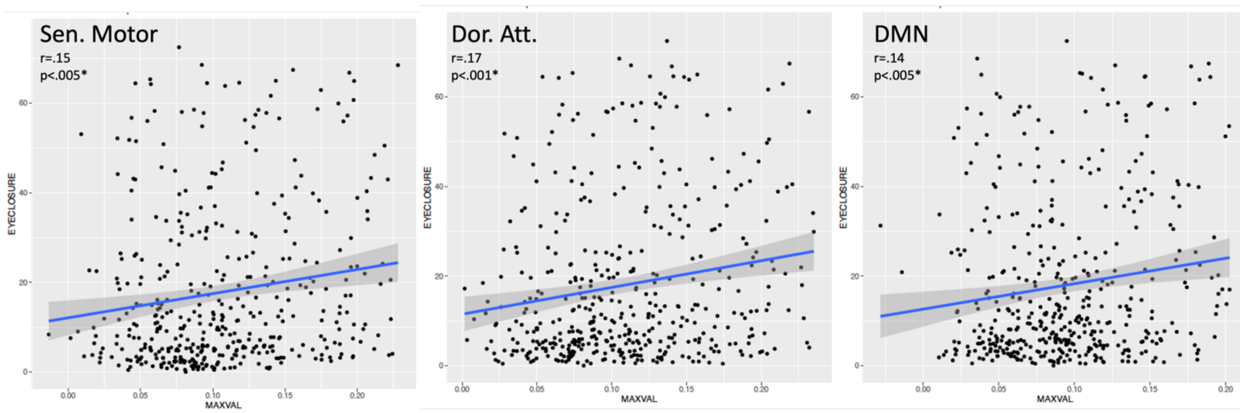
Thalamus
(Below * indicates multiple comparison corrected alpha = .05/7 = .007).
Analyses for the correlation with maximal amplitudes were positive and significant for Frontal (r=.18, p<.005*), PreMotor (r=.21, p<.001*), Parietal (r=.09, p=.057), and Temporal (r=.18, p<.005*) ROIs.
Latency: Negative correlations (higher the drowsiness earlier the peak) found for Motor (r=-.09, p<.056), PreMotor (r=-.16, p=.005*), and Parietal (r=-.25, p<.001*) ROIs.



Sup. Fig. 17 Regression analysis (for the blink activity convolved with temporal derivative of HRF) showing max amplitudes (x-axis) with drowsiness (y-axis) shown for thalamic Frontal, Pre-Motor, and Temporal ROIs.

Summary: We observed reliable amplitude and lag correlations in Thalamus ROIs. Frontal, Pre-Motor, and Temporal ROIs showed significant amplitude changes due to vigilance (Higher the drowsiness more positive amplitudes). (See **Figure**). In the lag analysis, for Pre-Motor and Parietal ROIs the correlation emerged later in the Vigilant state compared to the Drowsy state.

Cerebellum
(Below '*' indicates multiple comparison corrected alpha = .05/7 = .007).
Analyses for the correlation with maximal amplitudes were positive and significant for Sen. Motor (r=.15, p<.005*), Dor. Att. (r=.17, p<.001), Vent. Att. (r=.15, p<.005*), Orb. Frontal (r=.2, p<.001*), Fr. Par. Contr. (r=.14, p<.005*), DMN (r=.14, p<.005*) ROIs.
Max pre-blink latency: Negative correlations (higher the drowsiness earlier the max) found for Visual (r=-.22, p<.001*), Sen. Motor (r=-.24, p<.001*), Dor. Att. (r=-.25, p<.001*), Vent. Att. (r=-.25, p<.001*).



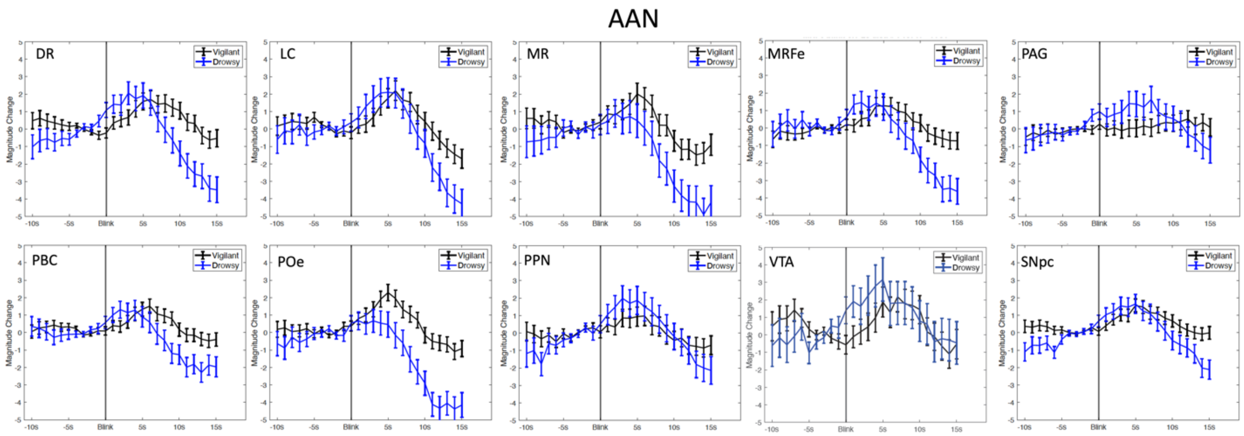
Sup. Fig. 18 Regression analysis (for the blink activity convolved with temporal derivative of HRF) plots showing amplitudes (x-axis) and drowsiness (y-axis) for Cerebellum Sensory, Ventral Attention and DMN ROIs.

Summary: For the blink activity convolved with temporal derivative of HRF, we observed reliable amplitude and lag correlations in Cerebellum ROIs similar to Thalamus ROIs; Sen. Motor, Dorsal and Ventral Attention ROIs, Orb. Frontal, Fr. Par. Contr. and DMN ROIs showed positive correlations for amplitude measures. Correlations in the drowsy state emerged earlier in the compared to Vigilant state in Visual, Sen. Motor, Dor. Att. and Vent. Att. ROIs.
Overall: We show that drowsiness induced higher blink-BOLD correlations close to the blink moment. Vigilance impacted the maximal correlation time lag such that more drowsy a participant was earlier the maximal correlation emerged.

Supplementary Report Part III

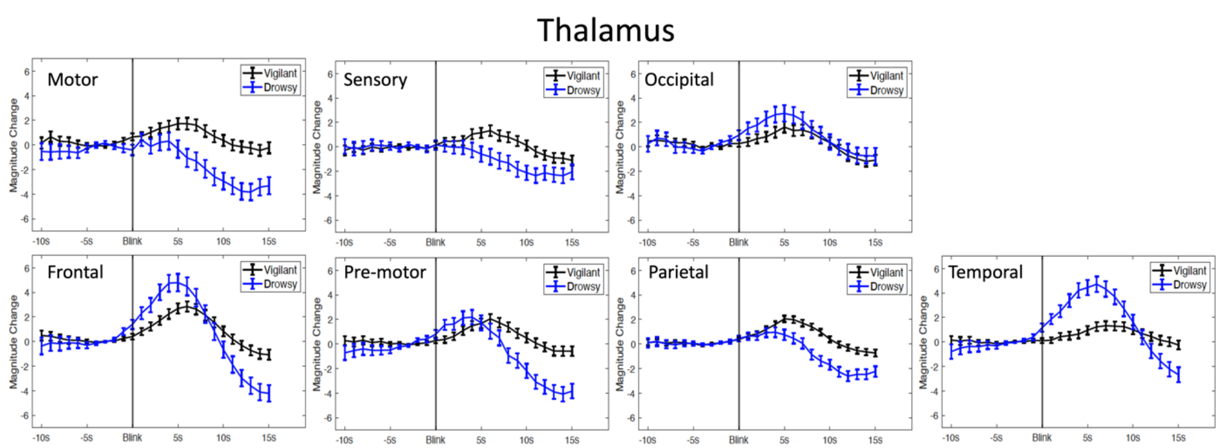
Blink-event BOLD signal changes per ROI. In this analysis 15717 vigilant and 7731 drowsy blink epochs were used.

AAN:



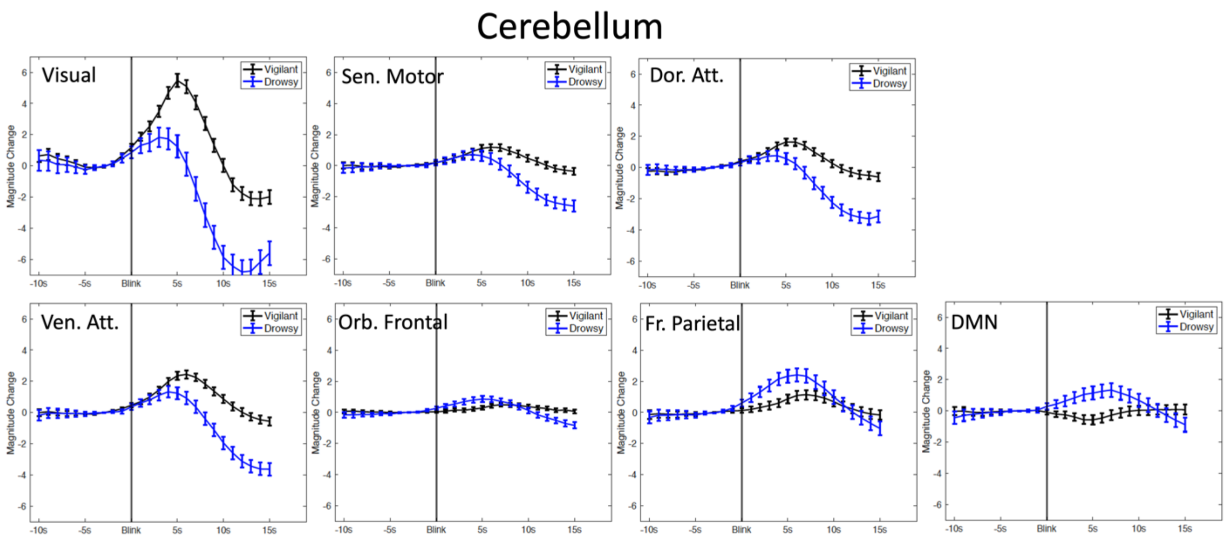
Sup. Fig. 19. Blink-event based BOLD signal changes shown for AAN. AAN ROIs shown separately in Vigilant and Drowsy states. Note of the later sharp drops in signal in the drowsy state.

Thalamus:



Sup. Fig. 20. Blink-event based BOLD signal changes shown for Thalamus. Thalamus ROIs shown separately in Vigilant and Drowsy states. Note of the later sharp drops in signal in the drowsy state.

Cerebellum:



Sup. Fig. 21. Blink-event based BOLD signal changes shown for Cerebellum. Cerebellum ROIs shown separately in Vigilant and Drowsy states. Note of the early peak time and later sharp drop in signal in the drowsy state compared to later and higher peak times in HRF. DMN showed an opposing pattern.