Cardiac responses to auditory irregularities reveal hierarchical information processing during sleep

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Abstract

Our ability to process environmental stimuli varies during sleep. Although much research focused on neural processing, emerging evidence shows that bodily signals may play a key role in understanding high-level sensory processing during sleep. Here, we tested how cardiac responses to the local-global paradigm, a typical oddball task probing the processing of simple (local) and complex (global) sensory irregularities. To do so, we analyzed electrocardiography (ECG) signals in a total of 56 participants from two existing datasets which contained cerebral responses to local auditory irregularities, but which did not analyze the ECG data before. We found that cardiac activity slowed down after global, but not local, auditory irregularities, revealing the presence of global deviance effect in Rapid Eye Movement (REM) sleep. In contrast, cardiac activity was faster after local, but not global, deviants in Non-Rapid Eye Movement (NREM) sleep. Overall, our results demonstrate that cardiac responses to auditory irregularities inform about hierarchical information processing and its variations during sleep beyond cerebral activity. They highlight the embodiment of cognitive function and the value of cardiac signals to understand the variations of sensory processing during sleep.

Introduction

Sleep is classically considered as a state of loss of vigilance to the external world (Peigneux et al., 2001). Yet, remaining sensitive to the environment during sleep might be crucial for survival, allowing, for example, to wake up if unexpected events occur (Blume & Schabus, 2019; Cirelli & Tononi, 2008; Coenen, 2024). Previous investigations on the neural responses to sounds of different complexities have revealed that the sleeping brain indeed processes from simple acoustic stimuli up to semantic information, but that this ability depends greatly on sleep states (Andrillon & Kouider, 2020; Hennevin et al., 2007).

In comparison, how the body is involved in complex auditory information processing during sleep has been so far understudied (Koroma et al., 2024). Yet, emerging evidence suggests that bodily signals play also a fundamental role in cognition and perception (Azzalini et al., 2019). Empirical support highlighting the importance of bodily signals has been obtained by showing for example that cardiac activity responses to sound inform about the classification of disorders of consciousness beyond neural activity in the local-global paradigm (Raimondo et al., 2017).

The local-global paradigm is a classical mismatch detection task probing loss of vigilance to hierarchical information by distinguishing between an automatic detection of low-level auditory irregularities (local mismatch effect), and a consciousness-dependent detection of high-level auditory irregularities (global deviance effect) (Bayne et al., 2024; Bekinschtein et al., 2009). By applying this paradigm to sleep, neural signatures of local mismatch detection, but not of global deviance detection, have been previously reported (Blume et al., 2022; Strauss et al., 2015, 2022). However, the investigation of the cardiac correlates of hierarchical information processing during sleep remained to be performed.

In the present study, we tested how cardiac responses were shaped by auditory irregularities of different complexities during healthy sleep. In line with brain results, we hypothesized that local mismatch and global deviance effects would be observed at the cardiac level during wakefulness (Blume et al., 2022; Strauss et al., 2015, 2022). In comparison, only local mismatch effects would be found during sleep, reflecting the breakdown of hierarchical information processing (Blume et al., 2022; Makov et al., 2017; Strauss et al., 2015).

As a secondary hypothesis, we predicted that cardiac effects would depend on sleep states. In particular, cardiac responses would be preserved in light NREM (*i.e.*, NREM2) and periods of REM sleep without eye movements (*i.e.*, tonic REM), during which a wide range of sensory processing (*e.g.*, preferentially reacting to one's own name) is preserved (Andrillon & Kouider, 2020; Perrin, 1999). In contrast, cardiac responses would be absent in deep NREM (*i.e.*, NREM3) and periods of REM sleep without eye movements (*i.e.*, phasic REM), during which auditory information is typically suppressed (Ermis et al., 2010; Koroma et al., 2020; Legendre et al., 2019).

Methods

Local-global paradigm during sleep

We extracted the electrocardiographical (ECG) signals of 56 healthy young adults from 18 to 35 years old who heard the local-global paradigm during wakefulness and sleep (n=28 for a morning nap from Strauss et al., 2015; n=28 for 2 full nights from Blume et al., 2022). Stimuli were pairs of phonetically distant vowels (100 ms duration). Five vowels with a 50 ms interstimulus interval were included in each trial. The first four vowels were identical, and the last one was either the same ("local standard") or different ("local deviant"; cf. Figure 1A, top).

Trials were presented in two types of blocks, the vowels serving as standards and deviants across blocks being counterbalanced across repetitions. In one block, 80% of the sequences were composed of five identical sounds (aaaaa), referred to as "Global Standard Local Standard" (GSLS), and 20% of four identical sounds and a deviant (aaaaB), referred to as

“Global Deviant Local Deviant” (GDLD). The proportions were reversed in another block with composing 80% of the sequences composed of four identical sounds and a deviant (aaaaB), referred as “Global Standard Local Deviant” (GSLD), and 20% of five identical sounds (aaaaa), referred as “Global Deviant Local Standard” (GDLS; Figure 1A, top).

Using the same methodology as adopted for cerebral signals (Bekinschtein et al., 2009; Blume et al., 2022; Strauss et al., 2015), the local mismatch effect was defined by subtracting local deviants from the local standards: (GSLD+GDLD) - (GSLS+GDLS); and the global deviance effect by subtracting global deviants from global standards: (GDLS+GDLD) - (GSLS+GDLD) (Figure 1A, bottom). To control for potential confounding effects between local mismatch and global deviance effects, we further checked the contrast between local deviants and local standards using global standard trials only, defining the ‘true local’ effect as: (GSLD - GSLS). We also controlled the contrast between global deviant and global standards using local standard trials only, defining the ‘true global’ effect as: (GDLS - GSLS).

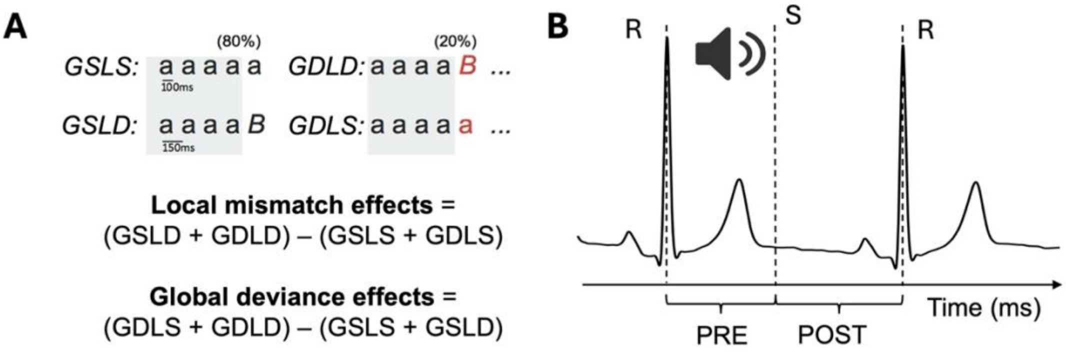

Figure 1. **Analysis of the local-global paradigm played during sleep across two datasets.** **(A)** A trial was composed of a sequence of 5 tones and belonged to one of the 4 following categories: global standard and local standard (GSLS, top left), global deviant and local deviant (GDLD, top right), global standard and local deviant (GSLD, bottom left), global deviant and local standard (GDLS, bottom right). The combination of responses to these trials allows to define local mismatch and global deviance effects. Adapted from (Strauss et al., 2022) **(B)** Heartbeat was extracted from ECG and the duration between onset of the 5th sound and the preceding (PRE) and following heartbeat (POST) was computed for each trial following the methodology of (Raimondo et al., 2017).

Cardiac analyses during wakefulness and sleep

Heartbeats were extracted after cleaning the ECG signal (sampled at 120 Hz) using the *ecg_process* function (high-pass Butterworth filter at 0.5 Hz and powerline filter at 50 Hz) and identifying R-peaks with the *neurokit* method from the Neurokit2 package (Makowski et al., 2021). For assessing variations of baseline cardiac activity, interbeat intervals (RR) were computed as a proxy for heart rate during wakefulness and sleep. The values were averaged for wakefulness and each sleep stages within each participant.

Following previous methodology (Raimondo et al., 2017), the cardiac responses to local mismatch and global deviance were obtained by comparing the modulation of the heartbeat timing before and after the occurrence of low-level and high-level auditory irregularities during wakefulness and sleep. The interval between the onset of the fifth sound of each trial with the preceding and following heartbeats defining respectively a PRE and a POST period for each trial (Figure 1C). Sufficient signal-to-noise ratio was ensured by keeping for further analyses sleep stages within each participant that counted at least 10 deviant trials.

As in Raimondo and colleagues (2017), our analyses were first restricted to trials for which both PRE and POST intervals were contained between 20 and 600 ms around the fifth sound onset. Using a grid-search procedure, we also extended analyses by testing for local mismatch and global deviance effects on time-windows between 20 and 600 ms up until 20 and 1200ms with 100ms step interval. To do so, values were first averaged within each participant and compared between PRE and POST periods for wakefulness and sleep.

Statistical comparisons of cardiac modulation during wakefulness and sleep

Sleep scoring was performed offline according to the AASM guidelines (Iber et al., 2007) as reported in associated publications (Blume et al., 2022; Strauss et al., 2015). Eye movements in REM sleep were identified by independent scorers (M.S. for the Strauss dataset; M.K. and

V.G. for the Blume dataset), defining trials with eye movements as phasic REM, and without eye movements as tonic REM (Simor et al., 2020). NREM1 was excluded from analyses as it is considered a transitionary sleep stage (Lacaux et al., 2024; Ogilvie, 2001).

The modulation of heart rate and the local mismatch and global deviance effects for PRE and POST periods were tested across sleep stages with linear mixed-effects models with participants as random factor using the *lmer* package in R. Post-hoc comparisons were tested with non-parametric Wilcoxon and Mann-Whitney tests using the *scipy* and Bayes Factors analyses using the *Pinguoin* toolboxes in Python. Correction for multiple comparisons were performed using false detection rate (alpha threshold=0.05) (Benjamini & Yekutieli, 2001).

Median and 95% confidence interval (95CI) of beta estimates (β), standardized β and t values (t) are reported for mixed-model analyses. Median and 95CI (bootstrap, n=2000) and effect sizes, according to the formula $r = z/\sqrt{n}$, z being the z-stats of the Wilcoxon signed rank test and n being the number of participants, were reported for non-parametric post-hoc tests. Bayes Factors (BF) were reported with values above 3 being considered as positive evidence in favor of the null hypothesis (Kass & Raftery, 1995).

Results

Cardiac activity slows down after global deviants in REM sleep.

In terms of the local mismatch effect, there was no evidence for a cardiac modulation (PRE *vs.* POST: β=4.11±[-3.0, 11.23], t(256)=1.14, p=0.26, standardized β=0.24±[-0.17, 0.64]). The effect was not evidenced across vigilance stages (POST *vs.* PRE with: Wakefulness *vs.* NREM: β=0.43±[-9.63, 10.49], t(256)=0.08, p=0.93, Std. β=0.02±[-0.55, 0.60]; Wakefulness *vs.* REM: β=3.47±[-7.18, 14.11], t(256)=0.64, p=0.52, Std. β=0.20±[-0.41, 0.81]). Post-hoc testing confirmed the absence of the local mismatch effect in both wakefulness, NREM and REM sleep (all tests: p>0.05, BF>3.0) (Figure 2A).

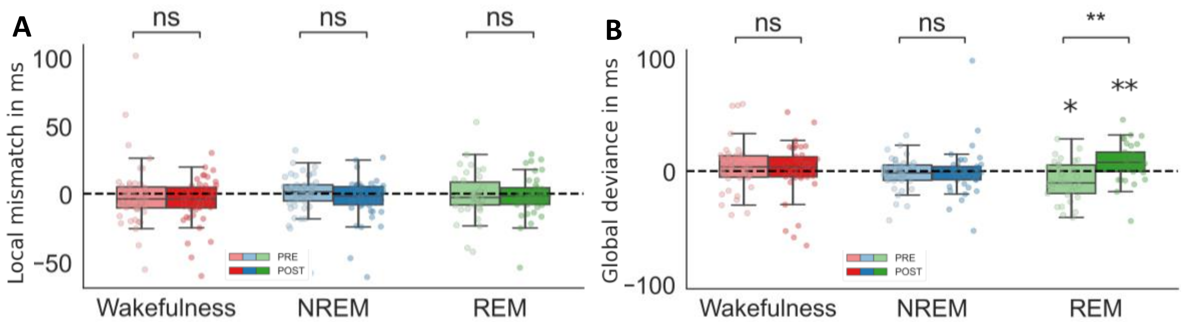

Figure 2. **Cardiac activity decelerates after global deviants in REM sleep**. Local mismatch **(A)** and global deviance **(B)** effects of cardiac responses were computed for Wakefulness, NREM and REM separately for the PRE and POST periods with respect to the fifth sound of the local-global paradigm (contained between 20 and 600ms). Boxplots represent median, 1st and 4th quartiles and deciles of effects across subjects are represented by boxplots in each sleep state. Datapoints represent individual subjects. Statistical significance of post-hoc tests, ns: not significant, *: p<0.05, **: p<0.01.

In terms of the global deviance effect, there was a difference between Wakefulness and REM sleep (POST *vs.* PRE and Wakefulness *vs.* REM: β=19.91±[6.52, 33.29], t(224)=2.93; p=0.004, Std. β=0.95±[0.31, 1.58]; POST *vs.* PRE and NREM *vs.* REM: β=13.07±[-0.38, 26.53], t(224)=1.91, p=0.06, Std. β=0.62±[0.31, 1.58]). Post-hoc tests uncovered a cardiac deceleration after global deviants in REM (POST *vs.* PRE: r=-0.52, p=0.002; PRE: -9.37±[-11.95, 1.38], r=-0.39, p=0.02; POST: 8.76±[4.51, 13.72], r=0.54, p=0.004). Such modulation was absent in Wakefulness and NREM (Wakefulness: POST *vs.* PRE: r=-0.03, p=0.84, BF=5.38; PRE: 4.72±[-0.16, 9.30], r=-0.14, p=0.84, BF=2.2; POST: 4.75±[-2.84, 7.50], r=-0.00, p=0.84, BF=5.3; NREM: POST *vs.* PRE: -0.56±[-5.18, 4.38], r=-0.03, p=0.85, BF=5.0; PRE: r=-0.11, p=0.84, BF=3.7; POST: 0.00±[-3.54, 2.48], r=-0.07, p=0.84, BF=5.9) (Figure 2B).

We also tested for the presence of the “true local” effects by restricting analyses on global standard trials only (GSLD - GSLS) and “true global” effects by restricting analyses on local standard (GDLS - GSLS). The linear mixed-effects model showed the presence of a “true global” deviance effect in REM sleep as compared to wakefulness (β=-27.9±9.0, t(38,184)=-

3.10, p=0.002), and post-hoc tests confirmed that this was due to a cardiac deceleration after global deviants in REM sleep (POST *vs.* PRE: r=0.50, p=0.009; PRE: -11.51±[-14.01, 0.71], r=-0.30, p=0.12; POST: -11.92±[3.58, 23.37], r=0.44, p=0.043, Figure S3B). There was no evidence for a modulation of cardiac responses for the true local mismatch effects neither in wakefulness and sleep (all tests: p>0.05, BF>3.0, Figure S3A).

Cardiac activity accelerates after local deviants in NREM sleep.

As NREM was characterized by lower heart rate than Wakefulness (β=0.70±25.5, t(146,55)=2.77, p=0.007; r=0.33, p=0.017; Figure S1A), we investigated local mismatch and global deviance effects beyond the restriction of analyses on PRE and POST periods between 20 to 600ms based on Raimondo and colleagues (Raimondo et al., 2017) (Figure S2). A grid search analysis revealed the presence of a local mismatch effect between 20 and 900ms during sleep (PRE vs POST: p=0.045, corrected Wilcoxon test). No other effects was evidenced neither in sleep nor wakefulness (p>0.05 for all tests) (Table S1).

Post-hoc comparisons showed that cardiac activity accelerated after local deviants in NREM sleep (POST vs PRE: r=-0.33, p=0.017; PRE: 3.92±[1.36, 5.16], r=-0.35, p=0.02; POST: -2.27±[-4.39, -0.35], r=-0.27, p=0.046). We also confirmed that an absence of modulation of cardiac activity after local deviants in Wakefulness and REM sleep (Wakefulness: POST *vs.* PRE: r=-0.29, p=0.61, BF=6.3; PRE: -1.67±[-5.79, 2.61], r=-0.06, p=0.64, BF=6.5; POST: -2.74±[-10.39, 6.02], r=-0.16, p=0.46, BF=4.1; REM: POST *vs.* PRE: r=-0.29, p=0.07, BF=1.3; PRE: 6.15±[0.65, 13.66], r=0.41, p=0.03, BF=0.32; POST: -0.83±[-5.13, 4.04], r=-0.08, p=0.62, BF=4.3). (Figure 3A). As expected from the grid search analysis, no global deviance effects were found during wakefulness and sleep (p>0.05 and BF>3.0 for all tests) (Figure 3B).

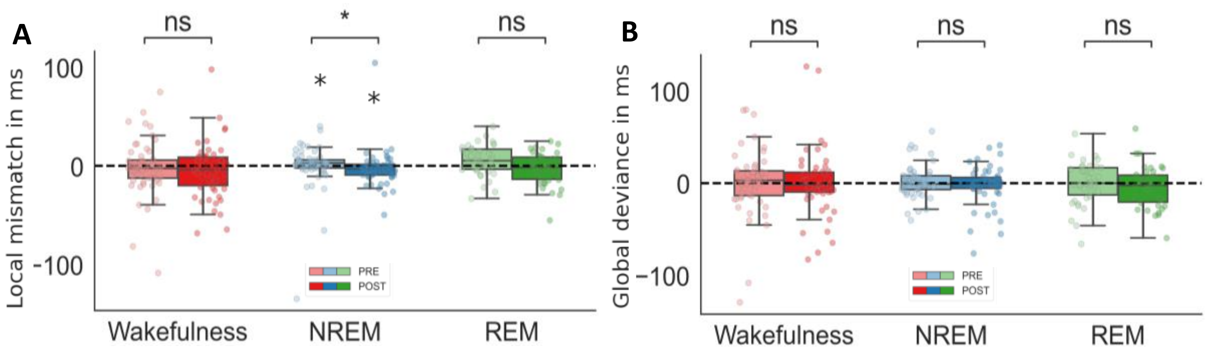

Figure 3. **Cardiac activity accelerates after local deviants during NREM sleep**. Local mismatch **(A)** and global deviance **(B)** effects were computed for Wakefulness, NREM and REM separately for PRE and POST periods (contained between 20 and 900ms, following a grid-search analysis). Boxplots represent median, first and fourth quartiles and whiskers deciles for each condition. Datapoints represent individual subjects. Statistical significance for post-hoc test, ns: not significant, *: p<0.05

We further checked whether "true local" effects were also observed in NREM sleep. Post-hoc effects showed that cardiac activity was modulated around local deviants after restricting our analyses on global standard trials only during NREM sleep (POST *vs.* PRE: r=-0.33, p=0.016; PRE: 3.77±[-1.09, 5.64], r=-0.25, p=0.07; POST: -2.76±[-5.00, 1.37], r=-0.26, p=0.07) (Figure S4A). We also confirmed that "true global" deviance effects were not observed in wakefulness nor sleep (all tests: p>0.05, BF>3.0, Figure S4B).

Cardiac activity is modulated by auditory deviants in light NREM and tonic REM sleep.

As local mismatch effects were evidenced during NREM sleep and global deviance effects during REM sleep, we tested our secondary hypotheses. We predicted that cardiac effects were observed in light NREM and periods of REM sleep without eye movements, referred to as tonic REM, during which auditory information is processed (Andrillon & Kouider, 2020; Ermis et al., 2010; Rechtschaffen et al., 1966). In line with the literature (Arnulf, 2011; Spreng et al., 1968), our scoring resulted in identifying 20±12% (mean±standard deviation) trials with elevated eye-movement activity during REM sleep, referred as phasic REM (Figure S1B).

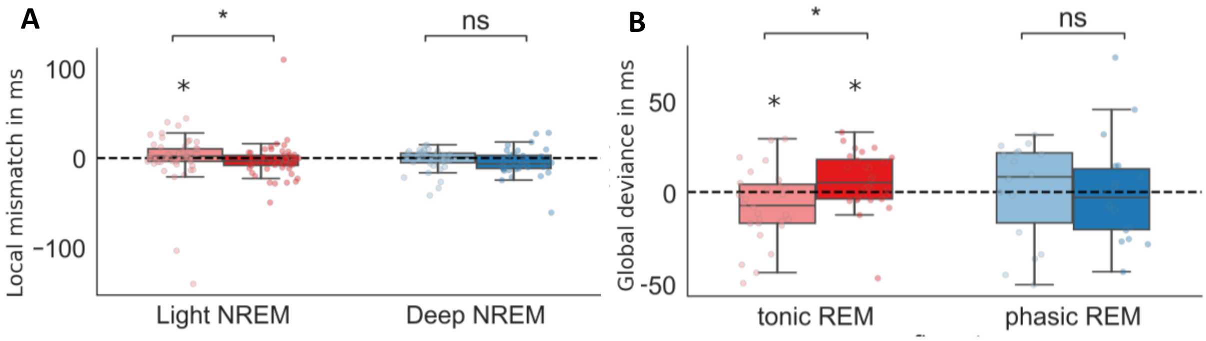

Figure 4. **Cardiac responses were observed in light NREM and tonic REM sleep**. Local mismatch effects were computed for PRE and POST periods contained between 20 and 900ms in light and deep NREM **(A)** and between 20 and 600ms global deviance effects in tonic and phasic REM **(B)**. Boxplots represent median, first and fourth quartiles and whiskers deciles for each condition. Datapoints represent individual subjects. Statistical significance for post-hoc test, ns: not significant, *: p<0.05

Using preprocessing time-windows between 20 and 900 ms, post-hoc tests confirmed the presence of local mismatch effects in light NREM (POST *vs.* PRE: r=-0.27, p=0.04; PRE: 2.94±[-1.22, 5.60], r=0.31, p=0.05; POST:-2.56±[-4.23, 0.47], r=-0.22, p=0.10). Effects were not significant in deep NREM (POST *vs.* PRE: r=-0.24, p=0.16, BF=4.3; PRE: 1.73±[-2.08, 5.34], r=0.08, p=0.65, BF=4.7; POST: -5.43±[-9.15, 1.37], r=-0.28, p=0.18, BF=2.0) (Figure 4A). Using preprocessing time-windows between 20 and 600 ms, post-hoc tests confirmed the presence of a cardiac deceleration after global deviants in tonic REM and its absence in phasic REM (tonic REM: POST *vs.* PRE: r=0.19, p=0.02; PRE: r=-0.12, p=0.12; POST: r=0.23, p=0.03; phasic REM: POST *vs.* PRE: r=0.08, p=0.77, BF=4.1; PRE: 9.29±[-10.18, 22.05], r=0.01, p=0.83, BF=4.0; POST: -2.01±[-18.37, 12.12], r=-0.10, p=0.83, BF=4.1) (Figure 4B).

"True local" mismatch effects failed to reach significant levels in light NREM sleep and deep NREM sleep (light NREM: POST *vs.* PRE: r=-0.21, p=0.09, BF=5.8; PRE: 2.93±[0.39, 5.43], r=0.22, p=0.22, BF=4.8; POST: -0.71±[-4.48, 2.00], r=-0.11, p=0.41, BF=6.6; deep NREM: POST *vs.* PRE: r=-0.14, p=0.41, BF=5.6; PRE: -0.01±[-3.50, 5.31], r=0.05, p=0.77, BF=2.32; POST: -4.60±[-8.47, -2.65], r=-0.33, p=0.10, BF=1.91) (Figure S4A). "True global" deviance effects were confirmed in tonic REM with a stronger cardiac deceleration after global deviants in local standard trials (POST *vs.* PRE: r=-0.18, p=0.27, BF=0.6; PRE: -9.65±[-15.68, 4.73], r=-0.12, p=0.37, BF=3.4; POST: 9.18±[0.78, 20.59], r=0.15, p=0.04) (Figure S4B). This effect was not observed during phasic REM (POST *vs.* PRE: r=0.18, p=0.56, BF=2.1; PRE: -28.42±[-52.78, 16.75], r=-0.21, p=0.31, BF=1.3; POST: -1.91±[-36.83, 29.51], r=-0.04, p=1.0, BF=2.6) (Figure S4B).

Discussion

We investigated the modulation of cardiac activity by hierarchical auditory irregularities presented during wakefulness and sleep. We report that cardiac activity slows down after complex auditory irregularities (global deviance effect) in REM sleep, and that it accelerates after basic irregularities (local mismatch effect) in NREM sleep. These results open a discussion not only about the contribution of bodily signals in understanding cognitive processing, but also about the variations of sensory processing depending on sleep stages and their associated markers, such as rapid eye movements and slow-wave activity.

In contrast to cerebral findings, we showed an absence of local mismatch and global deviance effects at the cardiac level during wakefulness. This absence of an effect can be explained by the inhibition of cardiac modulations by the prefrontal cortex, a region active during wakefulness and deactivated during sleep (Muzur et al., 2002; Wong et al., 2007). These findings also replicate previous observations that cardiac activity is not modulated by the local and global auditory irregularities in healthy awake controls (Raimondo et al., 2017).

Contrary to our hypothesis, we further found that cardiac activity slows down after global deviants during REM sleep. The detection of global deviance in REM sleep might indicate the preservation of a form of error-related monitoring that has been typically associated with the slowdown of cardiac activity (see Skora et al., 2022 for a review). The restriction of global deviance effects to tonic REM sleep is in line with the fact that the processing of auditory stimuli is suppressed in presence of rapid eye movements during REM sleep (Ermis et al., 2010; Koroma et al., 2020; Sallinen et al., 1996; Wehrle et al., 2007).

In line with our hypothesis, we observed that cardiac activity was faster after local deviants in NREM sleep. These findings confirm previous observations that auditory mismatch triggers an acceleration of cardiac activity accompanied with a transient increase of arousal in NREM sleep (de Zambotti et al., 2018). They also confirm that the detection of local mismatch is preserved during NREM sleep, as previously observed in cerebral responses to local deviants (Blume et al., 2022; Strauss et al., 2015).

The variations of cardiac responses to auditory irregularities of different complexities can be interpreted in the light of variations of brain-heart interactions during sleep (Chouchou & Desseilles, 2014). Global effects found in REM and local effects in NREM can showcase the different levels of cardiac control between higher-level cortical areas involved in complex interoceptive and sensory information processing (*e.g.*, insula) in REM sleep (Bamiou et al., 2003; Oppenheimer & Cechetto, 2016) and lower-level brain regions associated with automatic arousal reactions (*e.g.*, brainstem) in NREM sleep (Benarroch, 2018; Griffiths et al., 2001). The cardiac slowdown observed in REM and acceleration in NREM may further reflect the release from a cardiac control by the predominant sympathetic activity in REM sleep (Postuma et al., 2010) and parasympathetic tone in NREM sleep (Vigo et al., 2010; Viola et al., 2011).

Our results on cardiac responses during sleep can be further compared with those obtained in patients with disorders of consciousness (DOC) (Raimondo et al., 2017). In that study, cardiac responses to global deviance effects were found in patients who exhibit complex behaviors and cognitive processing in minimally conscious state as compared to unresponsive wakefulness syndrome (Laureys, 2005), which aligns with our findings considering that more complex cognitive activities are typically observed during REM sleep as compared to NREM sleep (Tononi et al., 2024; Tononi & Massimini, 2008). Noteworthy, global deviance effects manifested as a slowdown of cardiac activity in REM sleep and as a cardiac acceleration in DOC patients in minimally conscious states, further highlighting the differences in autonomic regulation between sleep and DOC states (Raimondo et al., 2017).

Overall, our results extend previous observations that cardiac activity encodes complex information processing and their variations depending on sleep states during sleep (Koroma et al., 2024; Pelentritou et al., 2024; Whitehurst et al., 2020). They also confirm previous demonstrations obtained in DOC patients that cardiac responses to the auditory local-global paradigm inform about variations of cognitive processing across conscious states beyond cerebral findings (Raimondo et al., 2017). Studies investigating the cerebral processing of cardiac responses (*e.g.*, heart-evoked potential) may complement our study by offering a more integrated account of the brain-body correlates of auditory irregularity processing during sleep, as it has already been done in DOC patients (Candia-Rivera et al., 2023).

At the same time, our complementary methodology to (Raimondo et al., 2017) shows that the duration of PRE and POST periods influenced the cardiac effects reported in NREM and REM sleep. We interpret this finding as an effect of baseline variations of heart rate on cardiac responses to auditory stimuli. Despite the study of the interaction between baseline and evoked changes of cardiac activity is beyond the scope of the current study, determining the origin of this effect in the future might help to better control for the parameters shaping cardiac reactivity to environmental demands.

Finally, global deviance effects were also observed in cerebral activity during sleep when analyses included trials that were also presented in wakefulness before (Strauss et al., 2015). The possibility of such carry-over effects from wakefulness to sleep due to previous exposure of stimuli is undermined at the cardiac level because we found an absence of cardiac modulation to auditory irregularities in wakefulness. The effect of training may nevertheless be investigated in future studies to gain insights on the role of automatized processes on cardiac responses to sensory information during sleep.

In conclusion, we report that cardiac responses to the auditory local-global paradigm reveal the processing of complex irregularities (*i.e.*, global deviance effects) during REM sleep, and basic irregularities (*i.e.*, local mismatch effects) in NREM sleep. Some of our findings diverge from our initial predictions based on the study of cerebral effects (Blume et al., 2022; Strauss et al., 2015, 2022), confirming previous demonstrations that cardiac signals encode information about cognitive processes that are partially independent from brain activity during sleep (Koroma et al., 2024; Whitehurst et al., 2016, 2022). Overall, our study provides novel evidence supporting the embodiment of cognitive functions and highlights the value of cardiac signals to gain insight on the correlates of complex information processing during sleep.

Competing interests

The authors declare no competing interests.

Data and code availability

Codes and dataframes used for analyses are in open access via https://gitlab.uliege.be/Matthieu.Koroma/sleep_localglobal/-/tree/master/preprint

Author contributions

Matthieu Koroma: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; project administration; formal analysis; software; data curation; resources; funding acquisition; supervision.

Paradeisos Boulakis: Methodology; validation; writing – review and editing; resources.

Vaia Gialama: Methodology; validation; formal analysis.

Federico Raimondo: Conceptualization; methodology; validation; resources.

Christine Blume: Methodology; validation; visualization; writing – review and editing;

project administration; formal analysis; data curation; resources; supervision. **Mélanie Strauss**: Conceptualization; Methodology; validation; visualization; writing – review and editing; project administration; formal analysis; data curation; resources; supervision; funding acquisition.

Athena Demertzi: Supervision; conceptualization; investigation; validation; visualization; writing – review and editing; formal analysis; project administration; resources; data curation; methodology; writing – original draft; funding acquisition.

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Supplementary Figures

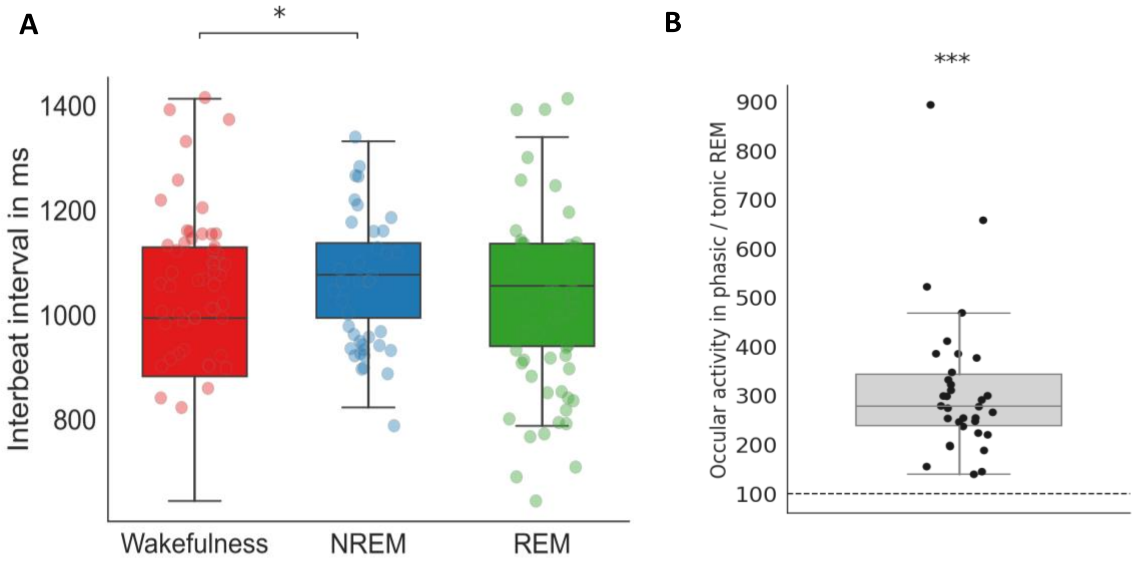


Figure S1. **Cardiac and ocular signals are modulated across sleep stages. (A)** Interbeat interval were computed by extracting R-peaks from electrocardiographic signals and averaging over sleep scoring windows of the same stage for each subject. **(B)** Ocular activity was defined as the standard deviation of electrooculographic signals around trial onset (-4s to 4s). Statistical significance for post-hoc tests, *: p<0.05, ***: p<0.001

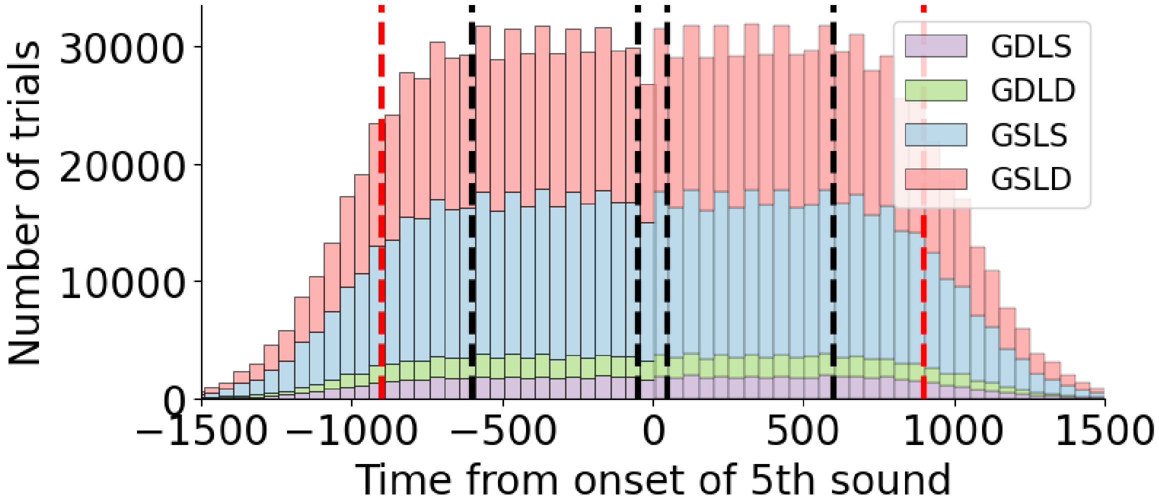


Figure S2. **PRE and POST periods were defined based on heartbeats around 5th sound onset**. PRE periods were defined based on heartbeats before the onset of the 5th sound (negative values) and POST periods based on heartbeats after the onset of the 5th sound (positive values). GDLS: Global Deviant Local Standard, GDLD: Global Deviant Local Standard, GSLS: Global Standard Local Standard, GSLD: Global Standard Local Deviant. PRE and POST periods were restricted between 20 and 600ms (black dotted lines) and 900ms (red dotted lines).

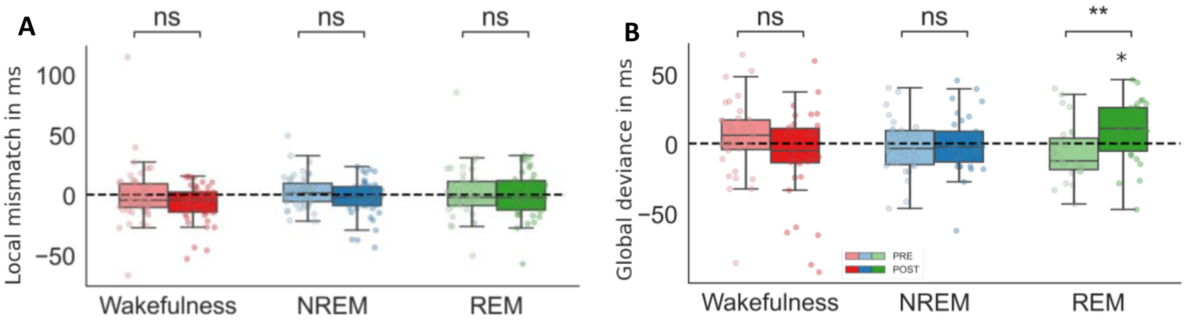


Figure S3. **Cardiac decelerates after “true global” deviants during REM sleep**. “True local” mismatch **(A)** and “true global” deviance **(B)** effects were computed for Wakefulness, NREM and REM seperately for PRE and POST periods contained between 20 and 600ms following Raimondo et al., 2017. Boxplots represent median, first and fourth quartiles and whiskers deciles for each condition. Datapoints represent individual subjects. Statistical significance for post-hoc test, ns: not significant,*: p<0.05, **: p<0.01

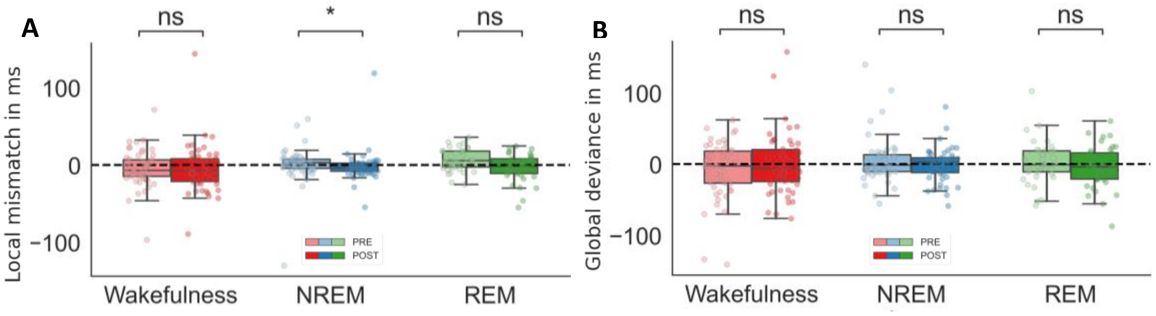


Figure S4. **Cardiac activity accelerates after "true local" deviants during NREM sleep**. "True local" mismatch **(A)** and "true global" deviance **(B)** effects were computed for Wakefulness, NREM and REM separately for PRE and POST periods contained between 20 and 900ms following the grid-search analysis. Boxplots represent median, first and fourth quartiles and whiskers deciles for each condition. Datapoints represent individual subjects. Statistical significance for post-hoc test, ns: not significant, *: p<0.05

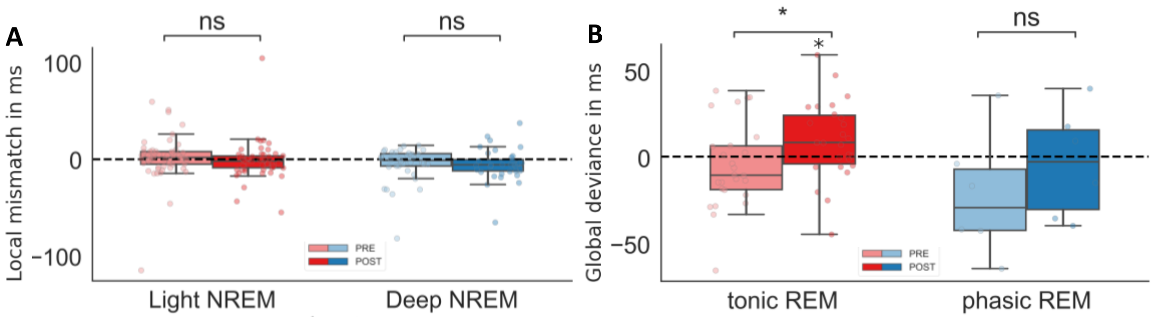
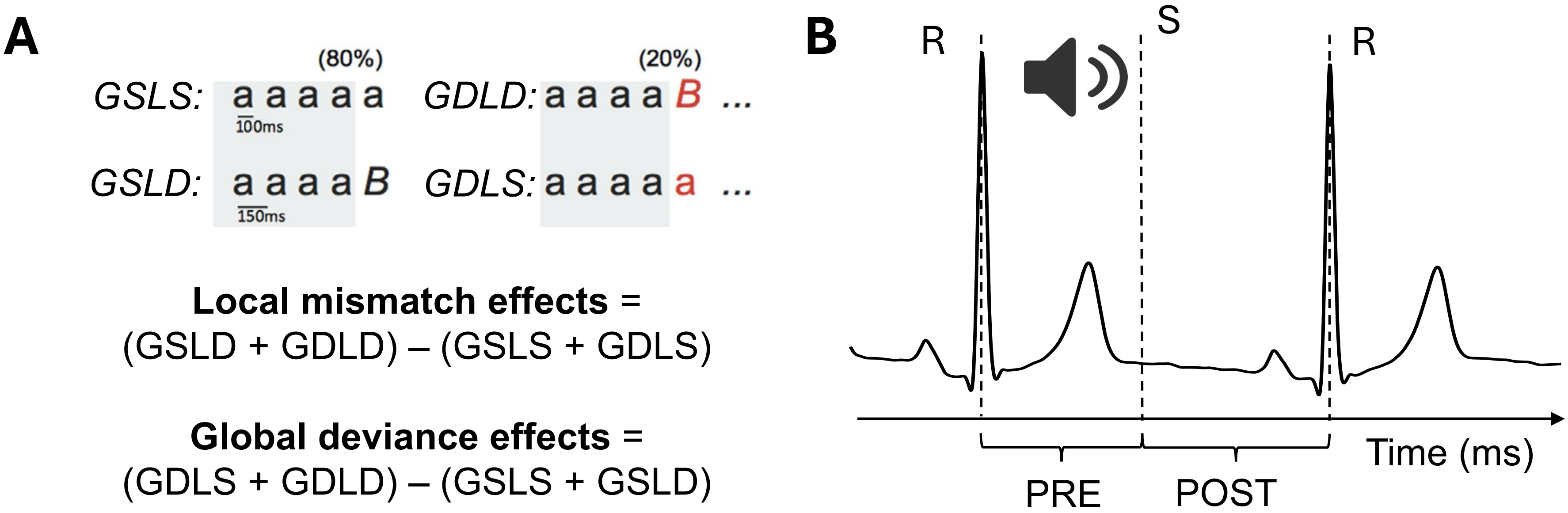
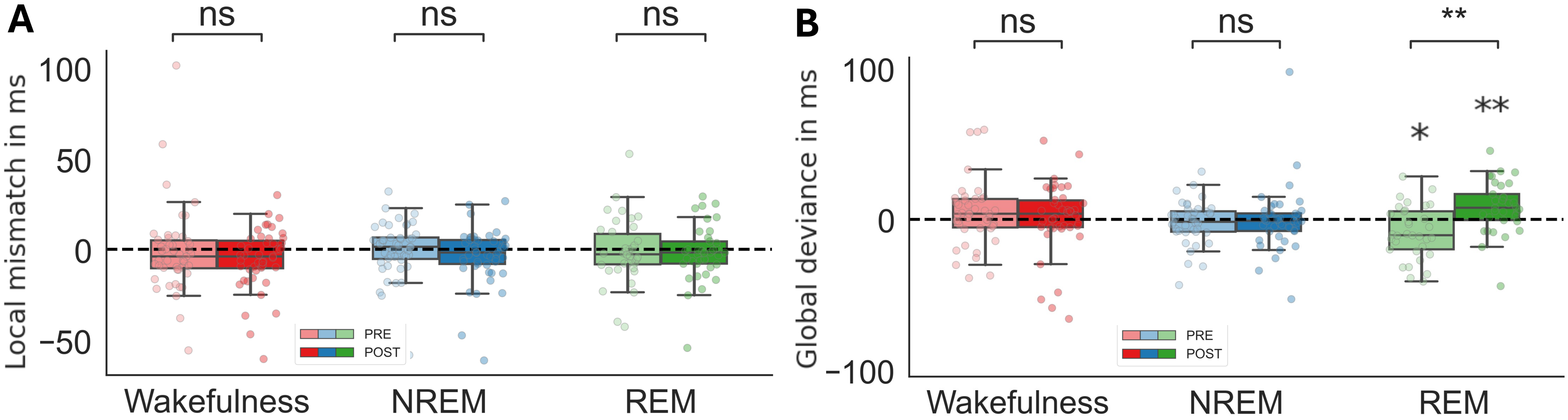


Figure S5. **Cardiac responses decelerate after "true global" deviants in tonic REM**. True local mismatch effects were computed for PRE and POST periods contained between 20 and 900ms in light and deep NREM **(A)** and true global deviance between 20 and 600ms effects in tonic and phasic REM **(B)**. Boxplots represent median, first and fourth quartiles and whiskers deciles for each condition. Datapoints represent individual subjects. Statistical significance for post-hoc test, ns: not significant, *: $p<0.05$

Table S1. **Grid-search analysis approach identifies a local mismatch effect during sleep when including PRE and POST periods from 20 to 900ms**. The median and 95% confidence interval (bootstrap, n=2000) of the POST-PRE and the post-hoc Wilcoxon test POST vs. PRE corrected for multiple comparisons were computed for the local mismatch and global deviance effects in wakefulness and sleep (NREM2, NREM3 and REM grouped together) on PRE and POST periods ranging between 20ms and 600 until 1200ms with 100ms step interval. Statistical significance, *: p<0.05

Effect	State	600ms	700ms	800ms	900ms	1000ms	1100ms	1200ms
Local mismatch	Wake	-2.6± [-8.6, 4.9]	-6.3± [-14.1, -1.8]	-3.2± [-8.5, 7.2]	0.01± [-12.4, 8.4]	-7.3± [-20.3, 0.3]	-3.7± [-16.6, -0.5]	-2.3± [-20.7, -2.5]
	Sleep	-2.2± [-5.0, -1.1]	-3.0± [-6.4, -0.8]	-3.4± [-6.0, -0.2]	**-5.4± [-10.2, -3.0]***	-3.3± [-9.1, 0.9]	-4.3± [-9.8, 0.5]	-4.4± [-9.2, 2.6]
Global deviance	Wake	0.9± [-10.3, 9.1]	-9.3± [-16.1, 4.7]	-2.5± [-12.3, 9.6]	-7.4± [-12.9, 7.9]	-0.1± [-15.4, 17.9]	1.7± [-13.4, 18.8]	6.5± [-8.6, 19.4]
	Sleep	3.5± [-1.1, 15.8]	1.2± [-6.4, 6.1]	0.8± [-8.8, 7.0]	-2.7± [-7.7, 2.3]	-2.8± [-9.1, 7.4]	-5.6± [-8.3, 3.4]	-4.7± [-9.0, 3.6]


A
(80%)
GSLS: a a a a a
100ms
GSLD: a a a a B
150ms
(20%)
GDLD: a a a a B ...
GDLS: a a a a a ...
Local mismatch effects =
(GSLD + GDLD) – (GSLS + GDLS)
Global deviance effects =
(GDLS + GDLD) – (GSLS + GSLD)
B
R
S
R
PRE
POST
Time (ms)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Local mismatch in ms
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Wakefulness
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Global deviance in ms
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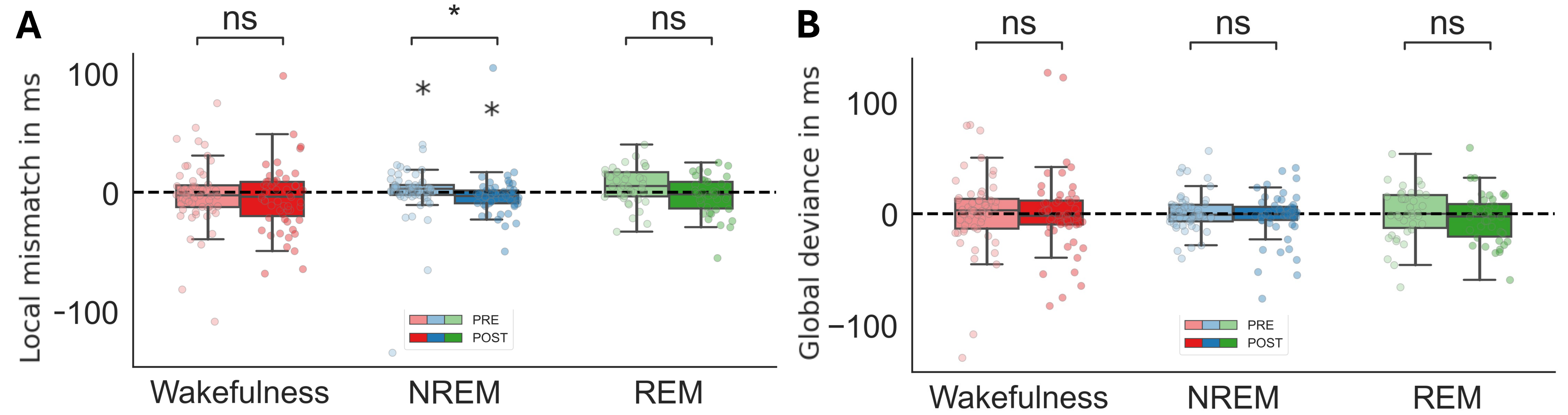
NREM
REM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Local mismatch in ms
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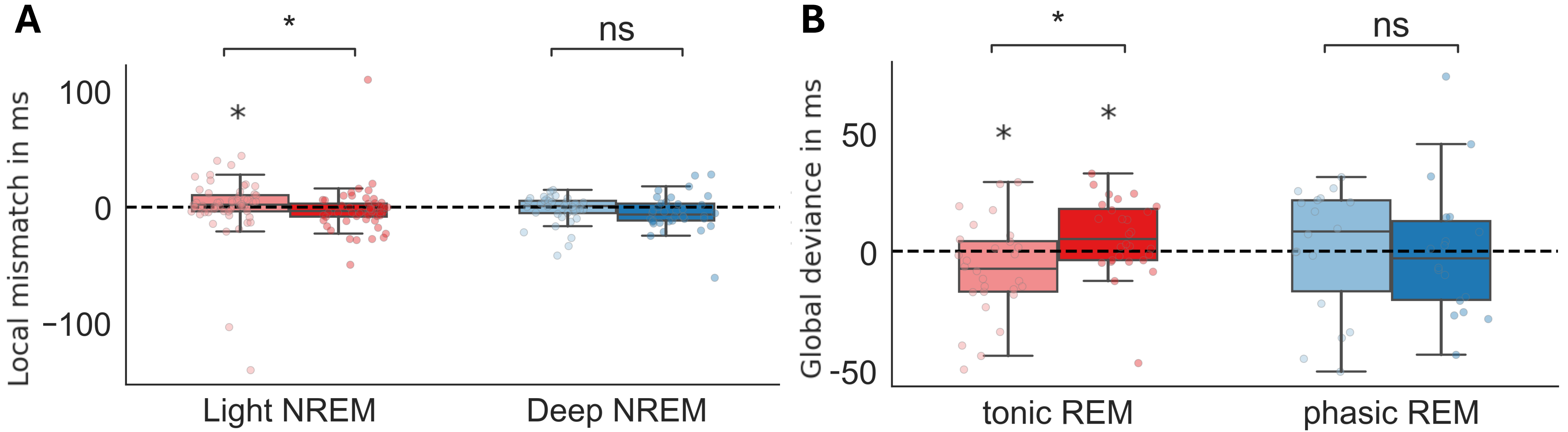
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Global deviance in ms
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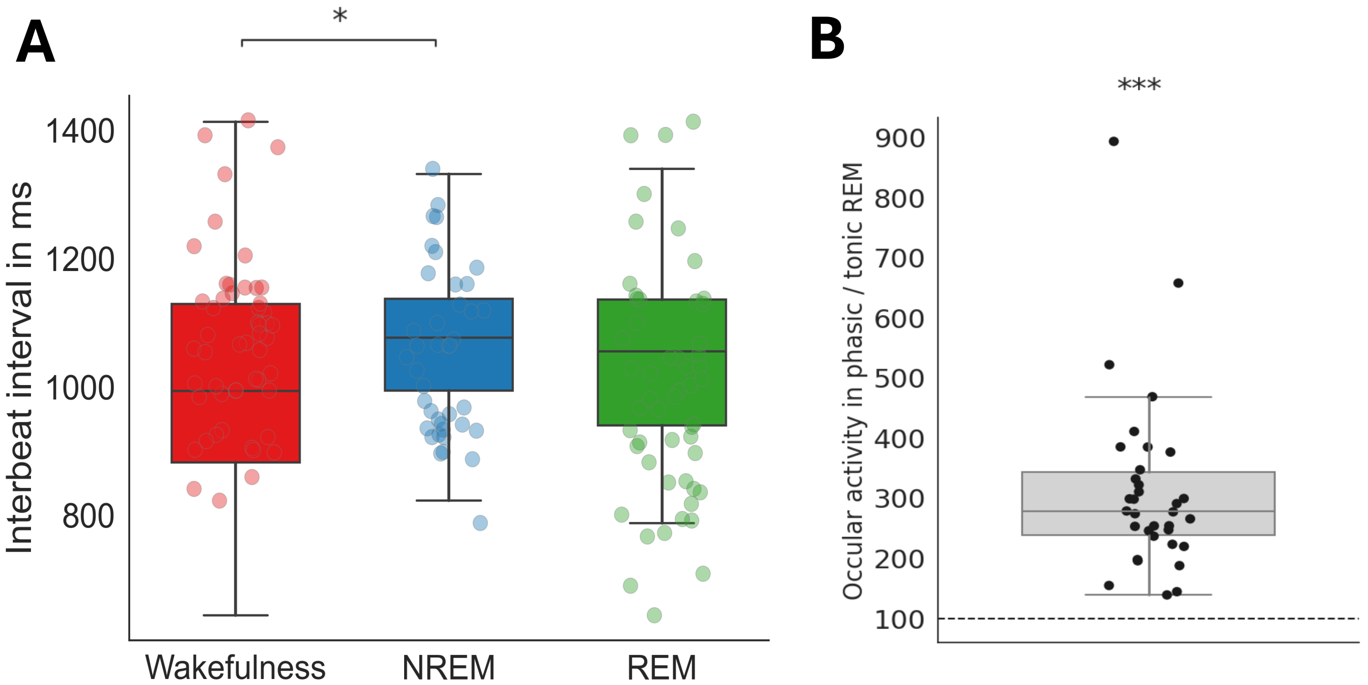
-50
tonic REM
phasic REM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Interbeat interval in ms
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1200
1000
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Wakefulness
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Occular activity in phasic / tonic REM
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400
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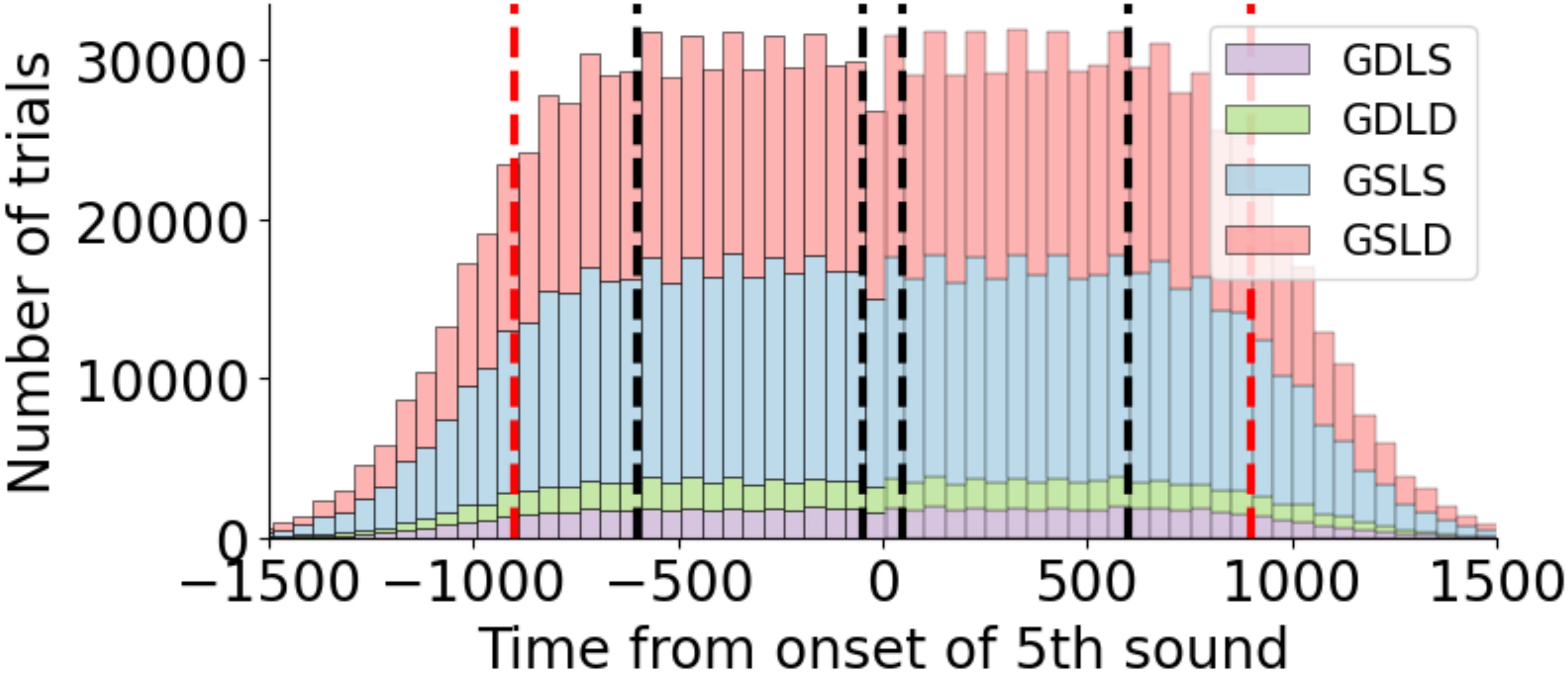
GDLS
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GSLD
Number of trials
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10000
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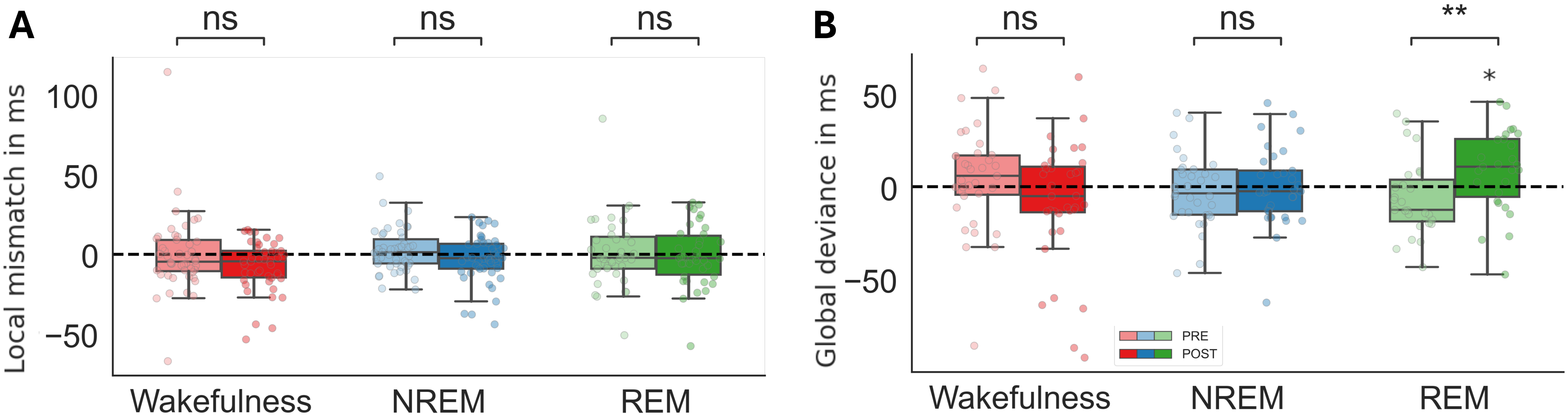
1000
1500
Time from onset of 5th sound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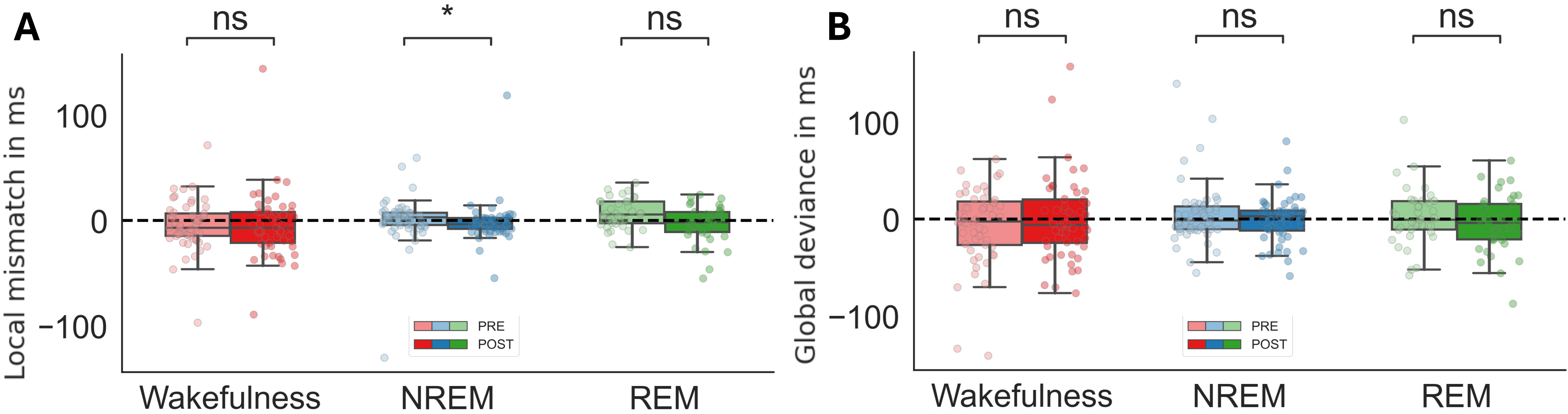
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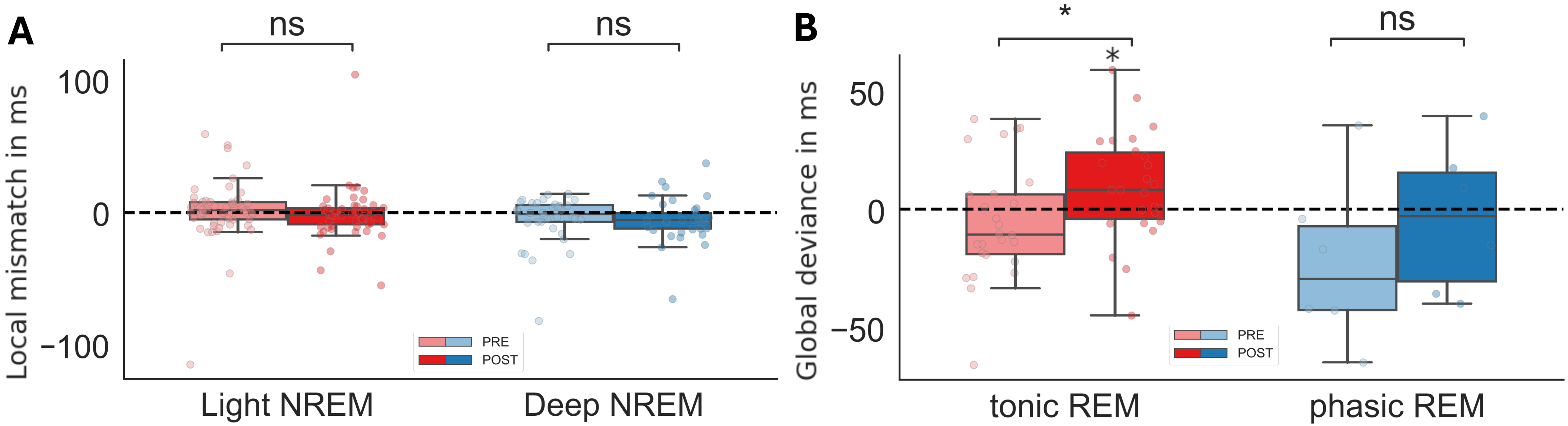
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Global deviance in ms
PRE
POST
tonic REM
phasic REM

Effect	State	600ms	700ms	800ms	900ms	1000ms	1100ms	1200ms
Local mismatch	Wake	-2.6± [-8.6, 4.9]	-6.3± [-14.1, -1.8]	-3.2± [-8.5, 7.2]	0.01± [-12.4, 8.4]	-7.3± [-20.3, 0.3]	-3.7± [-16.6, -0.5]	-2.3± [-20.7, -2.5]
	Sleep	-2.2± [-5.0, -1.1]	-3.0± [-6.4, -0.8]	-3.4± [-6.0, -0.2]	**-5.4± [-10.2, -3.0]***	-3.3± [-9.1, 0.9]	-4.3± [-9.8, 0.5]	-4.4± [-9.2, 2.6]
Global deviance	Wake	0.9± [-10.3, 9.1]	-9.3± [-16.1, 4.7]	-2.5± [-12.3, 9.6]	-7.4± [-12.9, 7.9]	-0.1± [-15.4, 17.9]	1.7± [-13.4, 18.8]	6.5± [-8.6, 19.4]
	Sleep	3.5± [-1.1, 15.8]	1.2± [-6.4, 6.1]	0.8± [-8.8, 7.0]	-2.7± [-7.7, 2.3]	-2.8± [-9.1, 7.4]	-5.6± [-8.3, 3.4]	-4.7± [-9.0, 3.6]