Timing between Cortical Slow Oscillations and Heart Rate Bursts during Sleep Predicts Temporal Processing Speed, but Not Offline Consolidation

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Abstract

■ Central and autonomic nervous system activities are coupled during sleep. Cortical slow oscillations (SOs; <1 Hz) coincide with brief bursts in heart rate (HR), but the functional consequence of this coupling in cognition remains elusive. We measured SO–HR temporal coupling (i.e., the peak-to-peak interval between downstate of SO event and HR burst) during a daytime nap and asked whether this SO–HR timing measure was associated with temporal processing speed and learning on a texture discrimination task by testing participants before and after a nap. The coherence of SO–HR events during sleep strongly correlated with an individual's temporal processing speed in the morning and evening test sessions, but not with their change in performance after the nap (i.e., consolidation). We confirmed this result in two additional experimental visits and also discovered that this association was visit-specific, indicating a state (not trait) marker. Thus, we introduce a novel physiological index that may be a useful marker of state-dependent processing speed of an individual. ■

INTRODUCTION

As the brain shifts into deeper stages of non-rapid eye movement sleep, neural firing becomes more synchronized, eliciting slow, cortical oscillatory rhythms that can be measured with scalp EEG. One of the predominant rhythms of non-rapid eye movement sleep is slow oscillation (SO; <1 Hz), which reflects underlying fluctuations between periods of neuronal activity (up-states) and silence (down-states; Dang-Vu et al., 2008). Autonomic nervous system (ANS) activity also changes as sleep deepens, undergoing a shift toward more parasympathetic dominance (as indexed by the high-frequency component of heart beat-to-beat intervals; 0.15–0.4 Hz), leading to progressive heart rate (HR) deceleration. Traditional frequency-based analyses that average across several minutes of sleep have reported that slow wave activity (SWA; 0.5–4 Hz) changes with and is preceded by parasympathetic activity (Jurysta et al., 2003; Brandenberger, Ehrhart, Piquard, & Simon, 2001). Additionally, seconds after spontaneous and evoked Stage 2 SOs (i.e., K-complexes), HR shows rapid acceleration followed by deceleration (de Zambotti et al., 2016). However, the functional significance of synchrony between SOs and cardiac autonomic activity during sleep remains elusive.

Importantly, large-scale neural activity and cognitive processing can be shaped by brain–body interactions. Park, Correia, Ducorps, and Tallon-Baudry (2014) examined the impact of brain–body activity on visual perception by measuring the magnitude of the neural activity locked to heartbeats using magnetoencephalography during a visual detection task. Previous studies reported that the amplitude of these heartbeat evoked potentials (HEPs) correlated with interoceptive and empathy abilities (Schandry & Montoya, 1996). Here, the authors showed that basic visual processing could be predicted by enhanced HEP responses before stimulus onset in ventral ACC and the right inferior parietal lobule. In addition, the slowing of postdecisional HR correlated with the amplitude of the prestimulus differential response to heartbeats in ventral ACC–ventral medial pFC. Although HEP is not well understood, these results emphasize the significance of on-task heart–brain interactions for visual detection. In other work, coupling between an autonomic measure (spontaneous pupillary fluctuations) and off-task resting-state activity (in regions associated with sympathetic activity) was found to be correlated with trait-level attention (Breeden, Siegle, Norr, Gordon, & Vaidya, 2017). More recently, increasing temporal alignment of EEG–vigilance states and autonomic

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signals (HR and skin conductance) during resting state corresponded to stronger cortical inhibition (Ulke et al., 2017). These findings suggest that adaptive autonomic shifts in response to salient environmental cues may be supported by intrinsic coordination between autonomic–central brain activity. Furthermore, both the magnitude and timing between central and autonomic events are reliable indicators of CNS–ANS interaction. Building on past research, the current study focuses on the impact of off-task heart–brain interactions on the speed of visual processing.

The goals of the current study were threefold. First, we used high-resolution analysis of the relative timing of HR bursts and cortical SOs during sleep to obtain a marker of autonomic–central timing. Second, we sought to measure the association between two independent measures of processing speed: SO–HR timing and texture discrimination (i.e., the speed at which individuals can reliably discriminate the orientation of three target elements against a background of distractor elements before a mask onset), as well as the improvement in discrimination that is known to occur after a period of sleep (Mednick, Nakayama, & Stickgold, 2003). Although the texture discrimination task (TDT) has traditionally been considered a task that investigated perceptual orientation learning, insightful work by Cong and colleagues demonstrated that a large amount of improvement on the TDT was accounted for by learning the temporal separation of the very brief target and mask (Wang, Cong, & Yu, 2013), and training increased the speed of temporal processing. In the current study, we utilized this task to examine baseline temporal processing speed at the first visit, as well as change in temporal processing speed after a nap. Third, we measured the reliability of the SO–HR and perceptual performance association across three experimental visits. Participants were tested on three occasions, 2 weeks apart. On each experimental day, participants completed a TDT at 9 a.m. and 5 p.m. and took a 90-min polysomnographically recorded nap (approximately 1:30 p.m. to 3:30 p.m.) between task sessions. The discrimination target was in a different visual field location at each visit, but constant within the day. We found that SO–HR timing during the nap is associated with temporal processing speed during each test session, but not necessarily with the change in performance across sessions. Furthermore, we found that this association was specific to the current state of the individual, as measured by poor cross-visit correlations.

METHODS

Participants

Data reported here come from a larger, minilongitudinal study that included up to seven visits per participant. Data from this study have been reported elsewhere (McDevitt et al., 2018; Sattari et al., 2017; Cellini, Whitehurst, McDevitt, & Mednick, 2016; Whitehurst, Cellini, McDevitt, Duggan, & Mednick, 2016). Fifty-five (30 women) healthy, nonsmoking adults between the ages of 18 and 35 years with no personal history of sleep disorders or neurological, psychological, or other chronic illness gave informed consent to participate in the study. The sample size was selected based on prior studies from our lab using the TDT that have typically included 20–30 participants in a napping condition (Mednick et al., 2013; McDevitt, Duggan, & Mednick, REM sleep rescues learning from interference, 2015). This study was originally designed to examine differences in nap-dependent learning in two groups of people (regular nappers and infrequent nappers), with 20 people in each group (total $n = 40$) based on the aforementioned studies. All experimental procedures were approved by the Human Research Review Board at the University of California, Riverside, and were in accordance with federal (National Institutes of Health) guidelines and regulations. Participants included in the study had a regular sleep–wake schedule (reporting a habitual time in bed of about 7–9 hr per night). Participants were thoroughly screened before participation in the study. The Epworth Sleepiness Scale (ESS) and the reduced Morningness–Eveningness Questionnaire (rMEQ) were used to exclude potential participants with excessive daytime sleepiness (ESS scores >10) or extreme chronotypes (rMEQ < 8 or > 21). Participants received monetary compensation for participating in the study.

Data Acquisition and Analysis

Study Procedure

Participants completed three in-lab study days, one each at the beginning (Visit 1), middle (Visit 2), and end (Visit 3) of the experimental period, spaced 2 weeks (14 ± 2 days) apart. Participants wore actigraphs to monitor sleep–wake activity for 1 week before the experiment to ensure participants were not sleep-deprived and spent at least 6.5 hr in bed the night before their visit. Participants arrived at the University of California, Riverside, Sleep and Cognition lab at 9 a.m. and completed the perceptual learning task (see below). At 1:30 p.m., participants took a polysomnographically recorded nap. They were given up to 2 hr time-in-bed to obtain up to 90 min total sleep time. Sleep was monitored online by a trained sleep technician. Nap sessions were ended if the participant spent more than 30 consecutive minutes awake. At 5 p.m., participants were retested on the perceptual learning task. Forty participants completed all three visits. After excluding outliers (participants with no Stage 2 sleep, missing/loose electrocardiogram (ECG), or outlier behavioral performance, $M \pm 3\ SD$), a total of 29, 28, and 25 participants from Visit 1, Visit 2, and Visit 3, respectively, were used for the analyses.

Sleep Recording

Polysomnography recordings, which included EEG, ECG, chin EMG, and EOG, were collected using Astro-Med Grass Heritage Model 15 amplifiers with Grass GAMMA software. Scalp EEG and EOG electrodes were referenced to unlinked contralateral mastoids (F3/A2, F4/A1, C3/A2, C4/A1, P3/A2, P4/A1, O1/A2, O2/A1, LOC/A2, ROC/A1), and two submental EMG electrodes were attached under the chin and referenced to each other. ECG was recorded by using a modified Lead II Einthoven configuration. All data were digitized at 256 Hz.

Sleep Scoring

Raw data were visually scored in 30-sec epochs according to Rechtschaffen and Kales (1968). Five stages (i.e., wake, Sleep Stage 1, Stage 2, SWS, and REM) were reclassified in continuative and undisturbed 3-min bins, which were used for further analysis.

Heart Beat Detection and Time Series Extraction

The ECG signals were filtered with a passband of 0.5–100 Hz by Butterworth filter. R waves were identified in the ECG using the Pan–Tompkins method (Pan & Tompkins, 1985) and confirmed with visual inspection. To extract continuous RR time series, the RR intervals were resampled (at 4 Hz) and interpolated by piecewise cubic spline.

Slow Oscillation

The EEG signals were filtered (zero-phase bandpass, 0.15–4 Hz). Then, SO was detected from the F3 and F4 electrodes based on a set of criteria for peak-to-peak amplitude, up-state amplitude, and duration of down- and up-states (Dang-Vu et al., 2008).

SO–HR Timing Calculation

Our focus on the temporal aspect of the SO–HR relation was due to the peaky nature of both signals, which allowed for a high degree of precision regarding the temporal dynamics of two signals. The SO peak is frequently used in SO detection algorithms and therefore is a robust feature to identify an EEG marker. We chose the peak of the HR burst because we found that this was the optimal time point for universal and accurate detection in the HR burst.

For each frontal electrode, an average RR time series in reference to the down-state trough of SOs was calculated in a 10-sec window. Then, the SO–HR timing was calculated by averaging the HR maximum times (i.e., RR minimum times) across the electrodes.

Texture Discrimination Task

Participants performed a TDT similar to that developed by Karni and Sagi (1991). Visual stimuli for the TDT were created using the Psychophysics Toolbox (Kleiner et al., 2007; psychtoolbox.org). Each stimulus contained two targets: a central letter ("T" or "L"), and a peripheral line array (vertical or horizontal orientation) in one of four quadrants (lower left, lower right, upper left, or upper right) at 2.5°–5.9° eccentricity from the center of the screen. The quadrant was counterbalanced across participants and visits. The peripheral array consisted of three diagonal bars that were either arranged in a horizontal or vertical array against a background of horizontally oriented background distracters, which created a texture difference between the target and the background.

An experimental trial consisted of the following sequence of four screens: central fixation cross, target screen for 33 msec, blank screen for a duration between 0 and 600 msec (the ISI), mask for 17 msec, followed by the RT interval (2000 msec) and feedback (250 msec, red fixation cross with auditory beep for incorrect trials and green fixation cross for correct trials) before the next trial. Participants discriminated two targets per trial by reporting both the letter at central fixation ("T" or "L") and the orientation of the peripheral array of three diagonal lines (horizontal or vertical) by making two key presses. The central task controlled for eye movements.

Each block consisted of 25 trials, each with the same ISI. A threshold was determined from the performance across 13 blocks, with a progressively shorter ISI, starting with 600 msec and ending with 0 msec. The specific sequence of ISIs across an entire session was (600, 500, 400, 300, 250, 200, 167, 150, 133, 100, 67, 33, 0). A psychometric function of percent correct for each block was fit with a Weibull function to determine the ISI at which performance yielded 80% accuracy. Within-day TDT performance change was calculated as the difference in threshold between Session 1 and Session 2, such that a positive score indicates performance improvement (i.e., decreased threshold in Session 2), whereas a negative score indicates deterioration.

Participants were given task instructions and practiced the task during an orientation appointment before starting the study. During this practice, the peripheral target was located in a quadrant that was not used during the study. This practice ensured that participants understood the task and accomplished the general task learning that typically occurs the first time a participant performs a task. Additionally, on the study day, participants were allowed to practice an easy version of the task (ISI of 1000–600 msec) before starting the test session to make sure participants were able to discriminate the peripheral target between 90% and 100% correct on an easy version of the task.

RESULTS

For each visit, we used an automated algorithm to detect SOs for left and right frontal electrodes (F3 and F4,

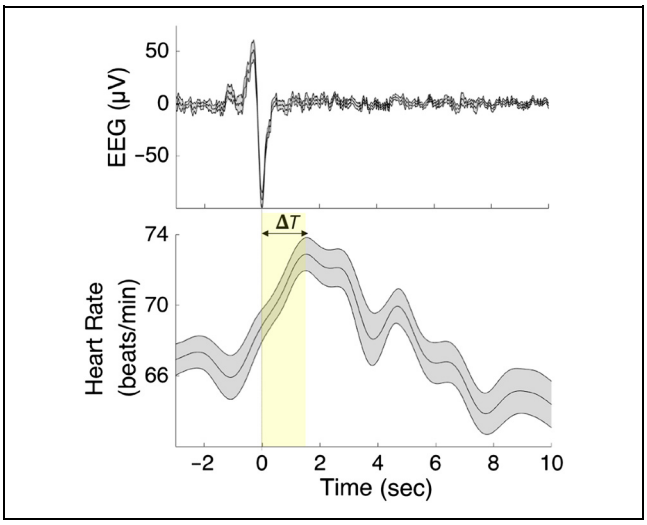

Figure 1. Heart rate reaches a peak following SOs during Stage 2 sleep. The SO–HR timing (ΔT) is defined as the time difference between SO down-state trough and the HR peak.

respectively) in Stage 2 and slow wave sleep (SWS). We then analyzed HR activity within the ±5 sec window (total 10-sec duration) following the SO downstate. During Stage 2 sleep, this activity window was characterized by an acceleration in HR, followed by a deceleration (Figure 1), in agreement with previous studies (de Zambotti et al., 2016). Detected SO events co-occurred with a peak in HR, which was 12.09 ± 1.48% above the average Stage 2 HR. The average duration of the HR acceleration and deceleration was 5.52 ± 2.51 sec. By comparison, during SWS, HR increased by only 3.35 ± 1.01% following SOs. As such, we focused on the heart–brain relationship during Stage 2 sleep in subsequent analyses.

We next measured duration of the SO–HR intervals. For each detected SO event in Stage 2 sleep, the SO–HR peak-to-peak interval was quantified by measuring the time difference between the trough of the SO down-state and the peak of the average HR acceleration (Figure 1). The average SO–HR timing across F3 and F4 electrodes was used as each participant's individual measure of SO–HR timing. Across participants, the average Stage 2 SO–HR timing for Visit 1, Visit 2, and Visit 3 naps was 2.15 sec (SD = 1.03), 2.10 sec (SD = 0.76), and 2.23 sec (SD = 0.72), respectively. We next used each participant's SO–HR timing specific to each visit to investigate its possible relation to temporal processing speed as measured by TDT thresholds (pre- and postnap sessions independently) and change in TDT performance after the sleep (change from pre- to postnap sessions).

Prenap TDT performance was correlated with SO–HR timing during the same-day nap in all three visits (Visit 1: $r = .47, p = .01$; Visit 2: $r = .58, p = .001$; Visit 3: $r = .58$, $p = .002$; Figure 2A). Since TDT performance was highly correlated within same-day sessions (Visit 1: $r = .89, p < .0001$; Visit 2: $r = .86, p < .0001$; Visit 3: $r = .80, p < .0001$), we expected the SO–HR timing and TDT performance relationship to be preserved during the postnap

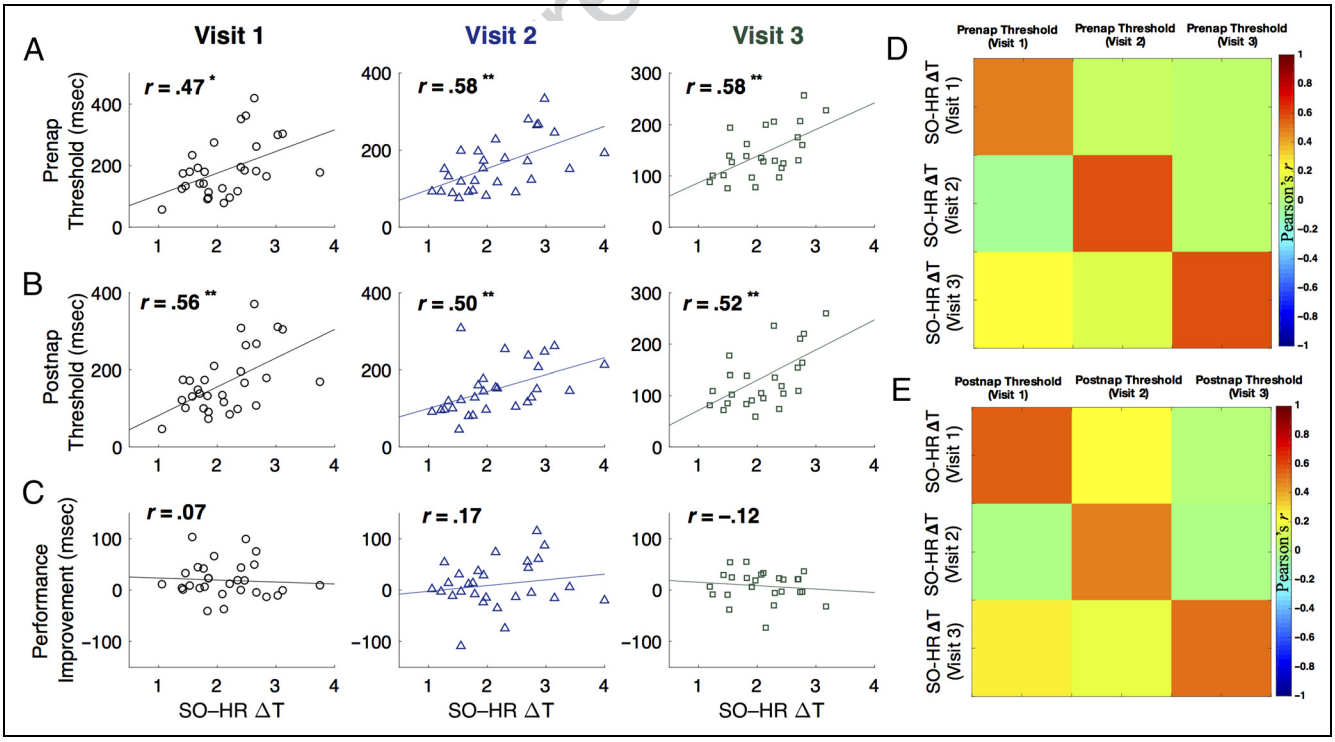

Figure 2. The scatter plots show the relationship between SO–HR timing and (A) prenap TDT threshold, (B) postnap threshold, and (C) improvement in TDT performance. The lower threshold implies better performance. (D–E) The cross-visit relationship between SO–HR timing and the TDT thresholds (asterisks mean significant correlations: *$p < .05$, **$p < .01$).

Table 1. Pearson Correlations between Cortical Functioning during Sleep and Performance and Cardiac Functioning during sleep and Performance

	SWA Stage 2	*Sigma Power Stage 2*	*SWA Stage 3*	*Sigma Power Stage 3*	*HF Stage 2*	*HFn Stage 2*	*HF Stage 3*	*HFn Stage 3*
Prenap threshold Visit 1	**−0.49 p = .016**	−0.22 p = .30	−0.21 p = .32	−0.27 p = .21	−0.20 p = .28	−0.08 p = .69	−0.14 p = .51	−0.09 p = .67
Postnap threshold Visit 1	**−0.48 p = .019**	−0.12 p = .59	−0.08 p = .71	−0.16 p = .47	−0.16 p = .42	−0.11 p = .56	−0.12 p = .59	−0.12 p = .58
Performance improvement Visit 1	−0.21 p = .32	−0.32 p = .13	−0.06 p = .78	−0.35 p = .10	−0.17 p = .37	0.06 p = .75	−0.08 p = .70	0.05 p = .82

sessions, which it was (Visit 1: $r = .56, p = .002$; Visit 2: $r = .50, p = .007$; Visit 3: $r = .52, p = .008$; Figure 2B). However, there were no significant associations between SO–HR timing and TDT performance change (Session 1–Session 2) at any visit (Visit 1: $r = -.07, p = .725$; Visit 2: $r = .175, p = .371$; Visit 3: $r = -.12, p = .561$; Figure 2C).

We investigated how SO–HR timing covaried with itself across visits. We did not find a significant correlation between Visit 1 and Visit 2 ($r = .26$, $p = .16$), whereas the correlation between Visit 2 and Visit 3 ($r = .40$, $p = .02$) as well as Visit 1 and Visit 3 ($r = .51$, $p = .003$) were significant. We also examined how prenap thresholds covaried across visits. The correlation between Visit 1 and Visit 2 was significant ($r = .41$, $p = .02$), whereas the correlation between Visit 2 and Visit 3 ($r = .34$, $p = .06$) was marginal and that between Visit 1 and Visit 3 ($r = .21$, $p = .27$) was the weakest. Thus, the heart–brain measure and the perceptual task showed dissimilar correlation trends across visits.

To confirm the visit specificity of these associations, we investigated the correlations between the SO–HR timings in each visit and TDT performance in other visits. We found no significant cross-visit correlations (Figure 2D–E), suggesting that the relation between these two measures is specific to the current state of the individual, at least at the level of weeks. Lastly, we checked whether the SO–HR was simply a proxy for sleepiness by examining the correlation between SO–HR and subjective ratings of sleepiness. No significant correlation was found between the SO–HR timing and average sleepiness in prenap (Visit 1: $r = .001$, $p = .99$; Visit 2: $r = .01$, $p = .97$; Visit 3: $r = -.06$, $p = .78$) and postnap (Visit 1: $r = .08$, $p = .66$; Visit 2: $r = .06$, $p = .74$; Visit 3: $r = .31$, $p = .12$) sessions. Although we focused on SO–HR timing here, we also conducted an exploratory analyses of the potential relationship between performance at Visit 1 and select sleep rhythms of interest during Stage 2 and SWS separately (at the dominant electrode site for each respective rhythm), including frontal SWA (0.5–1 Hz) and central sigma (12–15 Hz) activity. We found no significant associations between sleep rhythms and performance, except for the negative correlations between performance and Stage 2 SWA. In addition, we explored the impact of cardiac function alone on performance at Visit 1 by measuring correlations between performance and HF (0.04–0.15 Hz) and normalized HF (HFn HRV) in Stages 2 and 3 separately and found no significant correlations. The Pearson correlation coefficients are tabulated in Table 1.

In summary, our data suggest evidence for a general marker of processing speed in individuals as measured by the association between the speed of texture discrimination in the TDT and SO–HR timing during nap. This finding was confirmed across all three experimental visits, which were spaced 2 weeks apart. We did not find associations between our measure of autonomic–central coupling and sleep-dependent learning, and the cross-modal association in processing speed was highly specific to the experimental visit, with poor cross-visit correlations.

DISCUSSION

Prior work has demonstrated associations between autonomic measures including HEPs, HR, skin conductance, and gut–brain interactions and cognitive processes (Park et al., 2014; Tallon-Baudry, Campana, Park, and Babo-Rebelo, 2018). Here, we found that the timing between autonomic and central events during sleep is a state variable that is associated with an independent measure of temporal processing speed during a perceptual task. This is interesting for several reasons. First, the measure of perceptual performance and autonomic–central interactions was measured at different times and in different states of consciousness, which may suggest that this relationship reflects a more general marker of timing. Second, we found stronger within-visit than cross-visit associations between perception and heart–brain interaction, indicating a state-dependent measure of processing speed that is not simply a proxy for sleepiness. Third, it suggests that processing speed in other cognitive timing domains (i.e., motor, audition, tactile) may be predicted by ANS–CNS timing. Although we hypothesized that CNS–ANS interactions during sleep would be correlated with both baseline performance thresholds and improvements, we only found an association with baseline temporal processing speed and not improvement in speed. One possible reason why we could not find associations with improvement in TDT is that the heart–brain measure we used is

specifically found in Stage 2 sleep and not reliably detected in SWS or REM sleep, whereas the TDT improvement is typically related to REM sleep (Mednick et al., 2003; Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994).

In the current study, we examined both within-session variation across participants as well as variation in change scores across sessions. Consider the within-session variation, particularly Session 1 when participants were exposed to the stimulus for the first time: Some participants performed better than average, and some participants performed worse. What might explain why some are better than others? One possibility, extending from Wang's work (Wang et al., 2013), is that it reflects differences in "baseline" levels of temporal processing. However, more work is required to further characterize the nature of the temporal processes at work in this task.

Several candidate brainstem and cortical regions may be involved in the interaction between sleep oscillations and HR. One possibility is that the nucleus of the solitary tract (NTS), which acts as one of the main bridges between CNS and cardiovascular systems (Guyenet, 2006), mediates this interaction. NTS is one of the critical components of the central autonomic network with afferent and efferent connections to the cardiovascular system, and it receives projections from many cortical regions (van der Kooy, Koda, McGinty, Gerfen, & Bloom, 1994). In addition, studies of brainstem auditory evoked potentials in humans suggest that SOs are triggered by a transient activation of the ventral brainstem, and sustained dorsal brainstem activity is evident throughout the SO (Kohsaka, Sasaki, Kohsaka, Fukuda, & Ariga, 2012). Taken together, both SOs and HR increases are mediated by overlapping brain networks, and the HR burst may be a consequence of increases in spindle and SOs through widespread cortical projection to NTS (van der Kooy et al., 1994). This suggests that the increase and timing of SO before HR burst could mediate an increase of HR through combination of sympathetic and parasympathetic pathways. However, several other pathways are known to be involved in the interaction between neocortex and heart and have been examined to make definite conclusions. Given findings of age-related decreases in temporal processing speed (Andersen, Ni, Bower, & Watanabe, 2010) and dampened ANS activity (Stein, Barzilay, Chaves, Domitrovich, & Gottdiener, 2009), further studies should explore these associations in older adults, along with potential interventions to enhance cross-modal processing speed.

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