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Hippocampal activity mediates the relationship between circadian activity rhythms and memory in older adults

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ABSTRACT

Older adults experience parallel changes in sleep, circadian rhythms, and episodic memory. These processes appear to be linked such that disruptions in sleep contribute to deficits in memory. Although more variability in circadian patterns is a common feature of aging and predicts pathology, little is known about how alterations in circadian activity rhythms within older adults influence new episodic learning. Following 10 days of recording sleep-wake patterns using actigraphy, healthy older adults underwent fMRI while performing an associative memory task. The results revealed better associative memory was related to more consistent circadian activity rhythms, independent of total sleep time, sleep efficiency, and level of physical activity. Moreover, hippocampal activity during successful memory retrieval events was positively correlated with associative memory accuracy and circadian activity rhythm (CAR) consistency. We demonstrated that the link between consistent rhythms and associative memory performance was mediated by hippocampal activity. These findings provide novel insight into how the circadian rhythm of sleep-wake cycles are associated with memory in older adults and encourage further examination of circadian activity rhythms as a biomarker of cognitive functioning.

1. Introduction

Sleep and circadian rhythms change across the lifespan. Compared to young adults, older adults have shorter, less efficient, and more disrupted sleep (Ohayon et al., 2004) along with decreases in slow wave sleep (for review see: Fogel et al., 2012) and sleep spindle density (Martin et al., 2013; for review see: De Gennaro and Ferrara, 2003). The circadian rhythms of sleep-wake cycles become inconsistent, shift earlier in time, and reduce in amplitude with increased age (Huang et al., 2002; Neikrug and Ancoli-Israel, 2010). In animal models, the neural structure that mediates circadian rhythms, the suprachiasmatic nucleus (SCN), degenerates in older adults and is hypothesized to contribute to age-related disruptions in circadian rhythms (Farajnia et al., 2012). In parallel to the changes in sleep and circadian rhythms, older individuals demonstrate significant changes in cognitive functioning, including episodic memory performance (Naveh-Benjamin et al., 2004). Research has begun to link changes in sleep and cognition by suggesting that co-occurring sleep problems may uniquely contribute to cognitive deficits. Negative correlations have been observed in older adults between cognitive performance and disrupted sleep on tests of global cognitive impairment (Jelicic et al., 2002; Blackwell et al., 2006; Carvalho-Bos et al., 2007), working memory (Haimov et al., 2008; Nebes et al., 2009; Lim et al., 2012), mental speed (Oosterman et al., 2009), memory encoding (Mander et al., 2013a), memory retrieval (Westerberg et al., 2010), and memory consolidation (Wilson et al., 2012; Mander et al., 2013b; Sonni and Spencer, 2015).

Beyond the contribution of disrupted sleep, disturbances in the circadian rhythm of the rest-activity cycle are notably linked to age-related changes in cognitive functioning (Lim et al., 2012). More variability in the rest-activity cycle, known as the circadian activity rhythm (CAR), has been related to greater dementia severity (Gehrman et al., 2005) and higher mortality rates (Tranah et al., 2010). In longitudinal studies, older women who had more variable CARs were more likely to show cognitive decline 5 years later (Walsh et al., 2014), or in some cases, neurocognitive disorders such as mild cognitive impairment (MCI) or dementia (Tranah et al., 2011). Since these studies included broad and often insensitive measures of cognition in very old women (80s) with health problems (Scullin and Bliwise, 2015) little is known about

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whether disrupted CARs in healthy older individuals contribute to lower memory function.

Neuroimaging studies across the lifespan have targeted the hippocampus to understand how sleep quantity and physiology contribute to learning and memory. Work in young adults has demonstrated that sleep is essential to hippocampal-dependent learning (Yoo et al., 2007; Marshall and Born, 2007; Van Der Werf et al., 2009; Nguyen et al., 2013; for review see: Abel et al., 2013). In older individuals more hippocampal activity during memory tasks has been associated with greater total sleep time (Jonelis et al., 2012), higher sleep spindle density (Mander et al., 2013a), and more slow wave activity (Van Der Werf et al., 2009) which in turn led to better episodic learning. Although disrupted CARs are a common feature of aging and can be predictive of pathology (Tranah et al., 2011) it is unknown how CAR disruptions influence new episodic learning and whether the hippocampus plays an essential role in this relationship.

The purpose of this study was to investigate whether more consistent CARs (lower variability in the CAR) was related to better associative memory performance. Associative memory was chosen because it is highly sensitive to memory declines in older individuals (Dennis et al., 2008) and reliably recruits the hippocampus, a structure that shows consistent age-related changes (Giovanello et al., 2009). Furthermore, we examined whether hippocampal activity during successful associative memory retrieval mediates the relationship between CAR consistency and memory in older adults. We hypothesized that more consistent CARs would be associated with better memory performance as a result of greater hippocampal activity.

2. Materials and methods

2.1. Participants

Interested 60–80 year old Austin community members completed a self-reported health screening and a neuropsychological test battery prior to entrance into our research study. The health screening excluded those who reported a medical history of heart conditions or vascular disease, including hypertension and elevated body mass index (BMI greater than 30). The cardiovascular exclusion criteria was included because of previous work illustrating that beginning at middle age, cardiovascular risk factors are associated with significant neurological changes (Salat et al., 2012; Haley, 2014). Additionally, adults were excluded for any history of neurological injury or disorder, diabetes, current psychiatric disorder, major depression within the past five years, current sleep disorder or a score greater than 8 on Pittsburg Sleep Quality Index (PSQI; Fichtenberg et al., 2001), cancer in the last three years, or current medications that affect the central nervous system. All older adults included in the study were within 1 SD of normal performance on composite scores in the cognitive domains of memory, vocabulary, and executive function.

Forty-one participants (29 females, mean age $=66.8 \pm 5.1$, age range 60–78 years) were included in our final analyses from 45 eligible participants. Four participants were dropped due to incomplete actigraph data, sleep logs, and/or memory task data. All participants provided written informed consent that was approved by the Institutional Review Board at the University of Texas at Austin.

2.2. Procedure

2.2.1. Overview

Participants took part in two experimental testing sessions that were separated by a minimum of 10 days. Both experimental sessions occurred in the morning so older adults would perform during their optimal time of day (May et al., 1993). In the baseline session, participants were fitted with wrist actigraphs (Motionlogger Actigraphs; Ambulatory Monitoring, Inc., Ardsley, NY) to record objective measures of their sleep-wake patterns under normal environmental conditions. To obtain baseline measures of sleep quality, vigilance, and attention, participants completed the Pittsburg Sleep Quality Index (PSQI) and the Psychomotor Vigilance Task (PVT). For the next 10 days, participants wore the actigraph continuously except during situations where it could get wet or damaged. In addition, participants filled out daily, online sleep logs based on the Consensus Sleep Diary (Carney et al., 2012), usually in the morning after waking. Following the recording period, participants returned to the laboratory and completed the PSQI, Insomnia Severity Index (ISI), the PVT, and underwent structural and functional magnetic resonance imaging while performing a word-pair associates task (mean time of testing session: 10 am, SD: 30 min, range: 8:30–11:00 am).

2.2.2 Actigraphy

After the 10 day recording period, participants returned the actigraphs and data were downloaded from each device using the ambulatory monitoring software (Action 4; http://www.ambulatory-monitoring.com/action4.html). Actigraph recordings were collected in 1-min epochs in the proportion integration mode (PIM). The PIM captures the frequency and intensity of movement by calculating counts from the area under the receiver operating characteristic curve analysis (Tranah et al., 2010). This channel was chosen because the activity levels have been shown to best correspond to measures from the gold standard of sleep monitoring, polysomnography (PSG; Blackwell et al., 2011b).

Following the procedures described in previous work (Blackwell et al., 2011a, 2011b) we used the actigraphy and sleep log data to create valid profiles of each participant's sleep-wake patterns by defining intervals that designate when the participant was in bed trying to sleep each night (in-bed intervals). These procedures have been validated against PSG in older individuals (Blackwell et al., 2011a). Although some participants wore the actigraph for longer than 10 days, analyses only included data from the 10 days prior to the MRI testing session. The times when the participant removed the actigraph were not included in the analysis (Blackwell, et al., 2011b). No participant took the watch off for more than 10% of the recording period ($M=5.5$ h, range 0.73–19.95 h). We applied the University of California, San Diego (UCSD) Sleep Scoring algorithm to the data collected in the PIM channel. This algorithm codes each minute of data as sleep or wake based on the activity levels at that minute as well as the surrounding minutes of recording. Within each in-bed interval, the number of minutes scored as sleep by the algorithm was summed to calculate a measure of total sleep time for each night. Nightly sleep efficiency was calculated by dividing the total sleep time by the number of minutes within the in-bed interval (Blackwell et al., 2011b). Total sleep time and sleep efficiency across the 10 day period were averaged within each participant.

Central to the research question, the continuous collection of actigraph data allowed us to measure aspects of circadian activity rhythms (CARs) to effectively quantify the timing and consistency of the rest-activity cycle (Ancoli-Israel et al., 2002; Savard et al., 2009; Tranah et al., 2010; Witkowski et al., 2015; McKenna et al., 2014). CARs were computed by inputting the minute-by-minute PIM activity (from the 10 day actigraph recording) into a five-parameter extended cosine model (Martin et al., 2000). The extended cosine model characterizes the square-like shape of human activity data (Marler et al., 2006; Tranah et al., 2010) better than traditional cosinor methods that include underlying assumptions about the activity shape that are imprecise (Van Someren et al.

1997; Dowling et al., 2005) and too simplistic (Calogiuri et al., 2011). Parameters were estimated from the model using a non-linear least squares approach to data fitting. The parameters of interest included the mean (mesor), peak (acrophase), and amplitude of the activity rhythm. The mean, known as the mesor, is the average activity level of the modeled curve. The peak, called the acrophase, represents the time of day when the highest level of activity occurs. The amplitude is the difference between the maximum and minimum values of the activity curve. In addition, we investigated the time of day when activity moved from below the mean level to above the mean level on the modeled curve called up-mesor. These parameters were computed for each individual to create the best fitting activity curve. After we created the activity curve using the individually estimated shape, timing, and amplitude parameters, the F-statistic was computed to assess how well the activity data fit the curve – referred to as "CAR consistency". More consistent activity rhythms indicate less variability in the rest-activity pattern. If the timing, amplitude, and shape of activity are consistent across days, then the calculated parameters will closely match the actual data. This translates to a better fit of the curve (smaller standard error) and a more consistent CAR. More details about these measures can be found in previous publications (Tranah et al., 2010; Liu et al., 2013). The measures from this model have been shown to correlate with core body temperature and reliably match the circadian period of PSG data (Pollak et al., 2001; for review see: Ancoli-Israel et al., 2003).

2.2.3. Psychomotor Vigilance task (PVT)

Immediately before the scan session, participants completed a high-signal load computerized reaction time (RT) task that measures sustained attention and vigilance. The PVT has been employed in hundreds of studies to measure sustained attention because it is reliable, valid, and highly sensitive to changes in sleep (for review see: Lim and Dinges, 2008). Participants attended to a fixation cross at the center of a computer screen. At random intervals, a millisecond timer appeared at the screen center (2–10 s inter-trial intervals). Participants were instructed to press a button the instant they detected the start of the timer. The button press stopped the timer and displayed the reaction time for 1 s. The PVT was 10 min in length and required sustained attention in order to detect the onset of the timer. Response lapses (i.e. RTs $>$ 500 ms), and false starts (i.e. RTs $<$ 100 ms) were removed before computing summary statistics. Mean, median, and the standard deviation of RTs were calculated as well as the mean of the fastest and slowest 10% of the trials.

2.2.4. Image acquisition

Following the 10 day recording period, participants underwent structural and functional magnetic resonance imaging (MRI) on a 3T Siemens Skyra MRI scanner with a 32-channel phase array head coil at the University of Texas at Austin Imaging Research Center. Two high-resolution T1-weighted MPRAGE scans (TR$=$2.53, TE$=$3.37, flip angle$=7^\circ$, 1 mm slice thickness, 176 slices, FOV$=256\times256$ mm^2) were collected for anatomical coregistration with other datasets. The T1 scans were motion corrected and averaged to optimize the signal and contrast for analysis. Functional EPI images were collected using a GRAPPA reconstructed parallel image sequence with an acceleration factor of 2 and a slice orientation to reduce artifact (approximately 20° off the AC-PC plane, TR$=$2000 ms, TE$=$30 ms, flip angle$=90^\circ$). Thirty-five interleaved axial slices with voxel size $2.5\times2.5\times3$ mm^3 and 10% gap were collected for the best whole-head coverage. Head motion was minimized with foam inserts.

2.2.5. Word-pair associates task

The stimuli from the word-pair associates task were taken from a previously normed list of word pairs (Giovanello et al., 2009). The task consisted of a study phase immediately followed by a test phase. Participants were in the MRI for the duration of the task but fMRI data was only collected during the test phase. We collected fMRI data during retrieval based on previous work illustrating that the hippocampus is involved in associative memory retrieval during the word-pair associates task (Giovanello et al., 2004, 2009; Giovanello and Schacter, 2012). In the study phase, a series of two unrelated nouns were presented on a high-resolution, back projection system viewed by the participant via a mirror mounted on the head coil. Responses were collected with an MR compatible optical transmission device that was held in one hand. Participants were instructed to mentally create a sentence that incorporated the two words at their own pace. They were asked to press a button to indicate that they completed the sentence formation. They were informed that they would use these sentences to remember the word pairs for a later memory test. During the test phase, participants viewed 3 different types of word pairs-Intact (pair of words that were previously seen together), Rearranged (pair of words that were previously seen but not together), or New (pair of novel words). They were instructed to press one of 3 buttons to indicate which pair-type was presented. After each pair-type judgment, participants rated the confidence of their response (1-guess, 2–25% sure, 3–75% sure, 4-sure). An odd/even classification task (Stark and Squire, 2001) was randomly interspersed in between the pair-type judgments as an active control task. Participants had 5 s to respond to the pair-type judgment, 5 s to respond to the confidence rating, and 2 s to respond to the active control task. A fixation cross was presented during the inter-stimulus interval, which varied from 2 to 10 s. They alternated between study and test 3 times (3 runs). Each participant completed a practice run of the study and test phase outside of the MRI to demonstrate to the experimenter that they understood the instructions.

2.2.6. Behavioral data analysis

Accuracy on the associative memory task was assessed by calculating an "associative recognition accuracy" score (pR) by taking the percent of hits for the intact pair trials and subtracting the percent of the rearranged trials that were falsely identified as intact pairs (associative errors; de Chastelaine et al., 2011). All participants performed at greater than chance on associative recognition accuracy (pR; hits minus associative errors $>$ 0; $t(40)=19.45$, $p<.0001$ – range .27–.97).

2.2.7. fMRI data analysis

The imaging analyses included 36 participants because five participants did not have complete fMRI data due to participant discomfort, safety concerns, or they did not follow task instructions. Functional MRI data were analyzed using tools from the software package FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Images were motion-corrected, spatially smoothed using a 6 mm Gaussian filter, and high pass filtered at 100 s to remove low frequency drift components. Framewise displacement (fd) values from the motion correction processes were examined across each run to ensure that participants were not moving excessively. No participants had a mean fd value greater than 0.36 mm ($M=.17$, SD$=.06$), which is well below the threshold of what is problematic (Siegel et al., 2013).

The canonical hemodynamic response and its temporal derivative were modeled for all events. Correct trials were modeled for each memory condition (intact, rearranged, new). Mean reaction times (RT) for all memory trials within each run and participant were applied as a duration variable. The same procedures were completed for correct control trials and answered confidence trials. Nuisance regressors were added to the model for incorrect

memory trials, no response memory trials, no response and incorrect control trials, and no response confidence trials. To account for RT related effects, we included RT regressors for the memory, control, and confidence trials. The modulation column for all three RT regressors included the individual trial reaction times after mean-centering within each regressor. All events were entered into a first level analysis for each separate run of each participant. Multiple runs within a subject (no less than 2) were combined in a second level analysis using a fixed effects model (1 participant had 2 runs and all other participants had 3 runs) and individual subjects were registered to the MNI standard brain template. FLAME (FMRIB's Local Analysis of Mixed Effects) in FSL was used to create random effects group level maps of our critical contrast, successful associative memory retrieval (correct memory for intact vs. control). All group level comparisons are cluster-corrected for multiple comparisons where clusters were determined by $z > 2.3$ and $p < .05$ threshold.

3. Results

3.1. Behavioral results

3.1.1. The association between sleep, circadian activity rhythms (CARs), and associative memory.

A Shapiro–Wilks Normality Test ensured that CAR consistency as measured by the F-statistic values were normally distributed ($W=.97$, $p=.39$) and could be examined using linear statistical models. Age was not correlated with associative recognition accuracy (pR; $r=-.14$, $p=.38$) nor CAR consistency, $r=.03$, $p=.83$. More consistent CARs were correlated with better pR, $r=.33$, CI [.02, .58], $p=.04$ (see Fig. 1). Associative recognition accuracy (pR) was not related to the timing of the activity rhythm as indexed by acrophase ($r=$-.27, $p=.09$) and up-mesor ($r=-.29$, $p=.07$). In summary, more consistent activity rhythms were associated with better memory performance. Fig. 2

The average physical activity as measured by the circadian activity mesor was also not related to pR, $r=-.03$, $p=.85$. In addition, mesor was not a significant covariate in the linear regression using CAR consistency to predict pR, $\beta=-.10$, $p=.53$. Similar to mesor, the amplitude of the rhythm was not related to pR ($r=-.13$, $p=.42$) and it was also not a significant covariate in the model ($\beta=-.12$, $p=.45$).

Total sleep time the night before testing, average total sleep time, and sleep efficiency across the 10 day period were also not related to pR ($r=-.2$, $p=.20$; $r=.04$, $p=.82$; $r=-.09$, $p=.57$, respectively), nor were the global score from the PSQI, ISI, and the Geriatric Depression Scale (Yesavage et al., 1983; $r=.05$, $p=.74$; $r=.02$, $p=.85$, $r=.08$, $p=.63$, respectively). These findings suggest that physical activity, sleep calculated from the actigraph, and self-reported sleep and depression measures from survey instruments were not correlated with associative memory performance.

3.1.2. The association between sleep, circadian activity rhythms, memory, and sustained attention

The outcome measures from the PVT following the actigraph recording period were not correlated with pR (mean RT: $r=-.27$, $p=.08$; fastest 10% RT: $r=-.17$, $p=.28$; slowest 10% RT: $r=-.23$, $p=.14$) or CAR consistency (mean RT: $r=-.02$, $p=.90$; fastest 10% RT: $r=-.09$, $p=.58$; slowest 10% RT: $r=-.01$, $p=.93$). None of the PVT measures were significant covariates in the linear regression using CAR consistency to predict pR (mean RT: $\beta=-.27$, $p=.08$; fastest 10% RT: $\beta=-.14$, $p=.35$; slowest 10% RT: $\beta=-.24$, $p=.12$). In line with previous work, lower variability in reaction times on the PVT (measured by the standard deviation) was associated with greater average total sleep time, $r=-.34$ CI[$-.59$, $-.04$], $p=.03$.

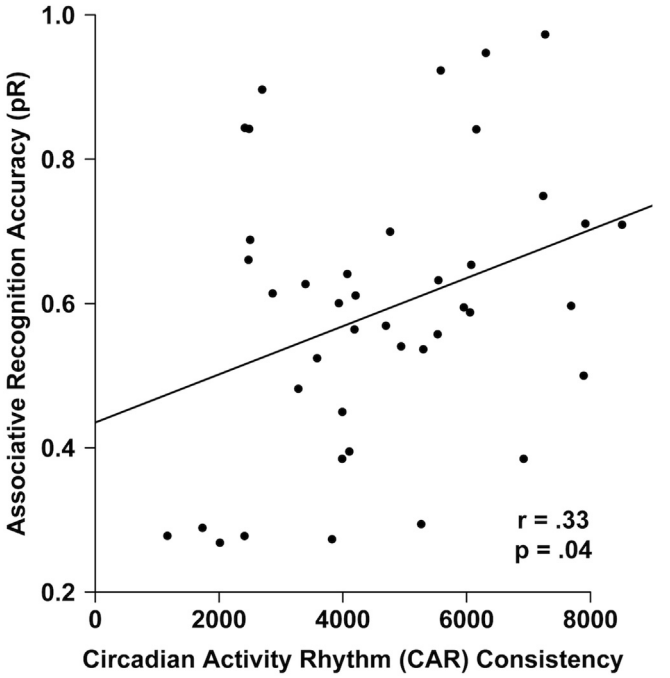

Fig. 1. More consistent circadian activity rhythms (F-statistic) were related to better associative recognition accuracy (pR).

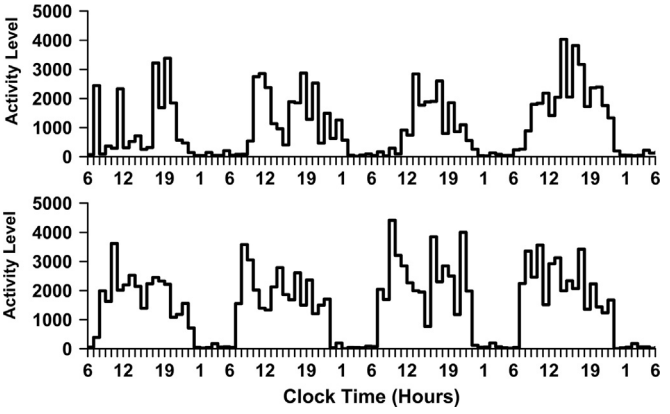

Fig. 2. Example actigraph activity levels from two participants are plotted across a 4-day period. The top panel displays data from a participant with low circadian activity rhythm consistency and the bottom panel shows data from a participant with high circadian activity rhythm consistency. Both participants received approximately 8 h of sleep on average across the recording period.

Therefore sustained attention was correlated with sleep quantity but not CAR consistency. Vigilant attention did not account for or contribute to the relationship between memory function and CAR consistency.

3.2. fMRI results

3.2.1. Whole brain analysis

Whole brain contrast maps for successful associative memory retrieval (correct memory for intact vs. control task) revealed a network of brain regions previously implicated in episodic memory retrieval (Rugg and Vilberg, 2013), including the left hippocampus and left inferior frontal gyrus (see Table 1 and Fig. 3). This was the primary contrast of interest since there were not enough associative errors to reliably examine the contrast representing associative recognition accuracy (correct memory for the intact condition minus associative errors).

Table 1
Max Z-stat represents the maximum *z* statistic for each cluster and the *x*, *y*, *z* coordinates represent the MNI coordinates at the peak of each cluster.

Brain regions	Hemisphere	Max Z-stat	*x*	*y*	*z*
Posterior cingulate gyrus	Left	7.35	−6	−50	10
Inferior frontal gyrus	Left	6.97	−52	32	−6
Lateral occipital cortex	Left	6.39	−40	−74	42
Caudate	Left	5.37	−12	14	4
Frontal pole	Right	4.23	30	66	−10
Angular gyrus	Left	4.22	−46	−62	26
Anterior hippocampus	Left	4.06	−14	−4	−18

3.2.2. ROI analysis

Analyses focused on a priori defined region of the anterior hippocampus (MNI coordinates: $x=-21$, $y=-9$, $z=-15$) because of its importance to retrieval of relational memory (Giovanello et al., 2009) and sensitivity to prior sleep physiology (Mander et al., 2013a). A 6 mm spherical ROI was created using the coordinates above as the central point (MNI coordinates: $x=-21$, $y=-9$, $z=-15$). Average percent signal change values were extracted from the ROI for the successful associative memory retrieval contrast (correct memory for intact vs. control) using a baseline-to-max scale factor (http://mumford.fmripower.org/perchange_guide.pdf). Separate linear regression analyses were performed to analyze whether percent signal change from the anterior hippocampus was related to pR and CAR consistency. Greater hippocampal activity was related to better pR ($\beta=.42$, CI [.11, .74], $t(34)=2.73$, $p=.0099$) and more consistent CARs ($\beta=.42$, CI[.10, .73], $t(34)=2.67$, $p=.01$). These relationships remained significant when adjusting for age (pR: $\beta=.48$, CI[.17, .79], $t(33)=3.19$, $p=.003$; CAR consistency: $\beta=.42$, CI[.11, .73], $t(33)=2.74$, $p=.0099$).

In order to explore whether these relationships were specific to activity in the hippocampus or are evident in other brain regions associated with episodic memory retrieval, average percent signal change was extracted from 8 mm spheres centered on peak activation locations from the whole brain analysis in the left angular gyrus (AG; MNI coordinates: $x=-46$, $y=-62$, $z=26$) and the left inferior frontal gyrus (IFG; MNI coordinates: $x=-52$, $y=32$, $z=-6$; Giovanello et al., 2004; Rugg and Vilberg, 2013). A whole brain mask was used to ensure no non-brain voxels were included in these ROIs. Neither region was related to pR (AG: $\beta=.25$, $p=.14$; IFG: $\beta=.19$, $p=.28$) or CAR consistency (AG: $\beta=.01$, $p=.94$; IFG: $\beta=-.05$, $p=.90$).

To ensure that the relationship between greater hippocampal activity and CARs was independent of sleep measures derived from the actigraph and sleep log data, predictors were added to the linear regression analysis using CAR consistency to predict hippocampal activity. The relationship between hippocampal activity and CAR consistency remained significant when adjusting for total sleep time the night before testing ($\beta=.42$, CI[.11, .73], $t(33)=2.77$, $p=.009$), average total sleep time ($\beta=.42$, CI[.08, .75], $t(33)=2.54$, $p=.02$), and sleep efficiency across the 10-day period ($\beta=.47$, CI[.14, .81], $t(33)=2.89$, $p=.007$). Similarly, after including the average physical activity level (mesor) in the model, CAR consistency significantly predicted hippocampal activity, $\beta=.39$, CI [.09, .74], $t(33)=2.57$, $p=.01$. Greater hippocampal activity was associated with more consistent CARs and better associative memory performance regardless of overall sleep time, sleep efficiency, and average physical activity measures from the actigraph.

3.3. Mediation analysis

A mediation analysis was conducted to examine whether hippocampal activity during successful associative memory retrieval (correct memory for intact vs. control) mediates the relationship between CAR consistency (independent variable) and associative recognition accuracy (dependent variable; Fig. 4).

First we tested whether conditions were met to conduct a formal mediation analysis (Baron and Kenny, 1986). Linear regression analysis was conducted using the independent variable (IV), CAR consistency, to predict the dependent variable (DV) pR. More consistent CARs were associated with better memory performance, $\beta=.35$, CI[.02, .68], $t(34)=2.15$, $p=.04$. As reported above, CAR consistency (IV) and the hypothesized mediator (M), hippocampal activity, were significantly associated. In addition, hippocampal activity (M) was related to pR (DV). To examine

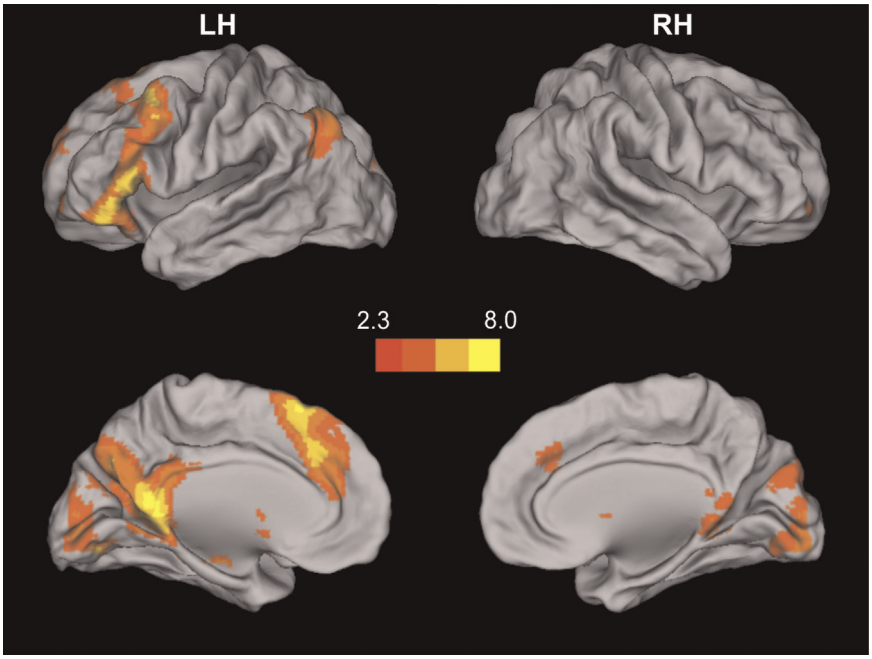

Fig. 3. The intact > control contrast map. Images are cluster-corrected for multiple comparisons where clusters were determined by $z > 2.3$ and $p < .05$ threshold.

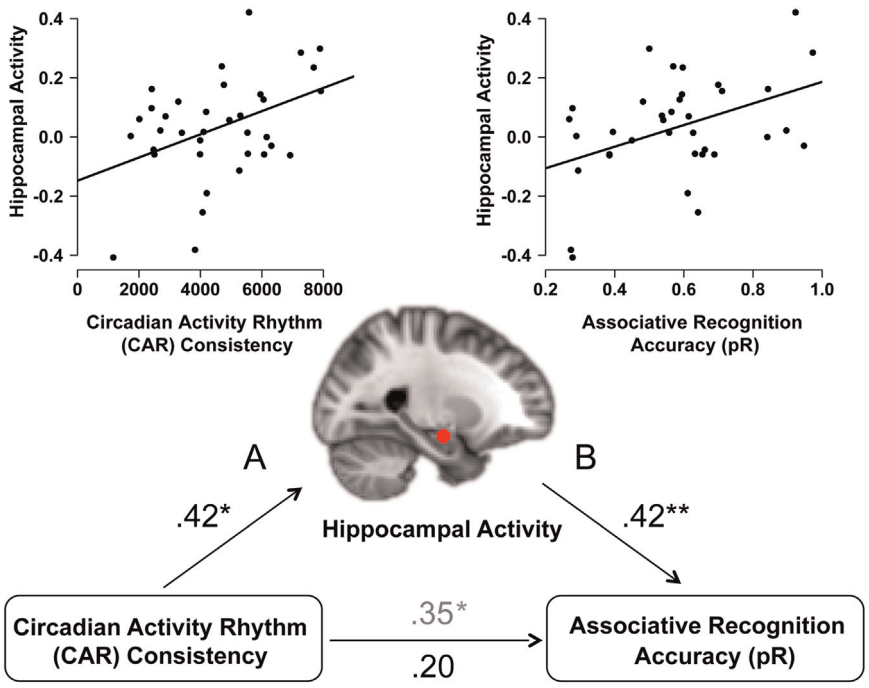

Fig. 4. The mediation model demonstrates that the relationship between circadian activity rhythm (CAR) consistency and associative recognition accuracy (pR) was meditated by hippocampal activity. Standardized beta values are included on the model paths in black. The gray value on the path represents the standardized beta value before hippocampal activity was included in the model. The scatterplots show path A and B, which illustrate the relationships between hippocampal activity, circadian activity rhythm consistency, and associative recognition accuracy. $^{*}p < .05$, $^{**}p < .01$.

whether the direct pathway from CAR consistency (IV) to pR (DV) was significantly reduced by hippocampal activity (M), hippocampal activity was added as a predictor to the linear regression analysis using CAR consistency to predict pR (DV). The association between CAR consistency and pR was reduced and no longer significant when hippocampal activity was included, $\beta = .20$, CI [−.14, .55], $t(33) = 1.20$, $p = .24$. Since these findings satisfy the mediation analysis requirements, we examined whether hippocampal activity significantly mediates the relationship between CAR consistency and associative recognition accuracy.

To formally test the mediation, we used a bias-corrected and accelerated bootstrap method (MBESS package in R). The indirect effect was significant suggesting that more consistent CARs were associated with greater hippocampal activity which in turn was related to better associative memory performance, $\beta = .14$ CI[.01, .40], $p = .04$. In summary, hippocampal activity mediates the relationship between CAR consistency and associative memory.

4. Discussion

Better associative memory performance was related to more consistent circadian activity rhythms (CARs) in healthy older adults. Moreover, this relationship was mediated by activity in the left anterior hippocampus. These findings are the first to demonstrate that more consistent CARs are directly related to functioning of the hippocampus and that in turn is associated with successful memory performance in older individuals. This builds upon previous work illustrating that CARs are related to cognition (Tranah et al., 2011; Walsh et al., 2014), by demonstrating that memory-related brain activity in the hippocampus is an essential component of this relationship.

These findings in healthy older adults support the hypothesis that the consistency of the CAR is linked to cognitive performance. The possibility that these are causally related is supported by several intervention studies demonstrating that improving the consistency of sleep-wake cycles with melatonin subsequently enhanced cognitive performance in older adults with and without cognitive impairment (Cardinali et al., 2012: Jean-Louis et al., 1998; Peck et al., 2004). This is important because previous work has shown that individuals with more variable CARs are at a higher risk of developing neurocognitive disorders. In a longitudinal study, sleep-wake cycles were monitored in cognitively intact older adults for 3 days using actigraphy (Tranah et al., 2011). Five years later, participants returned to the laboratory for a cognitive assessment. Those who had less consistent rhythms 5 years earlier were 1.57 times more likely to have developed dementia or mild cognitive impairment. Cross-sectional studies have provided similar results, suggesting that older participants with more fragmented patterns of rest and activity across multiple days showed greater cognitive deficits (Carvalho-Bos et al., 2007; Oosterman et al., 2009; Lim et al., 2012). Although activity rhythms may reflect systemic changes that are linked to low cognition (Tranah et al., 2011) the mechanism underlying disrupted rest-activity rhythms is still under investigation. Since activity rhythms in older adults are not always coupled with core biological rhythms maintained by the master circadian pacemaker – the suprachiasmatic nucleus (SCN; Duffy and Czeisler, 2002), it is unclear whether disrupted rest-activity cycles reflect age-related changes in the SCN (Monk and Kupfer, 2000; for review see: Zelinski et al., 2014), or a temporal misalignment between sleep-wake cycles and the circadian timing system (Tranah et al., 2011). Future work should examine whether the correspondence between circadian activity rhythms and core biological rhythms is associated with cognitive function in older adults.

Evidence of a neural mediator from the current work advances our understanding of how cognition is critically linked to CARs. These novel findings in humans are consistent with work in rodents identifying the hippocampus as a key brain structure to investigate the relationship between the circadian rhythm of the rest-activity cycle and memory functioning. Disrupting circadian rhythms in rats prior to training caused deficits in hippocampal-

dependent learning (Craig and McDonald, 2008). In this study, fragmented rhythms were induced in the rats by shifting the light/dark schedule. After two weeks of shifted rest-activity cycles, acquisition and retention of the platform location on the water maze task was impaired. The results were specific to hippocampal-dependent learning since performance on the hippocampal-independent learning fear-conditioning task was unaffected by the change in circadian rhythms. Learning on other tasks that involve the hippocampus such as discriminating a novel object from a familiar one was similarly disturbed following altered circadian rhythms in hamsters (Ruby et al., 2008). Furthermore, circadian disruptions following training impaired memory retrieval (Zelinski et al., 2013). Rats were trained on a spatial navigation task and a visual discrimination task. Following training, photoperiod shifts were used to disturb circadian rhythms. Photoperiod shifts significantly decreased retention on the spatial navigation task but not on the visual discrimination task, indicating that changes in circadian rhythms negatively impact hippocampal-dependent learning and memory. Prior research in animals has established a strong linkage between circadian rhythms and hippocampal-dependent learning and while the current study cannot definitively conclude that circadian activity rhythms in older adults are selectively associated with hippocampal-dependent memory the results here are certainly consistent with the animal findings.

4.1. Potential biochemical mechanisms of circadian influences on hippocampal functioning

Previous work has offered potential biochemical mechanisms to understand the relationship between alterations in circadian rhythms and functioning of the hippocampus. First, hippocampal function has been linked to changes in cortisol (Lupien et al., 1998), a hormone that follows a distinct circadian rhythm and is regulated by the suprachiasmatic nucleus – the main circadian pacemaker (Bailey and Heitkemper, 2001). Evidence has shown that high cortisol levels impair hippocampal-dependent memories (Li et al., 2006) and decrease hippocampal volume (Lupien et al., 1998). Additionally, aging is associated with increases in cortisol concentration, which may be linked to age-related cognitive decline (Lupien et al., 1994). Stress also contributes to elevated cortisol levels and similarly results in cognitive deficits (for review see: Lupien, et al., 2009). Therefore previous work suggests it is possible that increased cortisol levels in older individuals that occur in aging have a disruptive effect on hippocampal-dependent learning. This connection may have important implications for managing changes in memory functioning during the aging process.

Another potential contributor to the relationship between circadian rhythms and hippocampal functioning lies with the expression of circadian clock genes. The clock genes are associated with the regulation of circadian rhythms (Brancaccio et al., 2014) and are expressed in the suprachiasmatic nucleus as well as several other brain regions, including the hippocampus (Kyriacou and Hastings, 2010). Animal work illustrates that mice without clock genes, Period1 or Period2, show impaired hippocampal-dependent learning (Jilg et al., 2010; Wang et al., 2009). In addition, old age is accompanied by significant alterations in CLOCK gene expression within the mouse hippocampus, which is thought to contribute to age-related disruptions in circadian rhythms (Wyse and Coogan, 2010). Future research could focus on better understanding the relationships between changes in cortisol and/or clock gene expression, alterations in circadian activity rhythms, and hippocampal-dependent memory in humans.

4.2. Circadian activity rhythm disruptions as early indicator of cognitive impairment

It is possible that individual variations in CARs in older adults may reflect systemic changes associated with low cognition (Tranah et al., 2011; Scullin and Bliwise, 2015). Since disrupted circadian rhythms, which naturally occur with increased age (Huang et al., 2002; Neikrug and Ancoli-Israel, 2010), are also related to poor memory function, monitoring the consistency of CARs over time may be an important predictor of age-related cognitive decline. Recent longitudinal work supports this assertion by demonstrating that CARs predict deficits in executive function 5-years in the future (Walsh et al., 2014). Sleep-wake patterns were measured for 3 days in women without dementia and 5-years later, the same participants underwent cognitive assessments. Those who had significant alterations in CARs 5-years prior exhibited lower cognitive performance, especially executive function performance. Although this study along with the current work found that associations between CARs and cognition were independent of sleep measures derived from the actigraph (Walsh et al., 2014), it is unknown whether these associations are independent of other physiological measures of sleep, such as slow wave sleep or slow wave activity. This is especially important because hippocampal activity has been linked to slow wave sleep (Van Der Werf et al., 2009). Future work should examine sleep physiology in relation to CAR consistency and investigate whether these measures are independently associated with memory performance. Finally, it would be important to implement a careful longitudinal study focused on how changes in CARs in healthy older adults influence the association between hippocampal function and cognition, potentially revealing a predictor of cognitive decline that could be implemented for early diagnosis of neurocognitive disorders.

5. Conclusion

Our results illustrate a direct link between variations in circadian activity rhythms (CARs) and hippocampal function, which collectively relate to memory performance. Additionally these findings make an important link between the human and animal work by demonstrating that changes in the circadian rhythm of the rest-activity cycle leads to hippocampal dysfunction and contributes to memory deficits. Although aging is generally accompanied by changes in cognitive function (for review see: Drag and Bieliauskas, 2010), it is possible that the amount of disruption in sleep-wake cycles may differentiate cognitively healthy older adults from those who will later develop neurocognitive disorders (Tranah et al., 2011). Carefully designed longitudinal studies should examine whether changes in CARs identify systemic changes that detect early signs of neurocognitive disorders. In conclusion, these results provide novel insight into how the circadian rhythm of sleep-wake cycles are associated with memory performance and encourage further investigation of circadian activity rhythms as a biomarker of later life cognitive functioning.

Disclosure statement

The authors declare no competing financial interests.

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