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Quality of Sleep, Stress, and Exercise: Effects of Environmental and Lifestyle Factors on Spatial Navigation in Older Adults

Hannah Maybrier
Washington University in St. Louis

WASHINGTON UNIVERSITY IN ST. LOUIS

Department of Psychological & Brain Sciences

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by

Hannah Maybrier

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Table of Contents

List of Figures

List of Tables

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ABSTRACT OF THE THESIS

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Research Advisor: Professor Denise Head

Introduction: With increasing age, many adults experience reduced spatial navigation ability, with the most prominent reductions in tasks dependent on the hippocampus. Hippocampal dysfunction may be linked to age-related increases in sleep fragmentation, which results in reduced neurogenesis and long-term potentiation. This project aims to determine if age-related reductions in hippocampal-dependent navigation ability and strategy selection are mediated by impaired sleep. Further, we propose that the effects of sleep on navigation are moderated by psychological stress and physical activity.

Methods: 36 older (m: 70, sd: 7) and 33 younger (m: 20, sd: 1.5) adults recorded one week of sleep via wrist actigraphy. Sleep parameters included sleep fragmentation and total sleep time. Subsequently, participants completed navigation tasks probing hippocampal-dependent navigation performance (i.e., cognitive mapping) and striatal dependent navigation performance (i.e., route learning), as well a measure of spontaneous hippocampal vs. striatal strategy selection. Self-reported stress and physical activity were also collected.

Results: Age was significantly associated with reduced performance on the hippocampal-dependent and striatal-dependent navigation tasks as well as reduced use of a hippocampal-dependent strategy (*ps*<.001). Age was not associated with sleep fragmentation (*ps*>0.1) but was associated with reduced total sleep time (*ps<0.05*). Sleep fragmentation and total sleep time were associated with lower cognitive mapping performance across age groups ($p<0.01$, $p<0.05$, respectively). Total sleep time mediated effects of age on cognitive mapping ($p<.05$). Neither stress nor physical activity moderated effects of sleep on the navigation tasks (*ps*>.05).
Discussion: Fragmented sleep impairs hippocampal-dependent navigation performance and may be independent of age-related impairment. However, total sleep time may be one factor contributing to age-related reductions in hippocampally-based navigation performance.

Chapter 1: Introduction

As we age our ability to find our way in a novel environment declines (Moffat, 2009; Rodgers, Sindone, & Moffat, 2012; Wiener, Kmecova, & de Condappa, 2012). This reduction has large implications for quality of life; successful navigation is essential for everyday functional independence. In fact, a substantial proportion of older adults avoid travelling to unfamiliar places because of this difficulty (Bryden, Charlton, Oxley, & Lowndes, 2013). Determining mechanisms and moderators of age-related decline in spatial navigation is a valuable endeavor and could lead to interventions for improving quality of life and independence.

Spatial navigation has been divided into egocentric and allocentric learning. In egocentric processing the viewer remembers travel as a series of body turns in relation to objects in an environment from a first-person perspective. Allocentric processing refers to a world-centered perspective of the environment; objects are remembered in relation to one another forming a cognitive map. Egocentric processing has been associated with the caudate, whereas allocentric processing is hippocampal-dependent (Packard & McGaugh, 1996). A critical distinction is between selecting a strategy and successfully implementing a strategy. Thus, it is plausible that individuals may adopt a hippocampal-based allocentric strategy, but still demonstrate reduced ability to develop and use a cognitive map of the environment.

Hippocampal-dependent spatial navigation, in comparison with a striatal-dependent system, is particularly affected by advancing age (Moffat, 2009). Older adults also evidence a preference toward a striatal-dependent vs. hippocampal-dependent navigation strategy in dual-solution maze

environments (Rodgers et al., 2012). These age-related differences have a cost. When relying on egocentric compared to allocentric processing in navigation, older adults evidenced more difficulty reversing a route (Allison & Head, 2017; Wiener et al., 2012). Altogether, these findings indicate that older adults struggle in everyday navigation tasks (i.e., reversing a route). A few studies have observed associations between hippocampal volume and cognitive mapping in older adults (Daugherty et al., 2014; Head & Isom, 2010). A key question in considering age effects is what factors influence relative hippocampal strategy use and performance.

Sleep may be an important mediator of the effects of age on the hippocampal-dependent spatial navigation. Empirical studies have indicated that sleep deprivation is linked to reduced hippocampal function (Hagewood et al., 2010; Kreutzmann et al., 2015). For example, rodents with five hours of sleep deprivation after training sessions were more likely to use a striatal-dependent navigation strategy vs. hippocampal-dependent, and evidenced less hippocampal and more striatal plasticity than controls (Hagewoud et al., 2010). Importantly, sleep fragmentation, defined as frequency of brief arousals during a bout of sleep, also negatively impacts hippocampal-dependent spatial learning in rats, accompanied by decreased hippocampal neurogenesis and synaptic plasticity (Guzman-Marin, Bashir, Suntsova, Szymusiak, & McGinty, 2007; Sportiche et al., 2010; J. L. Tartar et al., 2010; Jaime L Tartar et al., 2006). Importantly, these results may be independent of cortisol levels, suggesting the association of sleep fragmentation and subsequent reduced cognitive performance is not mediated by psychological stress (Guzman-Marin et al., 2007). Sleep deprivation in humans can lead to reduced hippocampal-dependent spatial navigation performance (Mander et al., 2013; Van Der Werf et al., 2009; Yoo, Hu, Gujar, Jolesz, & Walker, 2007). However, there is a lack of research

assessing sleep fragmentation, a more relevant and ecologically valid form of sleep disturbance, and hippocampal-dependent spatial navigation in humans.

Older adults experience reduced sleep quality compared to younger and middle-aged adults. A meta-analysis found sleep becomes shorter in duration and more fragmented with increasing age (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Despite general trends, poor sleep is not synonymous with older age, and there is large variability in sleep quality within the aging population (Vitiello, Larsen, & Moe, 2004). Findings are mixed with regards to associations between average sleep fragmentation over 7-10 days and hippocampal volume in older adults, but different measures of fragmentation and hippocampal structure were used across the two studies (Lim et al., 2016; Van Someren et al., 2019). Sleep fragmentation measures averaged across several days have shown modest associations with cognitive performance in older adults (Blackwell et al., 2011; Luik et al., 2015; Oosterman, van Someren, Vogels, Van Harten, & Scherder, 2009). However, results of observational studies have been primarily conducted within the context of clinical presentations such as Alzheimer's disease (e.g.,(Lim, Kowgier, Yu, Buchman, & Bennett, 2013) and sleep-disordered breathing (e.g., (Findley et al., 1986; Yaffe et al., 2011). Additionally, previous research has been limited to observing effects of sleep fragmentation on general psychometric measures. Thus, there is a need for targeted research exploring the impact of sleep fragmentation specifically on hippocampal function in older adults.

The effects of sleep fragmentation on hippocampal-dependent spatial navigation may be moderated by several factors, including stress experience and regular exercise. Stress and exercise have both been shown to regulate hippocampal plasticity, with stress having a negative impact and exercise having beneficial effects in rodents (Lucassen et al., 2010). In humans, perceived stress is associated with reduced hippocampal volume whereas exercise is associated

with beneficial effects on the hippocampus (Erickson et al., 2011; Gianaros et al., 2007). However, their influence on sleep fragmentation effects on hippocampal-dependent spatial navigation have not been examined.

This study aimed to enhance understanding of potentially modifiable factors that influence age-related deficits on hippocampal-dependent spatial navigation by addressing these aims: 1) Determine the role of sleep fragmentation in age differences in hippocampal-dependent spatial navigation. I hypothesized that sleep fragmentation would be negatively associated with hippocampal-dependent spatial navigation performance and strategy use across age groups, but less so with striatal-dependent navigation. Furthermore, I hypothesized that sleep fragmentation would mediate age effects on hippocampal-dependent spatial navigation. 2) Determine the moderating effects of perceived stress. I hypothesized that perceived stress would moderate the effects of sleep fragmentation on hippocampal-dependent spatial navigation performance and strategy use such that individuals with greater perceived stress would evidence greater negative effects of sleep fragmentation, and that this moderating effect would be greater for older adults. 3) Determine the moderating effects of regular exercise engagement. I hypothesized that regular exercise engagement would moderate the effects of sleep fragmentation on hippocampal-dependent spatial navigation performance and strategy use such that individuals with greater levels of exercise engagement would evidence less negative effects of sleep fragmentation, and that this moderating effect would be greater for older adults. Total sleep time was also examined as a secondary measure of sleep quality, with the same hypotheses as for sleep fragmentation.

Chapter 2: Methods

2.1 Participants

Enrollment took place in the psychology department at Washington University in St. Louis between March and November 2019. Younger adult participants were between 18 and 25 years old and either undergraduates at Washington University receiving course credit or members of the St. Louis community receiving monetary compensation. Older adult participants were age 60 or older and members of the St. Louis community participating for payment. Participants from the larger community were recruited via Volunteer for Health; and older adults were also recruited from the department participant registry. Undergraduates participating for course credit were recruited via Sona, an online student participant pool. All participants were right-handed with normal or corrected vision. Participants were excluded if they had a diagnosed sleep (e.g., sleep apnea), psychiatric (e.g., major depressive disorder), or neurological (e.g., traumatic brain injury) disorder. Participants were also excluded if they took medication or supplements to promote sleep or if they had reduced mobility.

In total, 76 participants were enrolled (38 older adults, 37 young adults). See Figure 1 for a summary of participant inclusion. Sixty-five participants had valid sleep data and at least one navigation outcome (36 older adults, 33 young adults). Sample demographics for each outcome are detailed in Table 1.

2.2 Experimental Procedure

All participants came to the lab for two separate visits approximately one week apart. To maintain consistency between participants, all visits were attempted to be scheduled on the same day of the week. Forty-three participants (66%) had their actigraphy watch placed on a Thursday or Friday. The second visit was always scheduled on a Thursday or Friday to incorporate both weekend and weekdays for all participants. During the first visit, participants were screened for inclusion and exclusion criteria, consented, and provided with an actigraphy watch as well as instructions on completing a sleep diary. During the second visit, attention was always measured first. Administration order of the spatial navigation tasks was counterbalanced to control for fatigue. To minimize nausea or discomfort, participants were allowed a short (i.e., five minute) break between navigation tasks.

2.2 Measures

2.2.1 Sleep Fragmentation

The primary measure of sleep was obtained using wrist actigraphy (ActiGraph; Pensacola, FL). The actigraphy watch was placed on the left, non-dominant wrist by the experimenter during the first visit. Participants were instructed to always wear the watch except when showering or bathing. All participants wore an actigraphy watch for three to eight consecutive nights (mean: 6.1 sd: 1.5) prior to behavioral data collection.

Activity is measured along three axes and considered as a vector magnitude. Movement sampling frequency was set to 30 Hz and binned in 60 second epochs. Sleep periods were

calculated in ActiLife (Pensocola, FL) using the Cole-Kripke algorithm (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992). Sleep fragmentation is measured as a sleep fragmentation index (SFI), which indicates discontinuity of sleep rather than number of minutes spent awake between sleep periods. SFI is the sum of the movement index (total scored awake minutes divided by total time in bed in hours x 100) and the fragmentation index (total one-minute scored sleep bouts divided by the total number of sleep bouts of any length x 100).

2.2.2 Sleep Diary

The Consensus Sleep Diary is a commonly used tool in clinical and healthy populations (Carney et al., 2012) with good sensitivity (73–87%) and specificity (81–86%) in predicting wake after sleep onset, a measure related to sleep fragmentation, when compared to actigraphy in participants with insomnia (Maich, Lachowski, & Carney, 2018). Participants were instructed to complete the sleep diary by email as soon as possible in the morning. Each participant was asked approximately what time they awoke and would be able to complete the sleep diary. The sleep diary was sent as a link in an email automated via REDCap. Participants were instructed to complete this in the morning just after waking and that the survey would expire later that afternoon. If requested, participants were given paper forms of the diary (1 OA, 0 YA). The sleep diary was used to corroborate actigraphy-derived sleep bouts. When the processed actigraphy data failed to detect a night of sleep, self-reported times of sleep onset and offset were manually entered in ActiLife.

2.2.3 Spatial Navigation Tasks

Spatial navigation tasks were administered in Unity (San Francisco, CA) on 24-inch monitors. Prior to the experimental tasks, participants practiced using the joystick to traverse a virtual environment consisting of a long hallway with alternating turns. Next, visuomotor expertise was tested by requiring participants to traverse the environment within 60 seconds. All participants passed this visuomotor expertise test.

2.2.4 Spatial Navigation Strategy Use

To measure navigation strategy selection, participants were administered a dual-solution virtual maze task adapted from Marchette and colleagues (2011). Importantly, relative strategy use on this task correlates with relative activation of the hippocampus versus caudate (Furman et al., 2014; Marchette et al., 2011).

In order to familiarize participants with the landmarks in the experimental environment, participants were first shown pictures of each landmark with its associated name. Each landmark was presented twice. Next, participants encoded a route through an environment that included 12 landmarks, interconnecting hallways, and four unique surrounding mountains by viewing a video of the route across 9 trials. To ensure sustained attention, 5 matching trials were randomly interspersed with the experimental route trials. These matching trials were in a different environment from the experimental route environment with no landmarks, but instead with colored spheres along the route. Participants were instructed to attend to these spheres and then asked a yes/no question about the number, color, or sequence in which the spheres were presented.

For the test phase, participants were placed in locations in the maze and asked to locate a target landmark indicated at the top of the screen by name. Twenty-four combinations of locations and landmarks were given to each participant in random order. For sixteen of these trials, participants could either find the target by following the path originally shown or by taking a shortcut. Shortcut routes were defined as paths that were shorter than the original path and with more than half of the path deviating from the original path. Original routes were defined as having more than half of the participants' trajectory on the original path. Inefficient routes were defined as being longer than the original path. Unsuccessful routes were defined as not reaching the target location.

Because taking a shortcut route required the development of an allocentric, flexible representation of the environment, these were considered hippocampal-dependent. Original routes were considered striatal-dependent as they represented a fixed repetition of the encoded route. The navigation strategy index was considered as the proportion of routes in which a shortcut was taken. Higher numbers indicate a tendency toward hippocampal-dependent strategy use. Unsuccessful and inefficient routes were omitted when determining the strategy ratio.

2.2.5 Cognitive Mapping

To measure hippocampal-dependent navigation performance, participants were tested on their cognitive mapping ability using a task adapted from Allison and colleagues (2016). The environment consisted of interconnected hallways with twelve landmarks. During the study phase, participants freely explored a virtual environment with a joystick for four minutes. During the test phase, participants were asked to indicate the locations of the landmarks by making an X on a two-dimensional map of the environment. This was repeated for four trials. Cognitive

mapping performance was quantified as the percentage of correctly placed landmarks across all four trials.

2.2.6 Route Learning

To measure striatal-dependent navigation, participants completed a route learning task adapted from Allison and colleagues (2016). During the study phase, participants were instructed to follow a path marked by arrows in an environment consisting of interconnected hallways and landmarks using a joystick. During the test phase, participants were instructed to accurately complete the route as quickly as possible without the arrows. This was repeated for four trials. Route learning ability was quantified as average time to traverse the route in seconds.

2.2.7 Attention

In order to potentially account for contributions of attention, participants completed a Psychomotor Vigilance Task (PVT) prior to the spatial navigation tasks. This task was administered on The Psychology Experiment Building Language (PEBL) (Mueller & Piper, 2014). Participants were instructed to attend to a crosshair in the middle of the screen and quickly press the spacebar when a red dot appeared. The red dot appeared at randomly varying interstimulus intervals. Participants were shown their response time after each trial. The index of performance was a composite score that included the average reciprocal of response times, average response times for the slowest 10% of trials, and number of trials where response time exceeded 500 milliseconds. These PVT measures were previously found to be the most sensitive to sleep deprivation (Basner & Dinges, 2011).

2.2.8 Perceived Stress

Psychological stress was measured with the Perceived Stress Scale version 10 (PSS-10) (Cohen, Kamarck, & Mermelstein, 1994). This short, self-report measure has demonstrated excellent internal consistency in multiple studies (Cronbach's $\alpha > .70$) (Lee, 2012). Additionally, test-retest reliability was excellent (correlation coefficients >.70). The PSS-10 also demonstrated criterion validity with moderate to strong correlations with related measures (Lee, 2012).

2.2.9 Physical Activity

Physical activity was obtained with the International Physical Activity Questionnaire (IPAQ) 7-day Long version (Hallal & Victora, 2004). The IPAQ has exhibited excellent test-retest reliability (intraclass correlation coefficients 0.3-0.8) (Kurtze, Rangul, & Hustvedt, 2008). Analyses of IPAQ compared with activity monitors have demonstrated low to fair validity (Kurtze et al., 2008; Sanda et al., 2017). The IPAQ measures the frequency and duration of work, transportation, household, and recreational activities, and provides an estimate of metabolic equivalent task (MET) minutes per week.

The distribution of exercise engagement scores was heavily skewed due to the presence of many participants (n = 35) who scored 0 on the questionnaire, and transformations (e.g., logarithmic) would not resolve these distributional issues. Thus, rather than treating the exercise engagement score as a continuous variable, participants were assigned to low and high exercise engagement groups based on a median split.

2.2.9 Physical Activity

Within one day of behavioral data collection, participants rated their computer experience, experience playing computer games, and experience with computer games involving virtual reality on a 0-7 Likert scale.

2.3 Analytic Approach

2.3.1 Covariates

Gender, computer experience composite, visuomotor expertise, and psychomotor vigilance were considered as potential covariates. Missing covariate data was replaced with the mean value for the corresponding age group. Variables significantly associated with age were included as covariates. Gender was significantly correlated with age group in each task sample (*p-values* <.05) and included as a covariate in all models.

2.3.2 Mediation Analyses

All analyses were conducted in R version 3.5.0 with mediation analysis conducted using the "mediation" package (Tingley, Yamamoto, Hirose, Keele, & Imai, 2014), which incorporates a regression-based approach to estimate effects in conjunction with bootstrapping. In the mediation models, age group (coded 0=younger, 1=older) was the predictor variable, the sleep variable (sleep fragmentation or total sleep time) was the mediator, and spatial navigation tasks were the outcome variables. In these models, the total effect represents the association of age group with spatial navigation including both direct and indirect effects. The direct effects indicate the degree of association between a) age group and the sleep variable, b) the sleep variable and spatial

navigation controlling for age group, and c) age group and spatial navigation controlling for the sleep variable. Indirect effects indicate the degree to which age group influences spatial navigation via the sleep variable. Based on current recommendations, a significant association between the predictor and the outcome variable was not necessary to perform the mediation (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Rucker, Preacher, Tormala, & Petty, 2011). Indirect effects were examined using 10,000 bootstrapping samples and bias-corrected 95% confidence intervals (CIs).

2.3.3 Moderation Analyses

Following Baron and Kenny (1986), a series of hierarchical regression analyses were conducted to examine the moderating effects of perceived stress and exercise engagement. Exercise engagement was coded as 0 or 1. The continuous perceived stress score was standardized using a z transformation in order to minimize multicollinearity with the interaction terms in the model. Interaction terms were created by multiplying the relevant variables. In all analyses, the covariates, age group and perceived stress or exercise engagement were entered in the first step. The sleep variable was entered in the second step. The primary 2-way interaction of interest (sleep variable x perceived stress (or exercise engagement)) was entered in the third step. The remaining 2-way interactions with age group (age group x sleep variable; age group x perceived stress (or exercise engagement)) were entered in the fourth step. Finally, the 3-way interaction of primary interest was entered in the fifth step.

Chapter 3: Results

3.1 Effects of Age and Sleep

3.1.1 Spatial Navigation Strategy Use

The navigation strategy index, which indicates the use of a hippocampal-dependent navigation strategy (i.e., finding shortcuts) relative to a striatal-dependent strategy (i.e., following a familiar route), was significantly reduced with older age (total effect=-.75 (SE=.23), p=.002). Thus, older adults adopted the hippocampal-dependent strategy less than younger adults. Age group was not associated with sleep fragmentation (β=-.02 (SE=.13), p=.91), but was associated with reduced total sleep time (β=-.32 (SE=.13), p=.02), see Figure 1. Neither average sleep fragmentation nor total sleep time was associated with the navigation strategy index (sleep fragmentation: β=.00 (SE=.12), p=.91; total sleep time: β=-.06 (SE=.13), p=.63). Given the lack of associations between age and sleep fragmentation and between the sleep variables and the navigation strategy index, mediation was not examined.

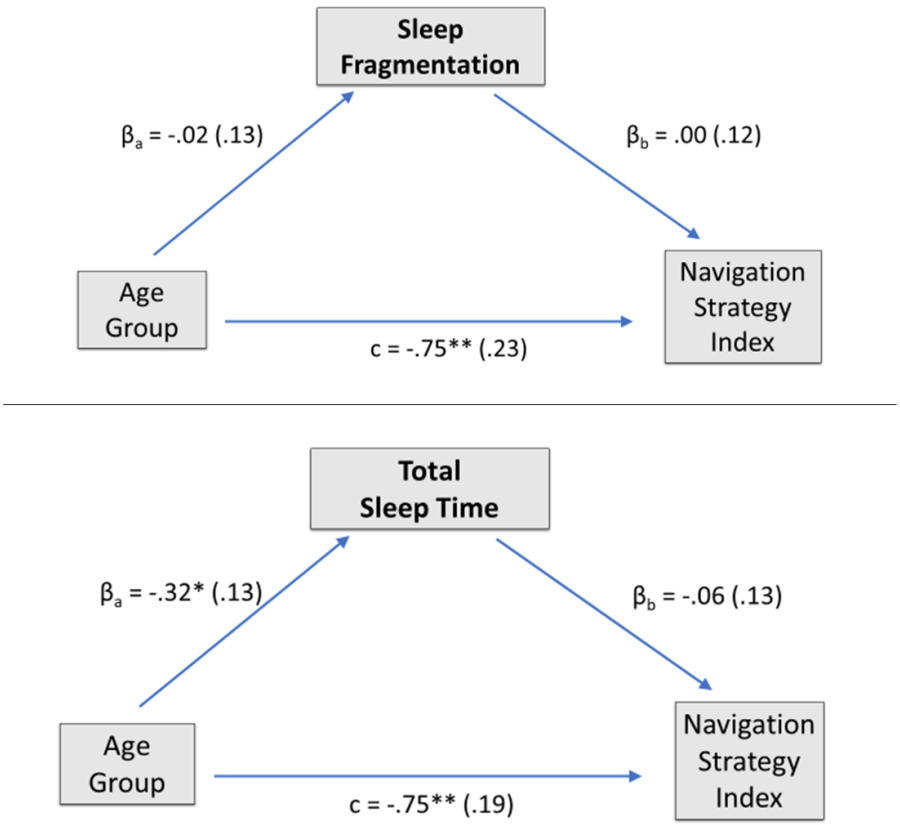

Figure 1. Age, Sleep and Spatial Navigation Strategy Use. Path models of the relationships amongst age group, sleep variables, and the use of a hippocampal-dependent strategy. High scores on the navigation strategy index indicate greater relative hippocampal-dependent strategy use. Standardized path coefficients are presented; c=total effect coefficient. **p< 0.01, *p<0.05

3.1.2 Cognitive Mapping

The ability to form a cognitive map, a hippocampal-dependent navigation strategy, was significantly reduced with older age (total effect=-1.33 (SE=.15), p<.001), see Figure 2. Greater sleep fragmentation was associated with reduced cognitive mapping performance (β=-.30 (SE=.09), *p*=.002). However, considering the lack of association between age and sleep fragmentation (β=-.01 (SE=.13), *p*=.91), mediation was not examined.

Age group was significantly associated with reduced total sleep time (β=-.32 (SE=.13), *p*=.01). In addition, less total sleep time was associated with lower cognitive mapping performance (β=.23 (SE=.10), *p*=.03). Finally, total sleep time mediated the effects of age on cognitive mapping (indirect effect =-.15, (SE=.08), *p*=.045).

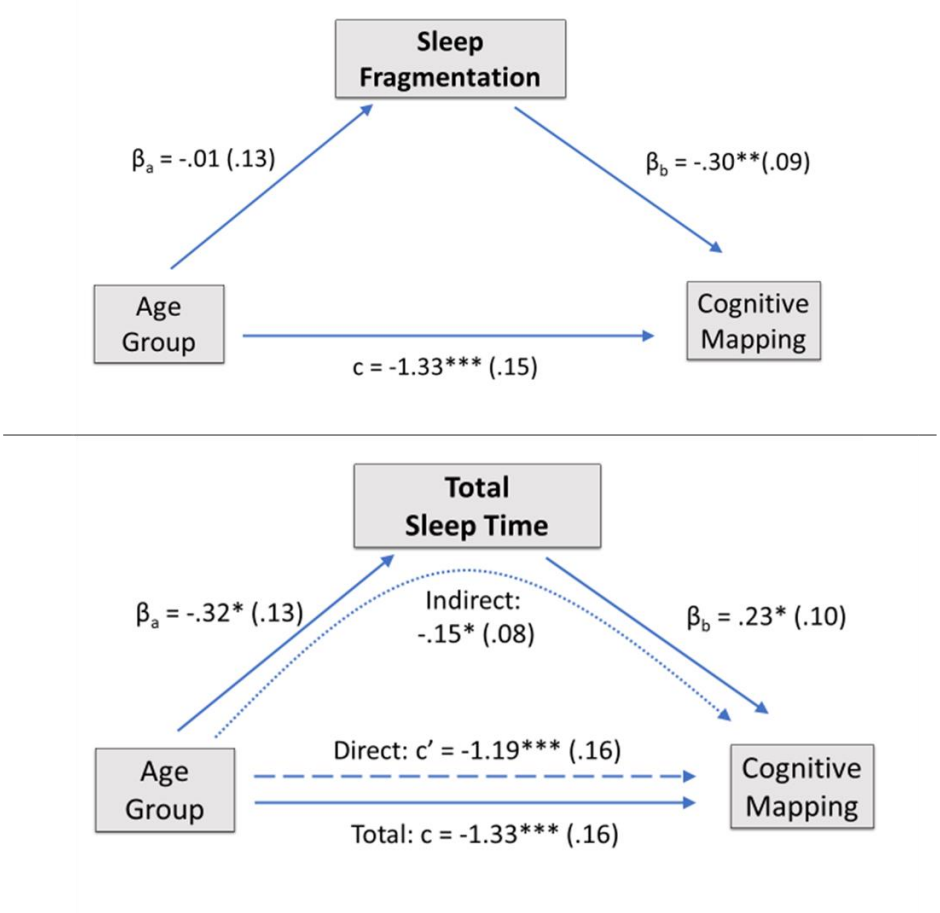

Figure 2. Age, Sleep and Cognitive Mapping. Path model of the relationships amongst age group, sleep variables, and hippocampal-dependent navigation ability. High scores on cognitive mapping indicate better performance. Standardized path coefficients are presented; c=total effect coefficient. ***p< 0.001, **p<0.01, *p<0.05

3.1.3 Route Learning

The ability to recreate a route learned from a first-person perspective, a striatal-dependent navigation task, was significantly reduced with older age (total effect=1.33 (SE=.21), $p<.001$), see Figure 3. As in previous subsamples, age was not associated with sleep fragmentation (β=-.04 (SE=.13), $p=.75$) but was associated with total sleep time (β=-.39 (SE=.13), $p=.003$). Neither sleep fragmentation nor total sleep time was associated with route learning (SFI: β=.11 (SE=.11), $p=.33$; TST: β=-.04 (SE=.11), $p=.73$). Considering the lack of relevant associations, mediation was not examined.

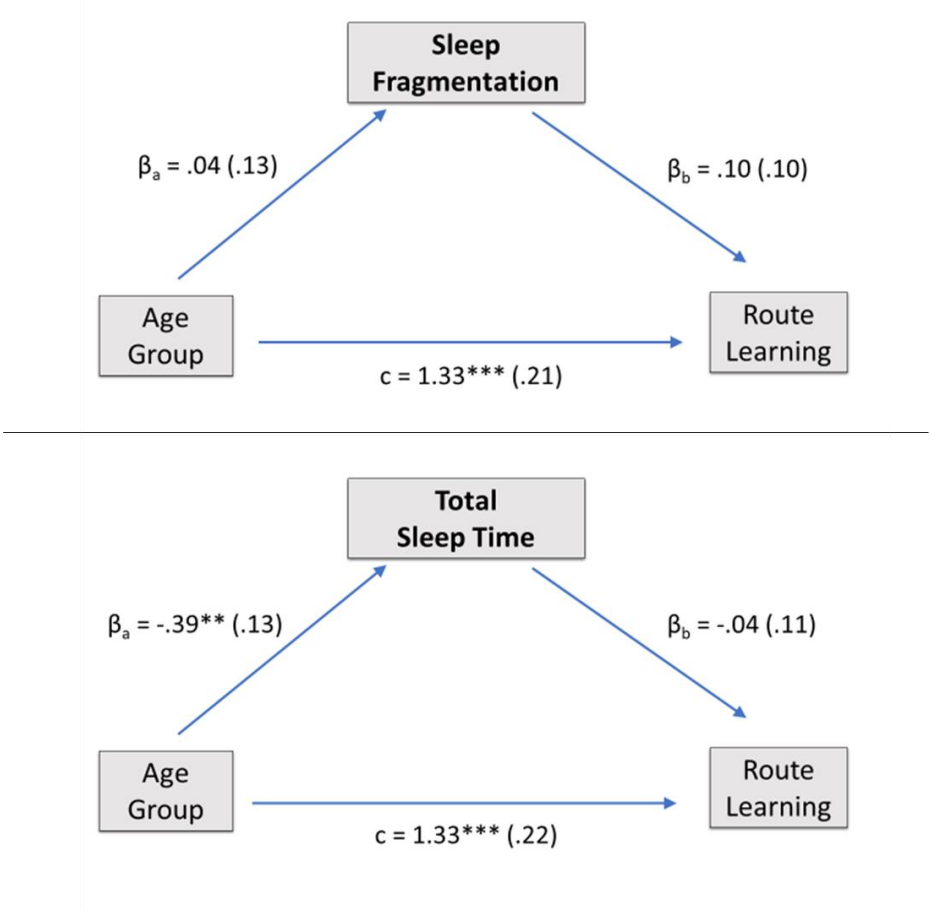

Figure 3. Age, Sleep and Route Learning. Path model of the relationships amongst age group, sleep variables, and striatal-dependent navigation ability. High scores on route learning indicate worse performance. Standardized path coefficients are presented. ***p< 0.001, **p<0.01

3.2 Moderating Effects of Stress

3.2.1 Spatial Navigation Strategy Use

Standardized coefficients for all models including sleep fragmentation index and total sleep time are listed in Tables 2 and 3, respectively. There was not a main effect of stress on the navigation strategy index (β = -.15 (SE=.14), p=.30). Also, there was no significant interaction between stress and sleep fragmentation in predicting navigation strategy selection (β=-.05 (SE=.13), p=.68). Additionally, there was not a significant age x stress x sleep fragmentation interaction in predicting navigation strategy selection (β<.001 (SE=.19), p=.99).

There was a non-significant trend for a stress x total sleep time interaction (β=.23 (SE=.14), p=.06). At higher levels of stress, there was a tendency for increased total sleep time to be associated with greater use of a hippocampal-dependent navigation strategy, whereas at lower stress increased sleep time was associated with greater striatal-dependent strategy use (see Figure 4). The age x stress x total sleep time interaction predicting navigation strategy was not significant (β=.10 (SE=.19), p=.59).

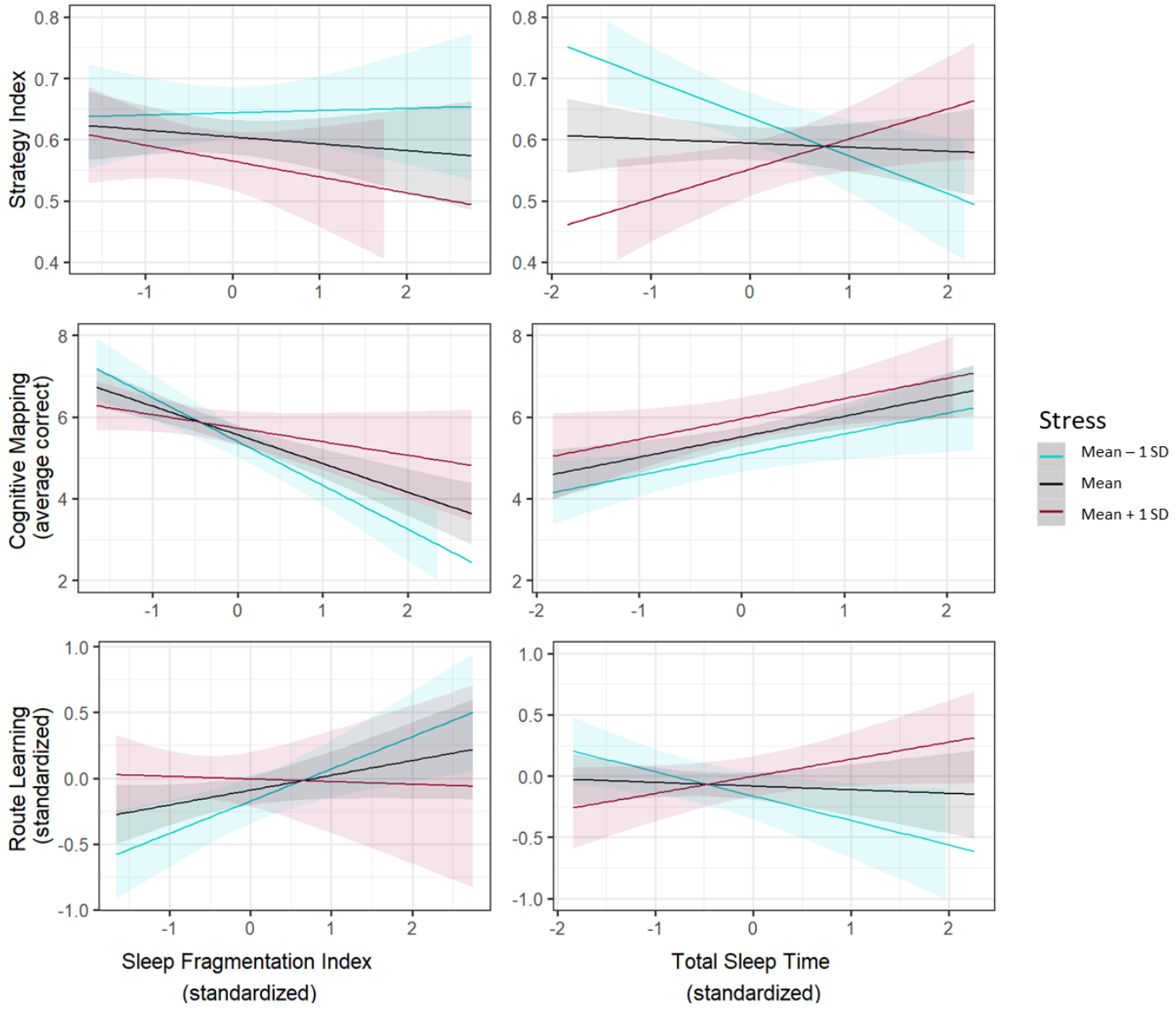

Figure 4. Stress Moderation of Sleep on Navigation. High scores on the navigation strategy index indicate greater relative hippocampal-dependent strategy use. High scores on cognitive mapping indicate better performance. High scores on route learning indicate worse performance.

3.2.2 Cognitive Mapping

There was not a main effect of stress predicting cognitive mapping (β=.12 (SE=.12), *p*=.30).

There was not a stress x sleep fragmentation interaction (β=.13 (SE=.10), *p*=.20); see Figure 4).

Also, the age group x stress x sleep fragmentation interaction predicting cognitive mapping ability was not significant (β= .12 (SE=.14), *p*=.39). There were no interacting effects of total sleep time with stress predicting cognitive mapping ability (β=-.04 (SE=.10), *p*=.69). Further, the total sleep time x stress x age group interaction was not significant (β=-.15 (SE=.17), *p*=.37).

3.2.3 Route Learning

There was not a main effect of stress predicting route learning (β=.07 (SE=.12), *p*=.55). There was not a significant stress x sleep fragmentation index interaction (β=-.10 (SE=.12), *p*=.38; see Figure 4). Additionally, there was not a significant age x stress x sleep fragmentation interaction (β=.02 (SE=.18), *p*=.91). Furthermore, there were no significant interaction effects of total sleep time, age or stress predicting route learning ability (stress x total sleep time: β=.15 (SE=.11), *p*=.17; stress x total sleep time x age: β=.08 (SE=.20), *p*=.69).

3.3 Moderating Effects of Physical Activity

There were no significant main effects of self-reported physical activity for any of the navigation outcomes (all ps>.05). Neither sleep fragmentation nor total sleep time interacted with physical activity in predicting navigation outcomes (all *ps*>.05; see Figure 5). The three-way physical activity by total sleep time by age group was found to predict navigation strategy index (β=-.62 (SE=.33), *p*=.01). This reflected that the interactive effects of physical activity and total sleep time tended to be in the opposite direction in the younger and older adult groups (see Figure 6). Thus, within the more active older adult group, there was a non-significant association in the negative direction between sleep time and hippocampal strategy use β= -.34 (SE=.23), *p*=.16).

For more active younger adults, there was a non-significant association in the positive direction (β=.36 (SE=.22), *p*=.12).

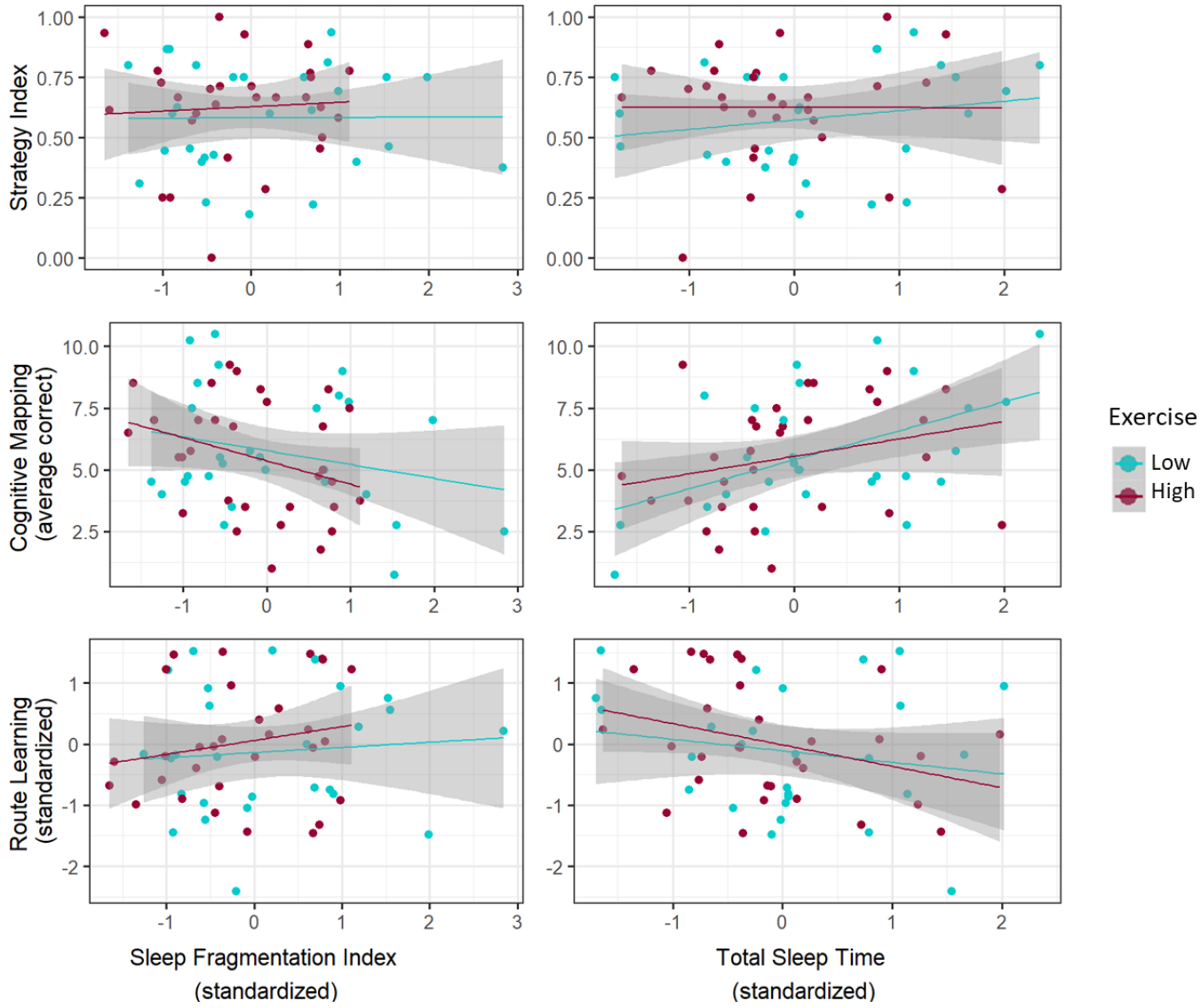

Figure 5. Physical Activity Moderation of Sleep on Navigation. High scores on the navigation strategy index indicate greater relative hippocampal-dependent strategy use. High scores on cognitive mapping indicate better performance. High scores on route learning indicate worse performance.

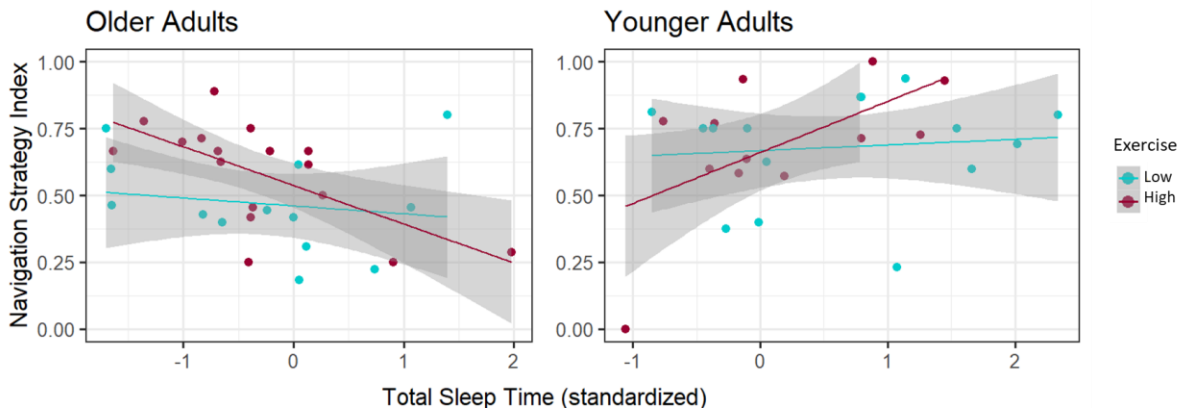

Figure 6. Navigation Strategy Predicted by Age, Sleep Time, and Physical Activity. Higher scores on the navigation strategy index indicate greater use of the hippocampal-dependent strategy.

3.4 Secondary Results

There was also a significant total sleep time x age group interaction in the stress (β=-.35 (SE=.26), *p*=.04) and exercise models. In younger adults, total sleep time was not associated with the navigation strategy index (β =.30 (SE=.18); *p*=.11). In older adults, greater total sleep time was associated with greater use of a striatal-dependent strategy (β =-.48 (SE=.16); *p*=.007).

Chapter 4: Discussion

The present results generally replicate age effects on spatial navigation. Older adults were less likely to select a hippocampal-dependent strategy in a dual-solution task. In addition, older adults were impaired in their ability to form cognitive map, a flexible, allocentric strategy reliant on the hippocampus. Lastly, older adults were impaired in their ability to recreate a route learned from a first-person perspective, stimulus-response, egocentric strategy reliant on the caudate nucleus. However, the age effect on cognitive map formation was numerically, but not significantly, greater than the age effect on route learning (Steiger's $Z=1.641$, $p=.101$). The novel goals of this study were to examine associations between sleep disturbance and spatial navigation as well as the role of sleep disturbance on age differences in spatial navigation. Finally, perceived stress and physical activity were examined as moderators.

4.1 Associations Between Sleep and Spatial Navigation

Sleep fragmentation was associated with reduced hippocampal-dependent navigation performance but was not associated with the striatal-dependent navigation task. The effect on hippocampal-dependent navigation was greater than the effect on striatal-dependent performance (Steiger's $Z=2.031$, $p=.042$). This differential pattern is consistent with observations from rodent studies (Hagewoud, Havekes, Novati, et al., 2010). The relationship between sleep fragmentation and hippocampal integrity has been well-documented in rodents. Considerations of possible mechanisms have linked sleep fragmentation to reduced hippocampal neurogenesis (Guzman-

Marin et al., 2007), increased reactive oxygen species (Nair et al., 2011; Williams et al., 2016), and reduced hippocampal long-term potentiation (E. Kim, Grover, Bertolotti, & Green, 2010; McDermott et al., 2003).

A similar pattern was observed for total sleep time such that reduced sleep was associated with lower cognitive mapping, but not significantly associated with route learning. However, the effect on hippocampal-dependent navigation was not significantly greater than the effect on striatal-dependent performance (Steiger's $Z=1.289$, $p=.197$). Total sleep deprivation is associated with reduced hippocampal synaptic plasticity and reduced allocentric strategy use in rodents (Kreutzmann et al., 2015). Recent studies have also indicated changes in hippocampal metabolite profile following induced sleep-deprivation in rats (Yoon et al., 2019). Humans with chronic insomnia exhibit greater hippocampal atrophy (Joo, Kim, Suh, & Hong, 2014). In addition, there is also evidence in humans that total sleep deprivation negatively impacts consolidation of hippocampal-dependent spatial navigation tasks (M. Ferrara et al., 2006; M Ferrara et al., 2008). The current results indicate that naturalistic reductions in sleep duration may have similar effects as total sleep deprivation, though the degree of a differential effect is inconclusive.

Notably, the rodent literature also observes reduced hippocampal-dependent strategy use in dual-solution tasks after experimentally induced sleep deprivation or sleep fragmentation (Hagewoud, Havekes, Tiba, et al., 2010; Sportiche et al., 2010). One trial induced five hours of sleep deprivation, whereas sleep fragmentation was induced by moving the rodents after only 30 seconds of continuous NREM sleep. Both studies implemented a relatively severe change in sleep compared with the unmanipulated sleep variances observed in our cohort. It is possible that a more significant alteration in sleep may be necessary to observe shifts in navigation strategy in humans.

Total sleep time did mediate the effects of age on cognitive mapping ability. Thus, age-related reductions in total sleep time may represent a modifiable lifestyle factor for improving this ability. Intervention studies would be beneficial for determining whether increasing sleep time is associated with improved cognitive mapping in older adults. In this study, older adults slept about an hour less than young adults on average. Therefore, modest increases in sleep time may be impactful for cognition.

Although not a focus of this work, we observed that in older adults more sleep time was associated with greater use of striatal strategy. This result was surprising given previous findings indicating sleep is beneficial for hippocampal. A similar effect was not observed for sleep fragmentation. Overall, this association between sleep time and striatal strategy selection may not be robust and should be replicated for further interpretation.

Sleep fragmentation did not differ between age groups. However, there was a significant increase in sleep fragmentation with age in the older adult subgroup (β=.42 (SE = .16) p = .014; n=32). This pattern is not consistent with previous literature. For example, a recent meta-analysis observed large effect sizes for differences between younger and older adults on measures of sleep fragmentation with mixed evidence for effects within the older samples (Ohayon et al., 2004). Most of the prior studies detecting fragmented sleep in older adults have used polysomnography, which provides more valid and reliable estimates of sleep parameters compared to wrist actigraphy (Marino et al., 2013). Actigraphy has previously underestimated intermittent nighttime awakenings when compared to polysomnography (de Souza et al., 2003). Therefore, the failure to detect differences in sleep fragmentation between age groups may be due to poor sensitivity of actigraphy. Future studies examining associations of sleep fragmentation with spatial navigation across the lifespan should incorporate polysomnography.

4.2 Moderating Effects of Perceived Stress

Self-reported stress was not significantly associated with any of the spatial navigation tasks. The lack of robust stress effects was surprising given prior evidence indicating a bidirectional relationship between stress and sleep loss (Van Reeth et al., 2000) . Studies have indicated that acute and chronic sleep deprivation leads to increased hypothalamic-pituitary-adrenal (HPA) axis reactivity to stressors in rodents (Suchecki, Tiba, & Tufik, 2002) and humans (Minkel et al., 2014). Additionally, sleep loss has been observed as a result of induced stressors (Pawlyk, Morrison, Ross, & Brennan, 2008). Stress leads to reduced hippocampal function by impairing excitatory synapses (Magariños, Verdugo, & McEwen, 1997) and reducing neurogenesis (Mirescu & Gould, 2006). Furthermore, stress leads to atrophy and functional deficits in human hippocampi (Gianaros et al., 2007; Kim & Diamond, 2002). Perhaps most significantly, experimentally induced stress reduced hippocampal-dependent spatial strategy selection in humans and rodents (Schwabe, Dalm, Schächinger, & Oitzl, 2008).

It is possible our failure to find robust effects is due to the stress measurement. The measurement of stress relied on self-report, which has previously exhibited mixed findings in terms of associations with the stress hormone cortisol (O'Brien, Tronick, & Moore, 2013). Additionally, stress was only measured in terms of the prior week and at one timepoint and may not be reflective of chronic stress. However, there is evidence of experimentally-induced acute stress impairing hippocampal functioning in rodents (Diamond & Rose, 1994; Schwabe, Schächinger, de Kloet, & Oitzl, 2009) and in humans (Henckens, Hermans, Pu, Joëls, & Fernández, 2009; Schwabe et al., 2007). Nonetheless, it may be important to systematically differentiate between

chronic and shorter duration stress exposure in modulating sleep effects on hippocampal-dependent navigation.

4.3 Moderating Effects of Physical Activity

Self-reported physical activity was not associated with any navigation task. However, there was a significant three-way interaction between age, total sleep time and physical activity predicting navigation strategy index. This reflected that in more active individuals, the direction of the association between total sleep time and hippocampal-dependent strategy use was opposite in the younger and older samples. However, the sleep time by physical activity interaction was not significant in either age group. Overall, this finding is difficult to interpret and may not be robust.

Evidence suggests that exercise is associated with larger hippocampal volume and better spatial memory in humans (Ahlskog, Geda, Graff-Radford, & Petersen, 2011), which contrasts with our null findings for both hippocampal-dependent navigation performance and strategy selection. Furthermore, aerobic exercise has been associated with improvements in sleep quality in older adults (Reid et al., 2010). Notably, the current measure estimated physical activity broadly rather than specifically targeting exercise engagement. The failure to find robust effects of physical activity may also be due to the self-report nature of the IPAQ. Specifically, our sample exhibited floor effects, which suggests this instrument may be failing to detect light physical activity. Additionally, physical activity was numerically, though not significantly, higher in older adults (β= .18 (SE=.13), p=.15). A meta-analysis of self-reported physical activity found only small to medium associations between the IPAQ and objective measures in older adults (Bauman et al.,

2011); specifically, older adults often overestimated activity with the IPAQ. Finally, the physical activity measure is limited to one week of self-report and may not represent long-term physical activity behavior, which may be more associated with hippocampal function. Future approaches will utilize actigraphy data to estimate physical activity.

4.4 Limitations and Future Directions

The present study did have limitations worth considering. One limitation is that derived sleep parameters were estimated with wrist activity and self-report. Although both methods were used in conjunction, actigraphy-derived measures have demonstrated poor specificity for differentiating sleep vs. wake, and subjective reports of sleep times may be incorrectly recalled. Although gold-standard polysomnography has the added benefit of detecting sleep architecture, participants are required to sleep in a laboratory environment. It is possible that older adults may be more sensitive to changes in sleep environment and therefore exhibit more disruptions than may have occurred at home. Nonetheless, future studies may benefit from replicating existing results with polysomnography. Further, the determination of the navigation strategy index categorized each trial as either hippocampal-dependent or striatal-dependent, thereby reducing the available information regarding trajectories. A recent review paper illustrated how spatial and temporal aspects of movement can be quantified and compared (Ranacher & Tzavella, 2014). This approach could provide a continuous measure of a participant's path indicating if it is more like a place-learning shortcut route or a response-learning familiar route. Additionally, as noted previously, this study is limited by a subjective, single timepoint estimate of stress. It is possible that an objective and/or repeated measure of stress, such as daily salivary cortisol or hair cortisol, would provide a more valid and sensitive estimate.

4.5 Summary and Conclusions

In conclusion, by implementing stringent exclusion criteria, current results demonstrate the effects of sleep disturbance on hippocampal-dependent spatial navigation in a non-clinical population. These results provide novel evidence that increased sleep fragmentation is associated with reduced cognitive mapping performance across age groups and that reduced sleep time may be a contributing factor to reduced cognitive mapping ability with advancing age Finally, findings present a lack of robust evidence for stress and physical activity as moderators of sleep effects. These and other moderating factors should be further explored in terms of what may mitigate effects of sleep disturbance on spatial navigation in older and younger populations.

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Tables

	NAVIGATION STRATEGY INDEX	COGNITIVE MAPPING	ROUTE LEARNING
Older Adults	N=31	N=30	N=31
Age years (sd)	69 (6.4)	69 (6.4)	69 (6.2)
Female (%)	14 (45)	13 (43)	14 (45)
Younger Adults	N=30	N=31	N=28
Age years (sd)	20 (1.2)	20 (1.5)	20 (1.6)
Female (%)	22 (73)	22 (71)	20 (71)

Table 1. Demographics separated by task sample. sd = standard deviation.

	NAVIGATION STRATEGY INDEX	COGNITIVE MAPPING	ROUTE LEARNING‡
	N=61	*N=61*	*N=59*
Age	**-0.428****	**-0.615*****	**0.713*****
Stress	-0.111	0.122	0.072
Age	**-0.432****	**-0.666*****	**0.735*****
Stress	-0.148	0.018	0.130
SFI	-0.038	**-0.296****	0.142
Age	**-0.432****	**-0.668*****	**0.738*****
Stress	-0.164	0.063	0.077
SFI	-0.044	**-0.287****	0.113
Stress x SFI	-0.065	0.150	-0.127
Age	**-0.448****	**-0.659*****	**0.739*****
Stress	-0.103	0.050	0.070
SFI	-0.164	-0.221	0.110
Stress x SFI	0.021	0.100	-0.130
Stress x Age	-0.181	0.045	0.015
SFI x Age	0.162	-0.087	0.002
Age	**-0.448****	**-0.636*****	**0.741*****
SFI	-0.164	-0.204	0.108
Stress	-0.103	0.025	0.061
Stress x SFI	0.021	0.021	-0.139
Stress x Age	-0.189	0.081	0.025
SFI x Age	0.162	-0.054	0.009
Stress x SFI x Age	0.000	0.129	0.021

Table 2. Stress as a Moderator of Sleep Fragmentation Index (SFI). All values are standardized coefficients. ‡Route Learning outcome was Box-Cox transformed to achieve normality. High scores on strategy index indicates greater relative hippocampal-dependent strategy selection. High scores on cognitive mapping indicate better performance. High scores on route learning indicate worse performance. ***p<0.001, **p<0.01, *p<0.05, †p<0.1

	NAVIGATION STRATEGY INDEX	COGNITIVE MAPPING	ROUTE LEARNING‡
	N=61	*N=61*	*N=59*
Age	**-0.428****	**-0.615*****	**0.713*****
Stress	-0.139	0.122	0.072
Age	**-0.441****	**-0.556*****	**0.698*****
Stress	-0.132	0.096	0.077
TST	-0.048	**0.217***	-0.045
Age	**-0.433****	**-0.556*****	**0.713*****
Stress	-0.177	0.108	0.043
TST	-0.043	**0.218***	-0.020
Stress x TST	0.251†	-0.042	0.169
Age	**-0.442****	**-0.556*****	**0.714*****
Stress	-0.134	0.082	0.007
TST	0.293	0.170	0.062
Stress x TST	0.058	-0.006	0.141
Stress x Age	-0.160	0.072	0.093
TST x Age	**-0.341***	0.051	-0.082
Age	**-0.436****	**-0.568*****	**0.726*****
TST	0.321	0.123	0.078
Stress	-0.119	0.045	0.022
Stress x TST	0.001	0.078	0.094
Stress x Age	-0.154	0.065	0.118
TST x Age	**-0.323***	0.027	-0.059
Stress x TST x Age	0.092	-0.136	0.073

Table 3. Stress as a Moderator of Total Sleep Time (TST). All values are standardized coefficients. ‡Route Learning outcome was Box-Cox transformed to achieve normality. High scores on the navigation strategy index indicate greater relative hippocampal-dependent strategy selection. High scores on cognitive mapping indicate better performance. High scores on route learning indicate worse performance. ***p<0.001, **p<0.01, *p<0.05, †p<0.1

	NAVIGATION STRATEGY INDEX	COGNITIVE MAPPING	ROUTE LEARNING‡
	N=57	*N=59*	*N=58*
Age	**-0.423****	**-0.691*****	**0.676*****
Exercise	0.137	0.033	-0.013
Age	**-0.423****	**-0.728*****	**0.671*****
Exercise	0.137	-0.004	0.003
SFI	-0.001	-0.251	0.089
Age	**-0.446****	**-0.694*****	**0.677*****
Exercise	0.146	-0.000	0.001
SFI	-0.089	**-0.281***	0.119
Exercise x SFI	0.250	0.082	-0.076
Age	**-0.498****	**-0.637*****	**0.588*****
Exercise	0.064	0.089	-0.103
SFI	-0.157	-0.170	0.074
Exercise x SFI	0.191	0.144	-0.129
Exercise x Age	0.131	-0.142	0.188
SFI x Age	0.098	-0.159	0.076
Age	**-0.486****	**-0.644*****	**0.609*****
Exercise	0.022	0.120	-0.132
SFI	-0.078	-0.251	0.153
Exercise x SFI	-0.080	0.234	-0.219
Exercise x Age	0.298	-0.302	0.360
SFI x Age	-0.016	-0.036	-0.054
Exercise x SFI x Age	0.332	-0.319	0.313

Table 4. Exercise as a Moderator of Sleep Fragmentation Index (SFI). All values are standardized coefficients. ‡Route Learning outcome was Box-Cox transformed to achieve normality. High scores on the navigation strategy index indicate greater relative hippocampal-dependent strategy use. High scores on cognitive mapping indicate better performance. High scores on route learning indicate worse performance. 4 participants were missing exercise data in the Navigation Strategy subsample (1 OA, 3 YA). 2 participants were missing exercise data in the Cognitive Mapping subsample (OA). 1 participant was missing exercise data in the Route Learning subsample (OA). ***$p<0.001$, **$p<0.01$, *$p<0.05$, †$p<0.1$

	NAVIGATION STRATEGY INDEX	COGNITIVE MAPPING	ROUTE LEARNING‡
	N =57	*N=59*	*N=58*
Age	**-0.423****	**-0.691*****	**0.676*****
Exercise	0.244	0.033	-0.013
Age	**-0.423****	**-0.637*****	**0.674*****
Exercise	0.137	0.056	-0.014
TST	0.002	0.176	-0.007
Age	**-0.420****	**-0.639*****	**0.680*****
Exercise	0.138	-0.066	-0.016
TST	0.055	0.268	0.096
Exercise x TST	-0.134	-0.207	-0.216
Age	**-0.414***	**-0.517****	**0.636*****
Exercise	0.149	0.192	-0.051
TST	0.345	0.275	0.178
Exercise x TST	0.003	-0.316	-0.156
Exercise x Age	0.050	-0.251	0.088
TST x Age	**-0.348***	0.058	-0.122
Age	**-0.473***	**-0.527****	**0.636*****
Exercise	-0.014	0.170	-0.049
TST	0.093	0.233	0.183
Exercise x TST	0.389†	-0.109	-0.093
Exercise x Age	0.366	-0.453	0.160
TST x Age	-0.116	0.112	-0.128
Exercise x TST x Age	**-0.652***	-0.117	0.012

Table 5. Exercise as a Moderator of Total Sleep Time (TST). All values are standardized coefficients. ‡Route Learning outcome was Box-Cox transformed to achieve normality. High scores on the navigation strategy index indicate greater relative hippocampal-dependent strategy use. High scores on cognitive mapping indicate better performance. High scores on route learning indicate worse performance. 4 participants were missing exercise data in the Navigation Strategy subsample (1 OA, 3 YA). 2 participants were missing exercise data in the Cognitive Mapping subsample (OA). 1 participant was missing exercise data in the Route Learning subsample (OA). ***$p<0.001$, **$p<0.01$, *$p<0.05$, †$p<0.1$