HHS Public Access

Author manuscript

J Int Neuropsychol Soc. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

J Int Neuropsychol Soc. 2018 January ; 24(1): 67–76. doi:10.1017/S1355617717000637.

Association of Sleep Quality on Memory-Related Executive Functions in Middle Age

Brinda K. Rana[1,3], **Matthew S. Panizzon**[1,2], **Carol E. Franz**[1,2], **Kelly M. Spoon**[2,4], **Kristen C. Jacobson**[5], **Hong Xian**[6,7], **Sonia Ancoli-Israel**[1,8], **Michael Lyons**[9], and **William S. Kremen**[1,2,10]

[1]Department of Psychiatry, University of California, San Diego, La Jolla, California

[2]Center for Behavioral Genetics of Aging, University of California, San Diego, La Jolla, California

[3]Sam and Rose Stein Institute for Research on Aging, La Jolla, California

[4]Computational Science Research Center, San Diego State University/Claremont Graduate University, San Diego, California

[5]Department of Psychiatry & Behavioral Neuroscience, University of Chicago, Chicago, Illinois

[6]Department of Biostatistcs, St. Louis University School of Public Health, St. Louis, MO

[7]St. Louis VA Healthcare System, St. Louis, Missouri

[8]Department of Medicine, University of California, San Diego, La Jolla, California

[9]Department of Psychological and Brain Sciences, Boston University, Boston, Massachusetts

[10]Center of Excellence for Stress and Mental Health, VA San Diego Healthcare System, San Diego, California

Abstract

Objectives—Sleep quality affects memory and executive function in older adults, but little is known about its effects in midlife. If it affects cognition in midlife, it may be a modifiable factor for later-life functioning.

Methods—We examined the association between sleep quality and cognition in 1220 middle-aged male twins (age 51–60 years) from the Vietnam Era Twin Study of Aging. We interviewed participants with the Pittsburgh Sleep Quality Index and tested them for episodic memory as well as executive functions of inhibitory and interference control, updating in working memory, and set shifting. Interference control was assessed during episodic memory, inhibitory control during working memory, and non-memory conditions and set shifting during working memory and non-memory conditions.

Correspondence and reprint requests to: Brinda K. Rana and William S. Kremen, Department of Psychiatry, University of California, 9500 Gilman Drive, MC-0738, La Jolla, CA 92093. bkrana@ucsd.edu and wkremen@ucsd.edu.

The authors have no conflicts of interest.

Supplementary material

To view supplementary material for this article, please visit https:/doi.org/10.1017/S1355617717000637

Results—After adjusting for covariates and correcting for multiple comparisons, sleep quality was positively associated with updating in working memory, set shifting in the context of working memory, and better visual-spatial (but not verbal) episodic memory, and at trend level, with interference control in the context of episodic memory.

Conclusions—Sleep quality was associated with visual-spatial recall and possible resistance to proactive/retroactive interference. It was also associated with updating in working memory and with set shifting, but only when working memory demands were relatively high. Thus, effects of sleep quality on midlife cognition appear to be at the intersection of executive function and memory processes. Subtle deficits in these age-susceptible cognitive functions may indicate increased risk for decline in cognitive abilities later in life that might be reduced by improved midlife sleep quality.

Keywords

PSQI; Cognition; VETSA; Memory; Resistance to interference; Executive function

INTRODUCTION

Good sleep quality contributes to successful aging (Driscoll et al., 2008; Jaussent et al., 2012; Reid et al., 2006), and better sleep has been shown to positively influence physical health-related quality of life and cognitive performance in successful agers (Driscoll et al., 2008). However, sleep disturbances are common in older adults and sleep quality often diminishes with age (Hoch et al., 1994). Longitudinal studies have found that poor sleep quality is associated with subsequent cognitive decline (Blackwell et al., 2011a; Potvin et al., 2012). Waters and Bucks (2011) reviewed the literature on the impact of sleep loss on cognition, concluding that even moderate reductions in sleep significantly reduce performance in multiple aspects of cognition. Specifically, evidence suggests that executive function, the control and regulation of thinking and behavior that is important for performing everyday tasks, is impaired by poor sleep in adults (Waters & Bucks, 2011). On the other hand, findings appear to be more mixed with respect to the effect of sleep loss on hippocampal-dependent episodic memory (Prince & Abel, 2013; Stickgold & Walker, 2005; Waters & Bucks, 2011).

Supporting the theory that improving sleep quality might improve cognitive performance or slow declines, the reversal of many reductions in cognitive performance have been observed with improved sleep quality (Waters & Bucks, 2011). For example, a meta-analysis of 35 obstructive sleep apnea (OSA) studies revealed that all domains of executive function were impaired due to OSA-related chronic sleep disturbances and these impairments improved with treatment (Olaithe & Bucks, 2013). However, in population studies of sleep disturbances driven by disorders such as OSA, it may be difficult to determine whether it is sleep disturbance or other factors related to the disorder that contribute to cognitive performance. Thus, studies designed to understand the relationship between sleep quality and cognition at midlife are needed and may lead to potential sleep-based interventions for maintaining or improving later-life cognitive functioning.

The majority of previous sleep studies of cognition have focused on individuals with sleep disorders (e.g., OSA), young adults in pre–post laboratory comparisons or sleep deprivation studies in which individuals with poor sleep quality are often excluded. Results of these studies may not be informative about the impact of typical, non-laboratory sleep quality or the relationship between sleep and cognition in middle-aged and older adults. Five studies on community-dwelling older adults that used the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and included measures in cognitive domains relevant to the present study (summarized in Table 1). Only two of these studies focused on middle age. One study found an association with episodic memory (Miller, Wright, Ji, & Cappuccio, 2014), but three did not (Potvin et al., 2012; Saint Martin, Sforza, Barthelemy, Thomas-Anterion, & Roche, 2012; Nebes, Buysse, Halligan, Houck, & Monk, 2009); one reported an association with set shifting (Nebes et al., 2009), but two did not (Blackwell et al., 2011b; Saint Martin et al., 2012); one found an association with working memory updating (Nebes et al., 2009); and two found no associations with inhibitory control (Nebes et al., 2009; Saint Martin et al., 2012).

The review by Waters and Buck (2011) strongly suggested the importance of poor sleep for executive function. A leading cognitive model organizes executive function into three components: updating (monitoring ongoing information in working memory, shifting (of mental sets), and inhibitory control (suppression of proponent responses) (Miyake et al., 2000). However, Friedman and Miyake (2004) subsequently conducted a detailed analysis that differentiated interference control/resistance to interference from inhibitory control. They found that resistance to distractor interference, which was not included in the present study, was strongly correlated with inhibition. Resistance to proactive interference (the tendency of prior material to interfere with learning subsequent material) was unrelated to inhibition.

Reduced interference and inhibitory control have been implicated as a key factor underlying age-related cognitive decline by one of the major theories of cognitive aging (Hasher, Lustig, & Zacks, 2008), and this cognitive decline may be linked to the reduction in sleep quality observed in older adults. The relationship between inhibitory control, sleep, and aging are suggested by findings of age-related increases in Stroop interference effects (Bugg, DeLosh, Davalos, & Davis, 2007) and the observation that inhibitory control is impaired in older sleep-deficient OSA patients (Olaithe & Bucks, 2013) but not in sleep-deprived young adults (Bratzke, Steinborn, Rolke, & Ulrich, 2012; Cain, Silva, Chang, Ronda, & Duffy, 2011; Sagaspe et al., 2006).

Even the impact of sleep on episodic memory may be *via* the resistance to interference component of executive function. As early as the late 19th century, it was proposed that protection against daytime sources of interference is how sleep primarily affects episodic memory consolidation (Stickgold, 2005). Indeed, there is evidence in support of the idea that newly formed verbal memories are vulnerable to interference, and that sleep stabilizes memories, making them resistant to subsequent interference (Deliens, Leproult, Neu, & Peigneuz, 2013; Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006; Sheth, Varghese, & Truong, 2012).

Neurocognitive assessment was limited in several of the studies in Table 1. For example, all but one in which episodic memory was examined in older adults included only verbal memory. All of the studies assessing set shifting used part B of the Trail Making Test. Although Trails B involves set shifting, it is also highly correlated with part A, which assesses processing speed without any shifting component. Without adjusting for part A scores, it is uncertain whether part B scores are measuring set shifting or processing speed. Inhibitory control measures in these studies had no memory component, leaving the possibility that inhibitory control in the context of memory demands is impaired by poor sleep quality. Only two of the studies included a focus on middle age.

To address these gaps, we investigated the extent to which sleep quality over a 1-month time interval, measured by the PSQI, in middle-aged adults is associated with verbal and visual-spatial episodic memory and all the components of executive function. In addition, we further examined inhibitory control in the context of working memory, and non-memory conditions, predicting that midlife sleep quality would be associated primarily with inhibitory control processes related to memory. If sleep quality affects executive function and memory in midlife, it might suggest sleep quality as a modifiable factor for improving later-life cognitive functioning.

METHODS

Participants

We assessed 1220 middle-aged (mean = 55.4 years; *SD* = 2.5) men in wave 1 of the Vietnam Era Twin Study of Aging (VETSA) (Kremen, Franz, & Lyons, 2013; Kremen et al., 2006). VETSA is a prospective longitudinal study of midlife and protective influences on cognitive aging in a community-dwelling sample comprising 1237 individual twins at baseline drawn from the larger Vietnam Era Twin Registry. The Registry is defined on the basis of military service sometime between 1965 and 1975. Average educational attainment was 13.8 years (*SD* = 2.1). VETSA participants are reasonably representative of American men of the same age in terms of lifestyle and health characteristics based on Center for Disease Control data (Schoenborn & Heyman, 2009). Nearly 80% reported no combat exposure. Participants were not selected or excluded on the basis of any diagnostic characteristics. The only criteria were that participants had to be 51–59 years old at recruitment, and both twins in a pair were willing to participate.

Participants were administered identical protocols at the University of California, San Diego, or Boston University. Individual twins chose their site, although brothers most often chose the same site. The complete protocol has been described previously (Kremen et al., 2013). The present analyses were based on 1220 participants with valid scores on the PSQI, relevant study instruments, and with no history of brain disease, stroke, or damage based on a medical history interview. The research was conducted in accordance with the Helsinki Declaration and approved by the University of California and Boston University Institutional Review Boards.

Measures

Pittsburgh Sleep Quality Index (PSQI)—The PSQI, a well-validated scale that assesses sleep quality and disturbance over the preceding month (Buysse et al., 1989), consists of 19 items with a total ranging from 0 to 21 (Table 2). PSQI > 5 has been found to best distinguish individuals with clinically significant sleep problems from those without significant sleep problems (Buysse et al., 1989). Total scores could not be computed for 17 individuals with incomplete data. Total scores (N = 1220) were positively skewed and achieved normal distribution when square root transformed. PSQI was obtained one the same day as the neurocognitive assessments and thus provides information on sleep quality up to a month's time leading to the neurocognitve data.

California Verbal Learning Test-II—We used the California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) to assess episodic memory and interference control in the context of episodic memory. Following standard instructions, a list of 16 nouns (list A) is read to the participant five times; participants then recite all the words they can remember in any order immediately after each trial. After the five trials a second list (B) is read, followed by short and long delayed recall conditions for list A. The CVLT Short and Long Delay Composite Scores (sum of both scores) was assessed for association with PSQI. Intrusions are words reported on any trial that were not on the list in question.

We used the average number of correct words recalled on the long- and short-delay free recall trials for list A as an episodic memory score. Total intrusions on all trials (CVLT-II Intrusions across All Trials) are the number of incorrect recalls across all trials (five List A, the List B, and free and cued short and long delay of List A) and served as an index of resistance to interference in the context of episodic memory. Because the B List follows the A list and the B list is then followed again by the A list, total intrusions may actually reflects some combination resistance to proactive and retroactive interference. Higher intrusion scores represent poorer performance.

Wechsler Memory Scale-III—The Wechsler Memory Scale-III (WMS-III; Wechsler, 1997) Logical Memory subtest includes two stories that are read to participants. Standard instructions are to read the second story twice, but we read each story only once. The Visual Reproductions subtest includes a set of drawings that are shown one at a time for 10 s; participants are then asked to draw them as best as possible from memory. Both the logical memory and visual reproductions scores are a composite score for the amount of correct information remembered on the immediate and delayed recall conditions with higher scores representing better performance on the test.

Stroop Color and Word Test—The Stroop is a widely used test of inhibitory control that assesses inhibition of a prepotent response; it has no memory demands (Golden & Freshwater, 2002; Stroop, 1935). Participants were presented a Word page with a list of color names printed in black ink and given 45 s to read as many words as they could. Participants were then given a Color page on which they call out the colors of a list of "XXXX" printed in red, green, or blue ink. For the inhibitory control trial, participants were

presented a Color-Word page in which each color name is printed in an incongruous colored ink. Participants had to name the color of the ink, forcing them to inhibit the prepotent tendency to read the word.

Although the manual refers to the Interference Score, consistent with our definitions, we refer to it here as the Stroop Inhibition Score. It is computed by subtracting the Predicted Color-Word Score (using a regression formula which predicts Color-Word from Word or Color) from the Raw Color-Word Score. It is then converted into an T-score (Golden & Freshwater, 2002). A higher Interference T-score represents better inhibitory control.

AX-Continuous Performance Test—We administered the version of the AX-Continuous Performance Test (CPT; Servan-Schreiber, Cohen, & Seingard, 1996), previously described (Kremen et al., 2011), to assess updating and inhibitory control in the context of working memory. This computer-administered test consisted of letters presented in pseudorandom order. Participants were instructed to press the target button only when they saw an *X* that was immediately preceded by an *A* (*AX* trials). On all other trials, they were to press the non-target button. Having 70 percent of trials as *AX* trials primes participants for a target response and requires inhibitory control on other trials.

The *AX*-error rate measures updating during working memory. Trials that require inhibiting a target response to *X* when followed by a non-*A* probe are referred to as *BX* trials; trials that require inhibiting a target response when an *A* probe is followed by a non-*X* letter are referred to as *AY* trials (Kremen et al., 2011). *AY* and *BX* error rates index inhibitory control in the context of working memory; higher error scores represent poorer performance.

Trail Making Test—This subtest of the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) was used to assess set-shifting in a non-memory setting. Participants were given a sheet with randomly distributed numbers and letters. In Trial 2, they were timed while connecting digits in numerical order; in Trial 3 they were timed connecting letters in correct alphabetical order. Trial 4 involved alternating between number and letter in sequence.

Time to complete Trial 4 was adjusted for the time to complete the separate number sequencing and letter sequencing trials. This score represents set-shifting ability adjusted for processing speed. Lower time scores indicate better set shifting ability.

Category Switching—The category switching trial from the D-KEFS Verbal Fluency test (Delis et al., 2001) assesses set shifting in the context of working memory. Participants were asked to alternate between naming fruit words and furniture words. The score was the number of correct switches in 1 min adjusted for category fluency in which participants had to name all the animals they could think of in 1 min. Controlling for category fluency ensured that the score primarily reflected the set-shifting component of the test.

Covariates

Mental health—The Short-Form 36 Health Survey (SF-36) version 1 is a validated multi-purpose health survey (McHorney, Ware, & Raczek, 1993). Because mental health may

affect cognitive function, we included the SF-36 Mental Component Summary (MCS) score as a covariate. It includes the Vitality Scale with questions regarding energy level and fatigue that are confounded with sleep quality. We modified the scale SF-36MCS/M by adjusting it for the Vitality Scale *via* linear regression.

Physical health—In a medical history interview, participants were asked if they had ever been told by a physician that they had particular conditions. Participants reported the first year they were diagnosed and whether the condition was still present. Sleep apnea was one of these conditions. In addition to using sleep apnea as a separate covariate, we also created a summation index of the following current medical conditions: asthma, chronic bronchitis, emphysema, hypertension, angina, heart attack, heart failure, peripheral vascular disease, thrombophebitis, hepatitis C, diabetes, migraine headaches, seizure disorder, multiple sclerosis, HIV infection/AIDS.

Medications—Typical of their age range, VETSA participants were taking a variety of medications. Almost all VETSA participants taking medications were on stable doses that had not been recently changed. Therefore, there should not have been any acute medication effects on the results and we did not add medication as a covariate. Moreover, the PSQI does include an item about the use of medications for sleep.

General Cognitive Ability—To account for the relationship between the cognitive measures and General Cognitive Ability (GCA), we included GCA as a covariate in the analyses. GCA was assessed with the Armed Forces Qualification Test (AFQT), a 50-min paper-and-pencil test with 100 multiple-choice items (Orme, Brehm, & Ree, 2001; Uhlaner, 1952). We used scores for the AFQT at average age 20 so that GCA measures were not confounded by age-related effects. The AFQT is highly correlated (r = 0.84) with Wechsler IQ and VETSA participants' AFQT scores were correlated .74 across 35 years (Lyons et al., 2009).

Statistical Analysis

We conducted generalized linear mixed model regression analysis with the R (Skaug, Fournier, Nielsen, Magnusson, & Bolker, 2011) package using separate regression models to predict each cognitive outcome (see Supplemental Data for R script). Ns vary slightly due to missing data for different measures. Age, GCA, current OSA, the SF-36 mental health rating (SF-36MCS/M score), and the summed physical condition index were included as covariates in all analyses (see Table 3). Twin pair family was included as a random effect to account for the clustering of data within twin pairs. For non-Gaussian distributed variables, models were based on a Poisson distribution and zero-inflation. We evaluated the Type III sums of squares in which the significance of each effect is based on its effect after controlling for all other effects in the model. To account for multiple comparisons, a false discovery rate at the 5% level was determined (Benjamimi & Hochberg, 1995).

RESULTS

Table 2 summarizes the statistics of the cognitive and health measures. Forty-one percent of the participants experienced poor sleep quality based on a global PSQI > 5. Of the 1220

participants on which we had a global PSQI score, 7% ($N = 83$) reported that they had previously been diagnosed with sleep apnea by a doctor. A total of 48% ($N = 40$) of these 83 participants had poor sleep quality (PSQI > 5). Eight percent ($N = 40$) of participants with poor sleep quality (PSQI > 5) reported that they had been previously diagnosed with sleep apnea. Sixty-one of the 83 who were previously diagnosed with sleep apnea reported that their sleep apnea was currently present when the assessments were administered.

Results for the associations of the continuous PSQI sleep quality measure with the 10 cognitive measures are presented in Table 3; significant results for the dichotomous PSQI measure were consistent with the continuous PSQI results (Supplementary Table 2).

Episodic and Working Memory

Among the three episodic memory measures (Table 3; measures 1–3), only the Visual Reproductions Immediate and Delayed Recall Composite score differed as a function of sleep quality. Better sleep quality was associated with better visual reproduction performance during episodic memory ($\beta = -.33$; $p < .004$). Working memory updating (measure 8) was also associated with sleep quality; fewer errors in the CPT-AX Errors task were associated with better sleep quality ($\beta = 0.014.$; $p < .0001$).

Resistance to Interference and Inhibitory Control

Resistance to interference in episodic memory was associated with better sleep quality (Table 3; measure 4); better sleepers made significantly fewer total intrusions measured by CVLT-II Intrusions across All Trials ($\beta = .013$; $p < .034$) than poor sleepers. In secondary analyses, we examined CVLT-II Intrusion subcomponent scores. These results indicate that the tendency to make intrusion errors as a function of poorer sleep quality was driven by intrusion on delayed recall and cued recall trials (Supplementary Table 1). However, confidence in these results may be reduced by the fact that the FDR-corrected p-value for CVLT-II intrusions was .09. Inhibitory control, whether in the context of working memory or non-memory tasks, was not significantly associated with sleep quality.

Set Shifting

Better performance on Verbal Fluency Category Switching Accuracy (Set Shifting in Working Memory) was associated better sleep quality (Table 3, measure 9; $\beta = -.077$; $p = .002$), but the Trail-Making Test score (Set Shifting in Non-Memory Setting) was not significantly associated with sleep quality (Table 3; Trail Making, measure 10).

PSQI Subcomponents

To examine which subcomponents of the PSQI were associated with cognitive performance, we examined the relationship between the significantly associated cognitive variables and the seven subcomponent scores. For Visual Reproductions Immediate and Delayed Recall Composite Score, sleep latency ($\beta = -0.90$, 95% CI = (−1.8, −.03); $SD = .44$; $z = -2.04$; $p = .04$), sleep quality ($\beta = -2.41$, 95% CI = (−3.5, −1.28); $SD = .57$; $z = -4.20$; $p < .0001$), and sleep medication ($\beta = -0.98$, 95% CI = (−1.88, −.07); $SD = .46$; $z = -2.11$; $p = .03$) were significantly associated with performance.

We observed a trend for sleep efficiency (β = −.80, *SD* = .42, z = −1.89; *p* = .06), but we did not observe significant associations with daytime dysfunction, sleep duration or night time disturbances. Verbal Fluency Category Switching Accuracy was associated with sleep latency (β = −.193, 95% CI = (−.38, −.01); *SD* = .094; z = −2.04; *p* = .04), efficiency (β = −.223, 95% CI = (−.40, −.05); *SD* = .092; z = −2.46; *p* = .014), sleep medication (β = −.228, 95% CI = (−.42, −.03); *SD* = .10; z = −2.29; *p* = .02), and daytime dysfunction (β = −.495, 95% CI = (−.76, −.23); *SD* = .133; z = −3.70; *p* = .0002).

CPT-*AX* errors were significantly associated with sleep duration (β = .08, 95% CI = (.04, .12); *SD* = .02; z = 4.1; *p* < .0001), sleep latency (β = .05, 95% CI = (.01, .10); *SD* = .02; z = 2.41; *p* = .02), sleep quality (β = .15, 95% CI = (.1, .2); *SD* = .03; z = 4.96; *p* < .0001), sleep efficiency (β = .04, 95% CI = (.005, .08); *SD* = .02; z = 2.26; *p* = .02), and daytime dysfunction (β = .11, 95% CI = (.05, .17); *SD* = .03 ; z = 3.78; *p* = .0002). Resistance to interference in episodic memory measured by CVLT-II Intrusions across All Trials was significantly associated with sleep efficiency (β = .050, 95% CI = (.01, .09); *SD* = .02; z = 2.28; *p* = .02).

DISCUSSION

To more fully understand cognitive trajectories over the adult lifespan, it is necessary to examine middle age, the period before older age. Prior sleep-cognitive function studies had little focus on middle age, and many studies of older adults had limited coverage of executive functions and memory. Here, we provided a more comprehensive assessment of these cognitive domains, and examined whether they are associated with sleep quality before old age.

Sleep quality was not significantly associated with verbal episodic memory accuracy (Table 3; CVLT-II, Logical Memory), but it was associated with visual-spatial episodic memory accuracy (Table 3; Visual Reproductions). Sleep quality was associated with three of four executive functions, but only when those executive functions were in conjunction with memory processes: resistance to interference in episodic memory; updating in working memory; and set shifting in a task with working memory demands. In total, 4 of 10 associations examined were statistically significant; after an FDR correction, 3 of the 4 were associated.

Our results are consistent with previous population-based studies of older adults that mostly have not found evidence of sleep quality affecting verbal episodic memory (Blackwell et al., 2011; Nebes et al., 2009; Saint Martin et al., 2012). Only one study (Saint Martin et al., 2012) we reviewed included a recognition visual-spatial memory test. It was not associated with sleep quality, but being a recognition memory test, the test may not have been sufficiently difficult to show an effect as was observed for visual-spatial recall in the present study.

Prior studies based on self-report of sleep or laboratory-based studies have found no evidence of sleep quality being associated with inhibitory control (Blackwell et al., 2011a; Nebes et al., 2009; Saint Martin et al., 2012). Our results are consistent with this lack of

association, and that was the case whether inhibitory control was examined in tests with or without demands on memory (Table 3: CPT-AY and BX errors, Stroop).

However, we did observe an association between sleep quality and resistance to interference in episodic memory (Table 3: CVLT-II Intrusions). Two studies of young adults (Cajochen, Khalsa, Wyatt, Czeisler, & Dijk, 1999; Drake et al., 2001) reported that laboratory-based sleep deprivation negatively affected resistance to proactive interference, but another (Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010) found no effect. The latter focused on recency effects that would emphasize short-term/working memory, whereas the studies that observed significant effects included delayed recall. Two studies of adults in their mid-30s and mid-40s, respectively, found that insomnia was associated with poorer resistance to interference, including one finding more CVLT-II intrusions (Fortier-Brochu & Morin, 2014; Griessenberger et al., 2013). Thus, our results regarding resistance to interference and episodic memory are consistent with the findings of these prior studies. It may be that extensive sleep deprivation is needed to produce this effect in younger adults, but as age increases it appears that their susceptibility may increase.

Set shifting is a phenomenon that takes place over relatively short time intervals, so it is primarily relevant to short-term/working memory rather than episodic memory. In our view, a parsimonious explanation of our finding that sleep quality was associated with set-shifting ability on Category Switching but not on the Trail-Making Test is that the former places demands on working memory but the latter does not. During the Category Switching test, one must hold words that were previously said in short-term memory to keep track of them so they are not repeated. In contrast, switching on the Trail-Making Test has very little working memory demands because number and letter sequences are so highly automated and overlearned, and participants can easily see their previous response as they proceed.

The link to working memory is also supported by our finding of an association between sleep quality and updating in working memory. Our finding that sleep quality was associated with updating in working memory is also consistent with the human study of Nebes et al. (2009) and with human-animal comparisons in the study of van Enkhuizen et al. (2014). Nebes et al. (2009) also reported an association between PSQI scores and set shifting in older adults, but the scores were not adjusted for Trails A. So their measure may be tapping processing speed as much or more than it does set shifting.

These associations between cognitive functions and midlife sleep quality could portend further susceptibility with increasing age. This issue warrants further investigation, in particular as it relates to the intersection of executive functions and memory. Our results also suggest the need for further study of sleep effects on visual-spatial memory, something that is lacking in the extant literature. These associations were small in magnitude. The mixed model analysis does not allow for precise effect size estimates, but the effects in the present study were roughly equivalent to Cohen’s d values of .15 to .25 as estimated (Supplementary Table 2) using the mean and standard deviation of the cognitive variables for individuals who were classified as poor sleepers (PSQI > 5) versus good sleepers (PSQI < 6). These approximate effect sizes are comparable to most of those found for insomnia in short-duration sleepers (Fernandez-Mendoza et al., 2010). No differences for insomnia were found

for longer-duration sleepers in that study, but the mean age of the short-duration groups was mid-50s compared with mid-40s for the longer-duration groups.

A meta-analysis of adults with average age in the mid-40s suggested many effects in the .40–.50 range, but the studies included almost all had very small samples (Fortier-Brochu & Morin, 2014). However, because small sample studies tend to need large effects to be published, there may have been a publication bias in this meta-analysis.

Despite the fact that these associations between sleep quality and aspects of cognition were small in magnitude, their already being present in midlife may be particularly important because it is reasonable to assume that their magnitude may increase with further aging. The notion that there may be increasing magnitude with age is consistent with the fact that, as noted in the introduction, sleep quality generally becomes poorer with increasing age (Hoch et al., 1994), and poorer sleep quality in older adults predicts later cognitive decline in longitudinal studies (Blackwell et al., 2011; Potvin et al., 2012). Given evidence for remission of cognitive performance reductions with return to normal sleep (Miller et al., 2014), interventions to improve sleep quality in middle-aged adults might thus be an effective tool for slowing or reducing later life cognitive declines (Scullin & Bliwise, 2015).

A limitation of our study is that no objective sleep data were collected. However, the PSQI is a reliable measure for studying adverse consequences of poor sleep in older men (Spira et al., 2012), and it provides a naturalistic snapshot of sleep habits (Buysse et al., 1989). The PSQI sheds light on day-to-day sleep quality, as opposed to more extreme laboratory-based sleep deprivation. It also captures sleep disturbances due to sleep disorders and medication for sleep. Our study cannot identify the direction of association between sleep quality and cognition, although it seems far more likely that sleep quality would affect cognition rather than the reverse.

Inclusion of specific psychiatric diagnoses would have provided more detailed information than SF-36 mental health component, but the former was beyond the scope of the study and we did not have sufficient data on current psychiatric diagnosis. Also, we cannot be certain that an unknown factor is responsible for the effects on both sleep quality and cognition. Finally, we do not know if our results are generalizable to women.

Because poor sleep quality is often treatable, these findings may contribute to identifying strategies to reduce some forms of age-related cognitive impairment. Our results suggest that the PSQI subcomponents of sleep efficiency and latency are likely to be the aspects of sleep quality that will be most important to address. Sleep efficiency is the proportion of time in bed during which the individual is actually sleeping. If poorer sleep quality is associated with poorer cognitive function, it could have negative impacts on important areas of real-world functioning such as increasing the likelihood of driving or work-related accidents or reducing work-related efficiency and productivity. As noted in the introduction, sleep quality often diminishes with age (Hoch et al., 1994) and poor sleep quality is predictive of later cognitive decline in older adults (Blackwell et al., 2011a; Potvin et al., 2012). Thus, our findings suggest that, for healthy cognitive aging, it may be of value to address the issue of sleep quality well before old age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The VETSA project is supported by National Institutes of Health/National Institute on Aging (NIH/NIA) Grants (K01 AG035031, B.K.R.; R01 AG018386, R01 AG022381, R01 AG022982, and R01 AG050595, W.S.K.; R01 AG018384, M.J.L.). The U.S. Department of Veterans Affairs has provided support for the development and maintenance of the Vietnam Era Twin Registry. Numerous organizations have provided invaluable assistance, including VA Cooperative Studies Program; Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Institutes of Health; National Opinion Research Center; National Research Council, National Academy of Sciences; the Institute for Survey Research, Temple University; Schulman, Ronca, and Bucuvalas, Inc. Most importantly, we gratefully acknowledge the cooperation and participation of the members of the Vietnam Era Twin Registry and their families. Without their contribution this research would not have been possible. We thank Xin Tu and Tian Chen for their statistical analysis advice.

References

Benjamimi Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approah to multiple testing. Journal of the Royal Statistical Society. Series B, Statistical Methodology. 1995; 57(1):289–300.

Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Ensrud KE, Stefanick ML, Stone KL. Association of sleep characteristics and cognition in older community-dwelling men: The MrOS sleep study. Sleep. 2011a; 34(10):1347–1356. [PubMed: 21966066]

Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Ensrud KE, Stefanick ML, Stone KL. Associations between sleep architecture and sleep-disordered breathing and cognition in older community-dwelling men: The Osteoporotic Fractures in Men Sleep Study. Journal of the American Geriatric Society. 2011b; 59(12):2217–2225.

Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Ensrud KE, Stefanick ML, Osteoporotic Fractures in Men Study Group. Association of sleep characteristics and cognition in older community-dwelling men: The MrOS sleep study. Sleep. 2011; 34(10):1347–1356. [PubMed: 21966066]

Bratzke D, Steinborn MB, Rolke B, Ulrich R. Effects of sleep loss and circadian rhythm on executive inhibitory control in the Stroop and Simon tasks. Chronobiology International. 2012; 29(1):55–61. [PubMed: 22217101]

Bugg JM, DeLosh EL, Davalos DB, Davis HP. Age differences in Stroop interference: Contributions of general slowing and task-specific deficits. Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition. 2007; 14(2):155–167.

Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Research. 1989; 28(2):193–213. [PubMed: 2748771]

Cain SW, Silva EJ, Chang AM, Ronda JM, Duffy JF. One night of sleep deprivation affects reaction time, but not interference or facilitation in a Stroop task. Brain and Cognition. 2011; 76(1):37–42. [PubMed: 21477910]

Cajochen C, Khalsa SB, Wyatt JK, Czeisler CA, Dijk DJ. EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. The American Journal of Physiology. 1999; 277(3 Pt 2):R640–R649. [PubMed: 10484479]

Deliens G, Leproult R, Neu D, Peigneux P. Rapid eye movement and non-rapid eye movement sleep contributions in memory consolidation and resistance to retroactive interference for verbal material. Sleep. 2013; 36(12):1875–1883. [PubMed: 24293762]

Delis, D., Kaplan, E., Kramer, J. Delis-Kaplan executive function system technical manual. San Antonio, TX: The Psychological Corporation; 2001.

Delis, D., Kramer, J., Kaplan, E., Ober, B. California Verbal Learning Test-Second Edition. San Antonio, TX: The Psychological Corporation; 2000.

Drake CL, Roehrs TA, Burduvali E, Bonahoom A, Rosekind M, Roth T. Effects of rapid versus slow accumulation of eight hours of sleep loss. Psychophysiology. 2001; 38(6):979–987. [PubMed: 12240674]

Driscoll HC, Serody L, Patrick S, Maurer J, Bensasi S, Houck PR, Reynolds CF III. Sleeping well, aging well: A descriptive and cross-sectional study of sleep in “successful agers” 75 and older. The American Journal of Geriatric Psychiatry. 2008; 16(1):74–82. [PubMed: 18070833]

Ellenbogen JM, Hulbert JC, Stickgold R, Dinges DF, Thompson-Schill SL. Interfering with theories of sleep and memory: Sleep, declarative memory, and associative interference. Current Biology. 2006; 16(13):1290–1294. [PubMed: 16824917]

Fernandez-Mendoza J, Calhoun S, Bixler EO, Pejovic S, Karataraki M, Liao D, Vgontzas AN. Insomnia with objective short sleep duration is associated with deficits in neuropsychological performance: A general population study. Sleep. 2010; 33(4):459–465. [PubMed: 20394314]

Fortier-Brochu E, Morin CM. Cognitive impairment in individuals with insomnia: Clinical significance and correlates. Sleep. 2014; 37(11):1787–1798. [PubMed: 25364074]

Friedman NP, Miyake A. The relations among inhibition and interference control functions: A latent-variable analysis. Journal of Experimental Psychology. General. 2004; 133(1):101–135. [PubMed: 14979754]

Golden, CJ., Freshwater, SM. The Stroop Color and Word Test: A manual for clinical and experimental uses. Wood Dale, IL: Stoelting; 2002.

Griessenberger H, Heib DP, Lechinger J, Luketina N, Petzka M, Moeckel T, Schabus M. Susceptibility to declarative memory interference is pronounced in primary insomnia. PLoS One. 2013; 8(2):e57394. [PubMed: 23451218]

Hasher, L., Lustig, C., Zacks, RT. Inhibitory mechanisms and the control of attention. In: Conway, A.Jarrold, C.Kane, M.Miyake, A., Towse, J., editors. Variation in working memory. New York, NY: Oxford University Press; 2008. p. 227-249.

Hoch CC, Dew MA, Reynolds CF III, Monk TH, Buysse DJ, Houck PR, Kupfer DJ. A longitudinal study of laboratory- and diary-based sleep measures in healthy “old old” and “young old” volunteers. Sleep. 1994; 17(6):489–496. [PubMed: 7809561]

Jaussent I, Bouyer J, Ancelin ML, Berr C, Foubert-Samier A, Ritchie K, Dauvilliers Y. Excessive sleepiness is predictive of cognitive decline in the elderly. Sleep. 2012; 35(9):1201–1207. [PubMed: 22942498]

Kremen WS, Franz CE, Lyons MJ. VETSA: The Vietnam Era Twin Study of Aging. Twin Research and Human Genetics. 2013; 16(1):399–402. [PubMed: 23110957]

Kremen WS, Panizzon MS, Xian H, Barch DM, Franz CE, Grant MD, Lyons MJ. Genetic architecture of context processing in late middle age: More than one underlying mechanism. Psychology and Aging. 2011; 26(4):852–863. [PubMed: 21875218]

Kremen WS, Thompson-Brenner H, Leung YM, Grant MD, Franz CE, Eisen SA, Lyons MJ. Genes, environment, and time: The Vietnam Era Twin Study of Aging (VETSA). Twin Research and Human Genetics. 2006; 9(6):1009–1022. [PubMed: 17254445]

Lyons MJ, York TP, Franz CE, Grant MD, Eaves LJ, Jacobson KC, Kremen WS. Genes determine stability and the environment determines change in cognitive ability during 35 years of adulthood. Psychological Science. 2009; 20(9):1146–1152. [PubMed: 19686293]

McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Medical Care. 1993; 31(3):247–263. [PubMed: 8450681]

Miller MA, Wright H, Ji C, Cappuccio FP. Cross-sectional study of sleep quantity and quality and amnestic and non-amnestic cognitive function in an ageing population: The English Longitudinal Study of Ageing (ELSA). PLoS One. 2014; 9(6):e100991. [PubMed: 24968354]

Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: A latent variable analysis. Cognitive Psychology. 2000; 41(1):49–100. [PubMed: 10945922]

Nebes RD, Buysse DJ, Halligan EM, Houck PR, Monk TH. Self-reported sleep quality predicts poor cognitive performance in healthy older adults. Journals of Gerontology. Series B, Psychological Sciences and Social Sciences. 2009; 64(2):180–187.

Olaithe M, Bucks RS. Executive dysfunction in OSA before and after treatment: A meta-analysis. Sleep. 2013; 36(9):1297–1305. [PubMed: 23997362]

Orme D, Brehm W, Ree M. Armed Forces Qualification Test as a measure of premorbid intelligence. Military Psychology. 2001; 13:187–197.

Potvin O, Lorrain D, Forget H, Dube M, Grenier S, Preville M, Hudon C. Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. Sleep. 2012; 35(4):491–499. [PubMed: 22467987]

Prince TM, Abel T. The impact of sleep loss on hippocampal function. Learning & Memory. 2013; 20(10):558–569. [PubMed: 24045505]

Reid KJ, Martinovich Z, Finkel S, Statsinger J, Golden R, Harter K, Zee PC. Sleep: A marker of physical and mental health in the elderly. The American Journal of Geriatric Psychiatry. 2006; 14(10):860–866. [PubMed: 17001025]

Sagaspe P, Sanchez-Ortuno M, Charles A, Taillard J, Valtat C, Bioulac B, Philip P. Effects of sleep deprivation on Color-Word, Emotional, and Specific Stroop interference and on self-reported anxiety. Brain and Cognition. 2006; 60(1):76–87. [PubMed: 16314019]

Saint Martin M, Sforza E, Barthelemy JC, Thomas-Anterion C, Roche F. Does subjective sleep affect cognitive function in healthy elderly subjects? The Proof cohort. Sleep Medicine. 2012; 13(9): 1146–1152. [PubMed: 22875008]

Schoenborn CA, Heyman KM. Health characteristics of adults aged 55 years and over: United States, 2004–2007. National Health Statistics Reports. 2009:1–31.

Scullin MK, Bliwise DL. Sleep, cognition, and normal aging: Integrating a half-century of multidisciplinary research. Perspectives on Psychological Science. 2015; 10(1):97–137. [PubMed: 25620997]

Servan-Schreiber D, Cohen JD, Steingard S. Schizophrenic deficits in the processing of context. A test of a theoretical model. Archives of General Psychiatry. 1996; 53(12):1105–1112. [PubMed: 8956676]

Sheth BR, Varghese R, Truong T. Sleep shelters verbal memory from different kinds of interference. Sleep. 2012; 35(7):985–996. [PubMed: 22754045]

Skaug H, Fournier D, Nielsen A, Magnusson A, Bolker B. glmmADMB: Generalized linear mixed models using AD Model Builder. R Package Version 0.6. 2011; 5:r143.

Spira AP, Beaudreau SA, Stone KL, Kezirian EJ, Lui LY, Redline S, Stewart A. Reliability and validity of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in older men. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2012; 67(4):433–439.

Stickgold R. Sleep-dependent memory consolidation. Nature. 2005; 437(7063):1272–1278. [PubMed: 16251952]

Stickgold R, Walker MP. Sleep and memory: The ongoing debate. Sleep. 2005; 28(10):1225–1227. [PubMed: 16295206]

Stroop JR. Studies of interference in serial verbal reactions. Journal of Experimental Psychology. 1935; 18:643–662.

Tucker AM, Whitney P, Belenky G, Hinson JM, Van Dongen HP. Effects of sleep deprivation on dissociated components of executive functioning. Sleep. 2010; 33(1):47–57. [PubMed: 20120620]

Uhlaner, J. Development of the Armed Forces Qualification Test and predecessor army screening tests, 1946–1950. 1952. Retrieved from https://www.researchgate.net/publication/235047484_Development_of_Armed_Forces_Qualification_Test_and_predecessor_Army_screening_tests_1946-1950

van Enkhuizen J, Acheson D, Risbrough V, Drummond S, Geyer MA, Young JW. Sleep deprivation impairs performance in the 5-choice continuous performance test: Similarities between humans and mice. Behavioral Brain Research. 2014; 261:40–48.

Waters F, Bucks RS. Neuropsychological effects of sleep loss: Implication for neuropsychologists. Journal of the International Neuropsychological Society. 2011; 17(4):571–586. [PubMed: 21554786]

Wechsler, D. Manual for the Wechsler Adult Intelligence Scale - Third Edition. San Antonio, TX: Psychological Corporation; 1997.

Table 1

Five studies of community dwelling older adults assessing the relationship between PSQI score and cognitive function

Study	*N*	Age (years, range) Mean ± *SD*	Relevant Cognition Function (Test)[a]	PSQI
Nebes et al. (2009)	157	65–80 72.2 (4.1)[b]	Verbal episodic memory (Weschler Memory Scale-Revised, Logical Memory) Inhibition in non-memory setting (Stroop, Hayling Test) Updating in working memory Updating (N-Back) Set shifting (Trail Making Test, part B)	108 good sleepers (PSQI ≤ 5); 49 poor sleepers (PSQ ≥ 6)
Blackwell et al. (2011)	3132	65 + 76.4 (5.6)	Set Shifting (Trail Making Test, part B)[c]	Mean = 5.6 (3.3)
Saint Martin et al. (2012)	272	74.8 (1.1) Mean not available	Verbal episodic memory (Grober and Buschke Selective Reminding Test) Visuospatial episodic memory (Benton Visual Retention Test: *recognition*) Inhibition in non-memory setting (Stroop) Set Shifting (Trail Making Test, part B)[c]	Mean = 6.6 (3.5)[d]
Potvin et al. (2012)	1664	65–96 73.5 (5.5)[b]	Verbal episodic memory (3-word recall task of the MMSE)	Mean = 5.0 (3.5)[b]
Miller et al. (2014)	8789	50–89 Mean not available	Verbal episodic memory (10-word list)	Mean not available

[a] Tests listed are only those from the prior studies that are relevant to the cognitive domains covered in the present analyses.

[b] Weighted estimate of mean (*SD*) based on data provided for subgroups.

[c] Scores were not adjusted for Trails A performance.

[d] Women had significantly higher (worse) PSQI scores, but there were no sex differences on any cognitive measure.

Table 2

Summary of statistics of cognitive measures and health variables in the VETSA cohort

Cognitive measures	*N*	Mean (*SD*)[a]	Median[a]	Range
Episodic memory				
1 CVLT Short and Long Delay Composite Score	1158	8.9	—	1.5–16
2 Logical Memory Immediate and Delayed Recall Composite Score	1158	−21.8 (6.2)	—	3.5–40.5
3 Visual Reproduction Immediate and Delayed Recall Composite Score	1161	66.7 (14.5)	—	20.5–101
Executive functions				
Resistance to Interference in Episodic Memory				
4 CVLT-II Intrusions across All Trials	1194	42.9 (8.5)	3	0–30
Inhibitory Control in Working Memory				
5 CPT-*AY* Errors	1069	—	0	0–11
6 CPT-*BX* Errors	1069	—	0	0–14
Inhibitory Control in Non-Memory Setting				
7 Stroop Interference T-Score	1136	47.1 (6.6)	—	24–74
Updating in Working Memory				
8 CPT-*AX* Errors	1069	—	4	0–42
Set Shifting in Working Memory				
9 Verbal Fluency Category Switching Accuracy[b]	1160	6.3 (2.8)	—	−4.8–14.2
Set Shifting in Non-Memory Setting				
10 Trail-Making Test[c]	1153	−.5 (20.5)	—	−56.0–108.7
Health variables				
PSQI	1120	5.6 (3.6)	—	0–20
SF-36MCS/M[d]				
	1124	0 (5.5)	—	−23.3–15.8

[a]Mean and (*SD*) are reported for variables on which Gaussian distribution was assumed in the analysis; median is reported for variables on which Poisson distribution was assumed in the analysis.

[b]The score is the number of correct switches in 1 min adjusted for category fluency; these are residual scores, which is why they can have negative values.

[c]This score is the time (seconds) on the switching condition adjusted (*via* linear regression) for the time to complete number sequencing and the letter sequencing conditions; these are residual scores which can have negative values.

[d]SF-36MCS/M is the SF-36 Mental Component Score adjusted for the SF-36 Vitality Score.

Table 3

Association of PSQI sleep quality with executive function and memory variables.

Cognitive measures	*N*	β[a] 95% CI	Standard error[a]	*Z*-Value[a]	*p*-Value Pr(>|z|)[a]	FDR-corrected *p*-value[b]
Episodic memory						
1 CVLT-II Short and Long Delay Composite Score	1158	.017 (−.003, .01)	.022	.78	.433	ns
2 Logical Memory Immediate and Delayed Recall Composite Score	1158	−.024 (−.12, .07)	.050	−.48	.634	ns
3 Visual Reproductions Immediate and Delayed Recall Composite Score	1161	−.330 (−.56, −.11)	.117	−2.87	**.004**	**.01**
Executive functions						
Resistance to Interference in Episodic Memory						
4 CVLT-II Intrusions across All Trials	1151	.013 (.001, .025)	.006	2.12	**.034**	.09
Inhibitory Control in Working Memory						
5 CPT-*AY* Errors	1069	−.02 (− .05, −.002)	.013	−1.74	.081	ns
6 CPT-*BX* Errors	1069	.009 (− .016, .035)	.013	0.74	.460	ns
Inhibitory Control in Non-Memory Setting						
7 Stroop Interference T-Score	1136	−.041 (−.15, .07)	.057	−.72	.470	ns
Updating in Working Memory						
8 CPT-*AX* Errors	1069	.035 (.022, .005)	.006	5.51	<**.0001**	<**.0001**
Set Shifting in Working Memory						
9 Verbal Fluency Category Switching Accuracy	1160	−.077 (−.13, −.03)	.025	−3.12	**.002**	**.01**
Set Shifting in Non-Memory Setting						
10 Trail-Making Test (time in seconds)	1153	−.044 (− .39, .30)	.176	−.25	.804	ns

Note. Statistically significant *p*-values are in bold.

[a]Values are from Type III Sum of Squares in the Generalized Linear Mixed Model with covariates: cognitive measure = PSQI + SF-36MCS/M + GCA + Age + Current SleepApnea(Y/N) + Physical Conditions + Random Effect (Family); PSQI = Pittsburgh Sleep Quality Index; SF-36MCS-M = Modified SF-36 Mental Component Summary.

[b]Benjamini & Hochberg (1995) FDR-corrected *p*-value for the 10 tests was computed using R.

FDR = false discovery rate; ns = not significant.