Behavioral Neuroscience
2013, Vol. 127, No. 5, 803–810

© 2013 American Psychological Association
0735-7044/13/$12.00 DOI: 10.1037/a0034154

Sleep Quality in Healthy Older People: Relationship With ^{1}H Magnetic Resonance Spectroscopy Markers of Glial and Neuronal Integrity

Nathan E. Cross, Jim Lagopoulos, Shantel L. Duffy, Nicole L. Cockayne, Ian B. Hickie, Simon J. G. Lewis, and Sharon L. Naismith
The University of Sydney

The hippocampus and thalamus assume a significant role in the overnight consolidation of memories, a process that is negatively impacted by sleep disruption. Emerging evidence suggests that disturbances of sleep in older people may co-occur with underlying neurobiological changes. This study sought to assess glial and neuronal integrity in these regions in relation to subjective sleep disturbance in a healthy older sample. Forty-three healthy older people (mean age = 70, *SD* = 5.0) were assessed clinically and medically and screened for cognitive and depressive symptoms, as well as sleep disturbance. Single voxel hippocampal and thalamus metabolite ratios of N-acetyl aspartate (NAA) and myo-inositol (mI) with total creatine (Cr + PCr) were measured using magnetic resonance spectroscopy at 3-Tesla. Higher hippocampal mI/Cr + PCr ratios were significantly correlated with poorer self-reported sleep quality ($r = .42$, $p < .01$) and less sleep efficiency ($r = -0.42$, $p < .01$) as recorded by the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). No other significant correlations were observed within the hippocampus or within the thalamus. These results indicate that in healthy older people, subjective sleep disturbance may be associated with glial alterations in the hippocampus. Future research is now needed to examine these associations with respect to objective sleep measures and overnight memory consolidation.

Keywords: sleep, proton magnetic resonance spectroscopy, aging, myo-inositol, hippocampus

There are significant changes in sleep–wake functioning associated with normal aging. Indeed, self-reported sleep difficulties occur in around 50–60% of adults aged 60 years and over (Almeida & Pfaff, 2005). Relative to younger people, neurophysiological sleep changes have also been demonstrated, such as decreased time spent in slow-wave sleep (Floyd, 2002) and decreased amplitude and power of sleep spindles (Carrier, Land, Buysse, Kupfer, & Monk, 2001), which in turn are linked to overnight memory consolidation (Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010).

Studies that have examined the overnight consolidation of memories report a decline with age, and this has been demonstrated to impact daytime cognitive performance (Spencer, Gouw, & Ivry, 2007). Though the exact neurobiological processes responsible for memory consolidation require further delineation, human neurophysiological and animal data hitherto strongly implicate the hippocampus, and its relationship with thalamocortical activity, in sleep-dependant memory consolidation. In addition, temporal correlations have been reported between such thalamocortical activity and hippocampal ripples during non-REM (NREM) sleep, suggesting that these processes may interact (Siapas & Wilson, 1998; Marshall & Born, 2007).

Emerging evidence suggests that disturbances of sleep in older people may co-occur with underlying neurobiological changes. Although there is a relative paucity of research in older or elderly samples, data to date has shown that the severity of sleep disturbance relates to poorer cognitive performance in healthy older cohorts (Oosterman, van Someren, Vogels, van Harten, & Scherder, 2009), as well as in those with late-life depression (Naismith, Terpening, Shine, & Lewis, 2011), mild cognitive impairment (Naismith et al., 2010), Alzheimer's disease (Rauchs et al., 2008), and Parkinson's disease (Naismith, Rogers et al., 2011; Naismith et al., 2011). Thus, there is a confluence of evidence suggesting that sleep disturbance and neuropsychological

Nathan E. Cross, Healthy Brain Aging Program and Clinical Research Unit, Brain and Mind Research Institute, The University of Sydney, Camperdown, New South Wales, Australia; Jim Lagopoulos, Clinical Research Unit, Brain and Mind Research Institute, The University of Sydney; Shantel L. Duffy, Nicole L. Cockayne, Ian B. Hickie, Simon J. G. Lewis, and Sharon L. Naismith, Healthy Brain Aging Program and Clinical Research Unit, Brain and Mind Research Institute, The University of Sydney.

This study was approved by the University of Sydney Institutional Ethics Committee, which is in accordance with the code of ethics of the World Medical Association (*Declaration of Helsinki*, 2008) for experiments involving humans. Associate Professor Naismith is supported by a National Health and Medical Research Council (NHMRC) career development award. Ms. Duffy is supported by an Australian Rotary Health/Rotary Club of Parkes Funding Partners' scholarship. Professor Hickie is supported by an NHMRC Australia fellowship. Associate Professor Lewis is supported by an NHMRC practitioner fellowship. The authors gratefully acknowledge the generosity of the participants who undertook this research. We would also like to thank Southern Radiology at the Brain and Mind Research Institute, as well as Dr. Louisa Norrie and Dr. Matt Paradise for assisting with clinical and medical assessments.

Correspondence concerning this article should be addressed to Sharon L. Naismith, Director, Clinical Research Unit, Brain and Mind Research Institute, University of Sydney, 94 Mallet Street, Camperdown, NSW 2050, Australia. E-mail: sharon.naismith@sydney.edu.au

changes in older people are likely to share common neurobiological underpinnings.

Prior to understanding the neurobiological systems underpinning effective sleep and how it relates to the aforementioned disorders, it is important to first characterize these relationships with sleep in healthy older people. Investigating the neurochemistry involved in sleep can provide insight into the neurological characteristics of sleep quality. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive method of investigating the brain's underlying neurochemistry. More specifically, ^{1}H-MRS allows for the chemical sampling of metabolites, such as N-acetylaspartate (NAA) and myo-inositol (mI) in brain regions implicated in sleep, such as the hippocampus and thalamus. NAA is localized predominantly in neurons and their processes and as such it is considered a marker of neuronal integrity (Jessen et al., 2009). There is evidence of slight decreases in NAA within frontal brain regions in association with older age (Haga, Khor, Farrall, & Wardlaw, 2009), and changes in this metabolite within the hippocampus do appear to be associated with poorer verbal memory in healthy older adults (Zimmerman et al., 2008).

Myo-inositol is a glial marker (Brand, Richter-Landsberg, & Leibfritz, 1993) that has been identified as particularly sensitive to cognitive decline (Kantarci et al., 2004), as well as to the extent of pathology in Alzheimer's disease (Miller et al., 1993). Although glial function associated with sleep in humans has not specifically been investigated, animal studies have found robust changes in sleep variables (such as reduction in homeostatic sleep pressure, as well as an absence in compensatory sleep and cognitive impairment after sleep deprivation) in animals with dysfunctional astroglial cells and following the altering of gliotransmission (Frank, 2011). These findings suggest that glial processes may have roles in brain regions that are known to be involved in sleep-related processes.

However, in spite of the literature linking sleep and the metabolites NAA and mI independently with cognition, no study to date has examined combined markers of neuronal and glial integrity in the aging human brain, with specific hypotheses relating to sleep. Thus, in accordance with the extant literature, this study sought to examine in vivo levels of NAA and mI from the left hippocampus and thalamus in a large sample of healthy older people. Due to the known associations between sleep, neurometabolites, and cognition in aging, we hypothesized that altered levels of neuronal and glial functioning (represented by relative decreases in NAA and increases in mI levels) in the hippocampus and thalamus would be associated with poorer sleep quality in healthy older adults.

Experimental Procedure

Participants

Forty-three healthy older people aged over 60 years (age range 60–79 years, $M = 70$, $SD = 5.0$) were recruited from the Healthy Brain Aging Program at the Brain and Mind Research Institute (BMRI), Sydney, Australia. Exclusion criteria were suspected dementia and/or Mini-Mental State Examination score (MMSE; Folstein, Folstein, & McHugh, 1975) < 24, history of neurological or psychotic illness, current *Diagnostic and Statistical Manual of Mental Disorders (DSM–IV-TR;* APA, 2000) defined major depression, stroke, head injury (with loss of consciousness > 30 min), other medical conditions known to affect cognition, substance misuse, and medical contraindications to magnetic resonance imaging (MRI). This study was approved by the University of Sydney Institutional Ethics Committee and all participants gave written informed consent prior to participation.

Clinical Assessment

Using a semistructured interview, a geriatric psychiatrist recorded a full medical, clinical, psychiatric, and medication history. At the time of assessment, three participants were taking benzodiazepines and six participants were taking newer generation antidepressants. Participants completed the 30-item Geriatric Depression Scale (GDS, maximum = 30; Yesavage et al., 1983) to measure depressive symptomatology. For descriptive purposes, the MMSE was administered as a measure of gross cognitive abilities.

Self-Report Sleep–Wake Measures

All participants completed the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), an overall subjective measure of sleep quality over the previous month. The questionnaire consists of 17 items, with most questions rated on a 4-point Likert scale. The PSQI provides a global score based on the components of quality, latency, duration, efficiency, disturbance, use of sleeping medication, and daytime dysfunction. The global score has an upper limit of 21. For the purposes of this study, sleep quality referred to global PSQI score and *not* the PSQI subscale. By using the suggested cut-off score of 5, those subjects with a global PSQI score ≥ 5 (PSQI positive' + ve') and < 5 (PSQI negative' − ve') were defined to exhibit or not exhibit sleep-quality disturbance, respectively (Buysse et al., 1989).

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS)

Imaging was conducted within 2 weeks of clinical assessment and took place at the BMRI imaging center on a 3-Tesla GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) using an 8-channel phased-array head coil. The following images were acquired in order: (a) three-dimensional sagittal whole-brain scout for orientation and positioning of subsequent scans; (b) T1-weighted, magnetization-prepared rapid gradient-echo (MPRAGE) sequence producing 196 sagittal slices (repetition time [TR] = 7.2 ms; echo time [TE] = 2.8 ms; flip angle = 10°; matrix 256 × 256; 0.9 mm isotropic voxels) to aid in the anatomical localization of sampled voxels; and, (c) single voxel ^{1}H-MRS using Point RESolved Spectroscopy (PRESS) acquisition (Bottomley, 1987), with two chemical shift-selective pulses for water suppression. Spectra were shimmed to achieve full-width, half maximum (FWHM) of less than 13 Hz.

Spectra were acquired separately from voxels placed in the left hippocampus and thalamus. A voxel measuring 20 × 20 × 15 mm and 20 × 20 × 20 mm was used to acquire data from the hippocampus and thalamus respectively, with both acquisitions using the following imaging parameters: TE = 35 ms, TR = 2,000 ms and 128 averages. Anatomical localization of voxel placement was based on the Talairach brain atlas (Talairach & Tournoux, 1987) and positioning was guided by the T1

MPRAGE image (see Figure 1). To facilitate the hippocampal voxel placement, the long axis of the hippocampus, as viewed from the sagittal images, was used as the anatomical guide to align the voxel with the anterior-most aspect of the hippocampal body, such that the amount of gray matter was maximized.

All spectra in this study achieved line widths (FWHM) of less than 13 Hz with the use of higher order shimming. Data were then transferred offline for postprocessing using the LCModel software package (Provencher, 1993), in which metabolite concentrations were calculated as a relative ratio to creatine–phosphocreatine (Cr + PCr). All spectra were quantified using a PRESS TE = 35 basis set of 15 metabolites and incorporated macromolecule and baseline-fitting routines. Spectra were visually inspected, separately by two independent raters, to ensure the consistency of the data. Poorly fitting metabolite peaks as reflected by large Cramer–Rao lower bounds (greater than 20) were excluded from further analysis. Finally, all scanning was undertaken between the hours of 10 a.m. and 4 p.m.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS; Version 20 for Mac). Pearson coefficients were used for all correlations unless otherwise stated and comparisons between groups were conducted using Student's *t* tests. All analyses were two-tailed and used an alpha level of .05. We did not correct for multiple comparisons in our analyses.

Results

Participants

Demographic characteristics for the sample are presented in Table 1. Consistent with the screening protocol, participants were cognitively intact, as evidenced by a mean score of 29.0, and a range of 26–30 on the MMSE. Levels of depressive symptoms as measured by the GDS were in the 0–19 range. Although a score of

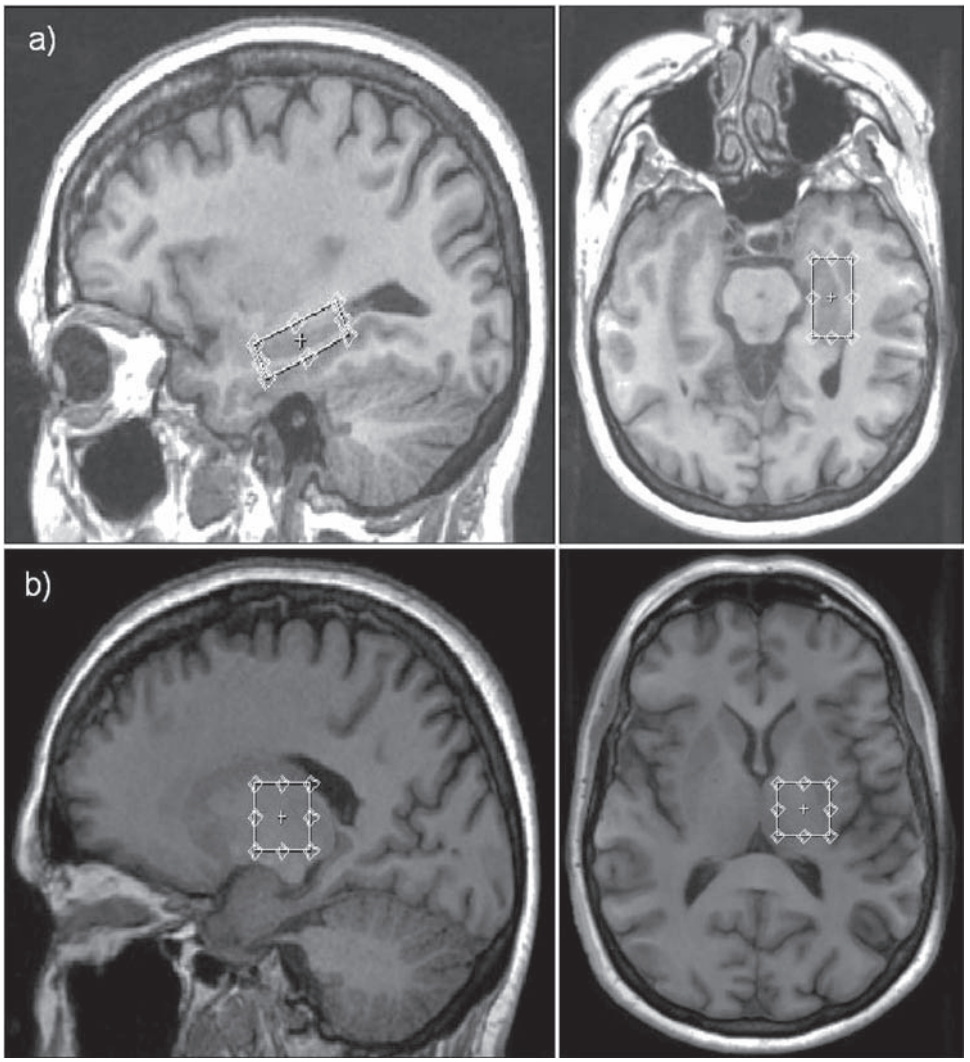


Figure 1. Sagittal and Axial views of representative T1-weighted images illustrating the voxel placement for the (a) hippocampus and (b) thalamus voxels in one subject.

Table 1
Demographic, Cognitive, Depression and Sleep Characteristics for 43 Healthy Older People

Variable	Mean + *SD*
Gender, % female	28 (25/43)
Age, years	70.0 ± 5.0
Education, years	13.1 ± 2.6
Mini Mental State Examination, /30	29.0 ± 1.1
Geriatric Depression Scale, /30	5.2 ± 4.9
PSQI global score, /21	5.7 ± 4.0
PSQI % sleep efficiency, /100	78.3 ± 15.3

Note. Data are mean ± *SD* or % (*n*).

11 or greater on the 30-item GDS is indicative of mild depressive symptoms (Yesavage et al., 1983), 86% of the sample fell below this cutoff, and all subjects were confirmed through psychiatric examination to not meet *DSM–IV-TR* (APA, 2000) criteria for current major depression. Thirty-eight participants were right-handed.

Sleep Disturbance

For the whole sample, the mean global PSQI (Buysse et al., 1989) score was 5.74 (*SD* = 4.01), suggesting on average, only mild levels of sleep-quality disruption. However, when data were analyzed according to the suggested cut-off for sleep quality disruption (≥5), 56% of the sample demonstrated PSQI + ve scores, indicating a significant proportion of sleep disturbances within this sample. Neither age ($p = .93$), GDS ($p = .07$), nor MMSE ($p = .37$) scores were significantly associated with PSQI scores (when analyzed as a continuous variable or according to the PSQI cut-off scores).

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS)

As shown in Table 2, there were no significant correlations between age, gender, or GDS score and ratios of any metabolite in the hippocampus or thalamus (all $p > .05$). Due to scan quality, not all participant spectra were acceptable for MRS analysis, and so were excluded from the analysis. The sample size ranged from $n = 28$ to $n = 43$ across all spectra. Representative hippocampal and thalamic spectra for one individual with self-reported sleep disturbance and one without sleep disturbance is displayed in Figure 2.

Hippocampal ^{1}H-MRS

There was no significant correlation between ratios of Glu/Cr + PCr, Glx/Cr + PCr, Cho/Cr + PCr or NAA/Cr + PCr and any self-reported sleep disturbances. Higher ratios of hippocampal mI/Cr + PCr were associated with poorer sleep efficiency ($r = -0.42$, $p < .01$; see Figure 3) and greater sleep-quality disturbance ($r = .42$, $p < .01$) as evidenced by higher PSQI global scores. Accordingly, when those with (PSQI + ve) and without (PSQI − ve) sleep disturbance were compared, there was a significant difference in mI/Cr + PCr ratios between these groups ($t = 0.36$, $p < .05$; see Table 3). Note that since six participants in this sample were taking psychotropic medications, these analyses were repeated after exclusion of these individuals. The resultant statistics showed that these differences remained significant, and in fact were slightly stronger (sleep quality: $r = .52$, $p = .001$; sleep efficiency: $r = -0.50$, $p = .002$). In addition, a slight trend was observed between global cognition as measured by the MMSE, and mI/Cr + PCr ($r = -0.30$, $p = .05$). There was no relationship with NAA/Cr + PCr ($r = .14$, $p > .05$) ratios and MMSE score.

In order to examine if the relationship between hippocampal mI and PSQI scores was confounded by poor cognition, we repeated the analyses after controlling for MMSE scores. The resultant partial analyses remained significant (partial $r = -0.42$, $p = .006$) for PSQI global score and sleep efficiency, respectively.

Finally, absolute levels of Cr + PCr were not found to correlate with age ($p = .78$), MMSE ($p = .55$), sleep quality ($p = .50$), or sleep efficiency ($p = .86$). However, Cr + PCr levels were associated with GDS scores ($r = .34$, $p = .03$).

Thalamic ^{1}H-MRS

Thalamic metabolite ratios were not significantly associated with any measure of sleep disturbance. Age and global cognition as measured by the MMSE were also not significantly correlated

Table 2
Pearson Correlations Between Hippocampus and Thalamus Metabolite Concentration Ratios and Demographic, Cognitive, Depression, and Sleep Characteristics

Brain region	Ratio	Age	GDS	MMSE score	Global PSQI score	PSQI-sleep efficiency, %
Hippocampus	mI ratio (mI/CrPCr; $n = 42$)	−0.010	−0.033	−0.304	0.421**	−0.419**
	Glu ratio (Glu/CrPCr; $n = 38$)	0.005	−0.104	−0.006	0.026	−0.132
	Cho ratio (PCh/CrPCr; $n = 43$)	−0.009	−0.064	0.005	0.126	−0.128
	NAA ratio (NAA/CrPCr; $n = 43$)	−0.144	0.037	0.142	0.057	0.015
	Glx ratio (GluGln/CrPCr; $n = 42$)	−0.067	−0.242	−0.067	−0.175	0.043
Thalamus	mI ratio (mI/CrPCr; $n = 28$)	−0.012	−0.073	0.148	0.037	−0.243
	Glu ratio (Glu/CrPCr; $n = 28$)	0.110	0.002	−0.034	0.151	−0.132
	Cho ratio (PCh/CrPCr; $n = 28$)	−0.277	0.151	0.080	−0.217	0.066
	NAA ratio (NAA/CrPCr; $n = 28$)	0.014	−0.004	−0.018	−0.147	0.162
	Glx ratio (GluGln/CrPCr; $n = 28$)	−0.152	0.082	−0.031	0.028	0.033

Note. GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Exam; PSQI = Pittsburgh Sleep Quality Index; mI = myo-inositol; CrPCr = creatine + phosphocreatine ratio; Glu = glutamate; Cho = choline; NAA = N-acetylaspartate; Glx = glutamate + glutamine. Sample sizes vary due to exclusion of spectra with insufficient quality.
** $p < 0.01$.

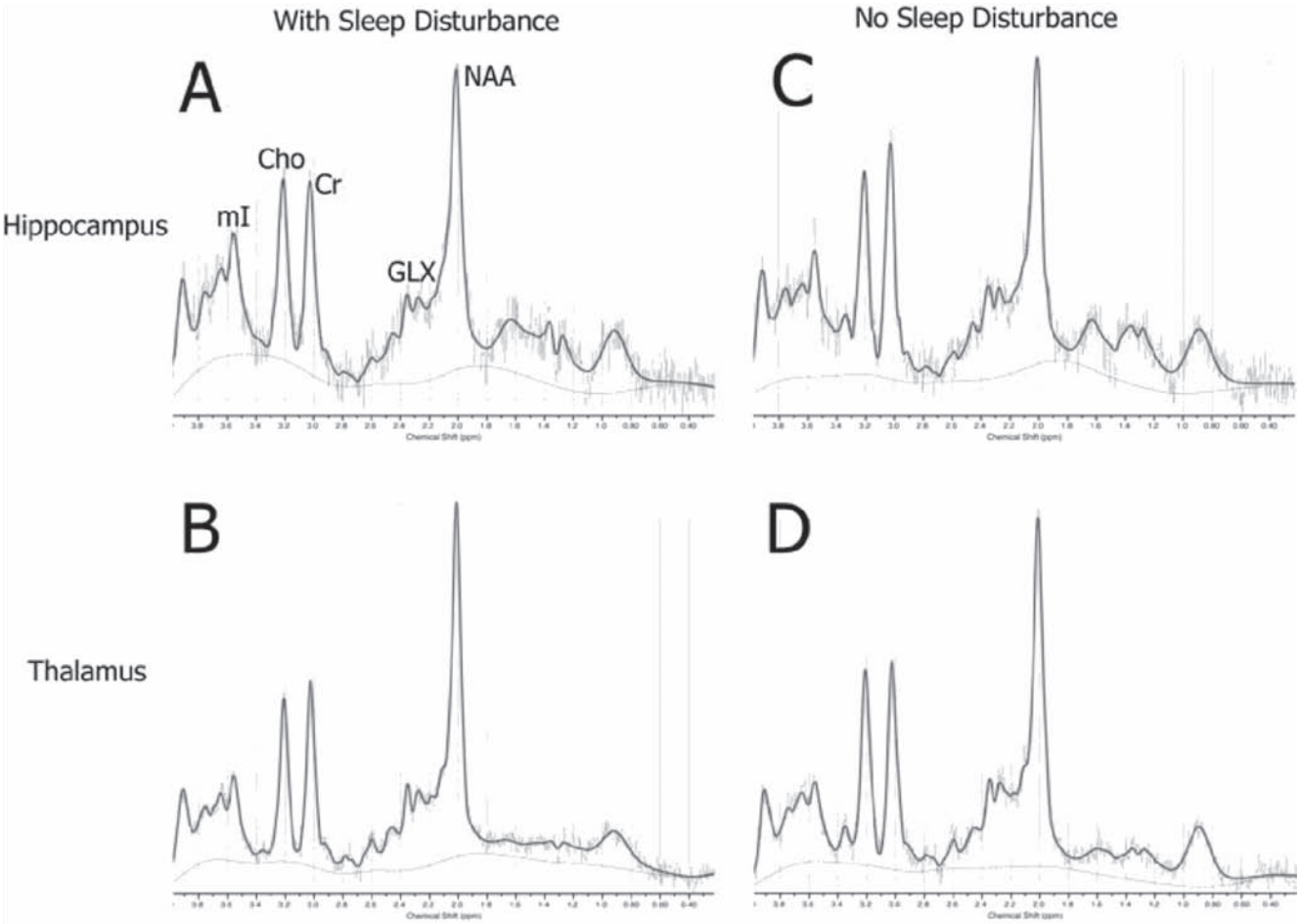


Figure 2. Water-suppressed metabolite spectra processed using LCModel (Provencher, 1993) for two patients with and without sleep disturbance. The figure illustrates that increased mI/Cr + PCr ratio is related to sleep disturbance only in the hippocampus. Panel A, ^{1}HMRS metabolite levels acquired from a hippocampal voxel in a patient with sleep disturbance; Panel B, ^{1}HMRS metabolite levels acquired from a thalamic voxel in a patient with sleep disturbance; Panel C, ^{1}HMRS metabolite levels acquired from a hippocampal voxel in a patient without sleep disturbance and Panel D; ^{1}HMRS metabolite levels acquired from a thalamic voxel in a patient without sleep disturbance. Abbreviations are as follows: mI = myo-inositol; Cr = creatine; GLX = glutamate and glutamine; NAA = N-acetylaspartate; Cho = choline.

with any neurometabolite ratios within the thalamus ($p > .05$). In addition, absolute levels of Cr + PCr were not found to be associated with age, MMSE, GDS, sleep quality, or sleep efficiency (all $p > 0.05$).

Discussion

To our knowledge, this is the first study to examine sleep quality in relation to in vivo neuronal and glial markers in healthy older people. The results show that higher levels of hippocampal mI are associated with greater sleep complaints, specifically, poor sleep quality, and poorer sleep efficiency (i.e., of the time spent in bed, less time is spent sleeping). Thus, in our cohort of cognitively intact (but aging) participants, our findings suggest that glial processes within certain brain structures coexist with subjective sleep disturbance. Interestingly, there were no significant associations between any spectroscopic neurometabolite and age in any region investigated. This strengthens our interpretation that the association between increased mI and sleep disturbances is not simply reflective of older age.

The finding that altered hippocampal neurochemistry may be associated with reduced sleep quality is consistent with what is known about the activity of this structure during sleep. Data show that the hippocampus is more active during sleep than when in an aroused state (Ylinen et al., 1995; Buzsák, 1998), possibly due to the significant role the hippocampus plays in the consolidation of memories during sleep (Walker & Stickgold, 2006). Sleep loss results in changes of cellular and molecular properties of hippocampal *Cornu Ammonis* (CA)1 and dentate granule neurons, such as reductions in membrane excitability and induction of long term potentiation, which is essential for plasticity and learning (McDermott et al., 2003). Animal data also suggest that optimal

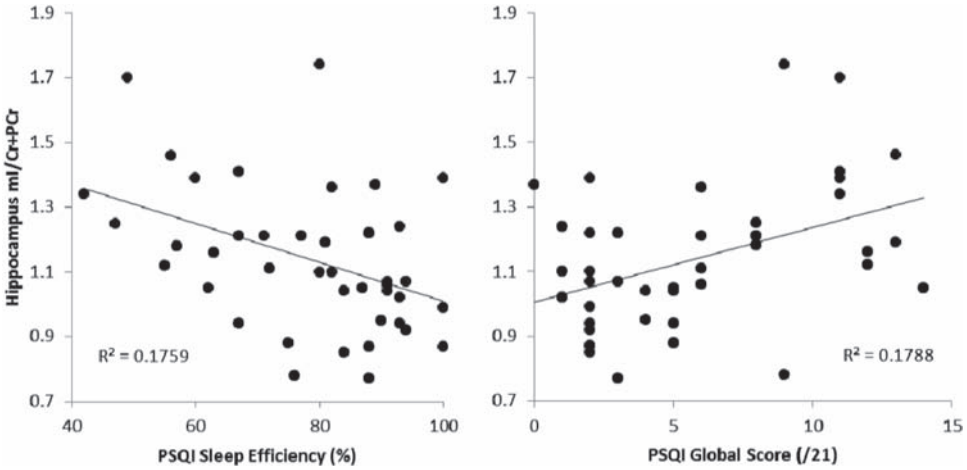


Figure 3. Scatterplot demonstrating the relationship between hippocampus myoinositol/Creatine + phosphocreatine ratio (mI/Cr + PCr) and Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) measurement of sleep efficiency, and PSQI global score, within 43 healthy older people. Line represents linear regression. R^2 value is given in the graph ($p < .01$).

sleep is critical for neurogenesis within the dentate gyrus (DG) of the hippocampal formation (Van Praag et al., 2002). Therefore, due to the significant role sleep plays in hippocampus-related memory consolidation and neurogenesis, the current results suggest that neurochemical alterations in the hippocampus are associated with poorer sleep, which may have the potential to impact upon these processes.

In terms of pathophysiological processes which may underpin the associations observed in this study, it is not clear whether sleep disturbance would impede hippocampal functioning, or conversely, whether neurobiological changes within this structure impact on sleep processes. The finding of *increased* mI in the hippocampus in association with poorer reported sleep does, however, implicate glial changes in sleep disturbance. It is conjectured that in the presence of disturbed sleep, glial processes may be induced into a compensatory role of maintaining energy homeostasis. Neuronal–glial coupling is important for the balancing of neuronal activity with energy supply in synaptic locations (Magistretti & Pellerin, 1999), and previous studies have reported significant increases in glycogen metabolism in astrocytes following sleep deprivation (Petit, Tobler, Allaman, Borbely, & Magistretti, 2002).

However, an alternative explanation could be that early glial changes co-occur with sleep disturbance in association with pathophysiological brain changes. Our data showing that increased mI tended to be associated with poorer cognition (albeit measured with a gross assessment tool) also aligns with this notion. Our prior work using actigraphy, has reported that, in older people with depression, as well as in those with mild cognitive impairment, sleep disturbance is associated with cognitive decline, as evidenced by detailed neuropsychological testing (Naismith, Rogers et al., 2010; Naismith, Rogers et al., 2011). Although no known studies have examined neuronal and glial integrity in association with sleep disturbance in those with clear neurodegenerative dis-

Table 3
Metabolite Ratios to Cr + PCr for Subjects With a PSQI Score of Greater or Equal to 5, and Less Than 5

Brain region	Ratios	PSQI score ≥ 5	PSQI score < 5
Hippocampus	mI ratio (mI/CrPCr; $n = 42$)	1.21* ± 0.23	1.05* ± 0.17
	Glu ratio (Glu/CrPCr; $n = 38$)	1.33 ± 0.32	1.36 ± 0.30
	Cho ratio (PCh/CrPCr; $n = 43$)	0.32 ± 0.04	0.32 ± 0.04
	NAA ratio (NAA/CrPCr; $n = 43$)	1.18 ± 0.12	1.19 ± 0.11
	Glx ratio (GluGln/CrPCr; $n = 42$)	1.40 ± 0.37	1.63 ± 0.30
Thalamus	mI ratio (mI/CrPCr; $n = 28$)	1.52 ± 0.16	1.47 ± 0.12
	Glu ratio (Glu/CrPCr; $n = 28$)	0.29 ± 0.04	0.30 ± 0.01
	Cho ratio (PCh/CrPCr; $n = 28$)	0.29 ± 0.02	0.29 ± 0.02
	NAA ratio (NAA/CrPCr; $n = 28$)	1.65 ± 0.14	1.68 ± 0.15
	Glx ratio (GluGln/CrPCr; $n = 28$)	1.54 ± 0.15	1.55 ± 0.20

Note. PSQI = Pittsburgh Sleep Quality Index (scores ≥5 are suggestive of sleep disturbance); mI = myo-inositol; CrPCr = creatine + phosphocreatine ratio; Glu = glutamate; Cho = choline; NAA = N-acetylaspartate; Glx = glutamate + glutamine. Data are mean ± *SD*. Sample sizes vary due to exclusion of spectra with insufficient quality.
* $p < .05$.

ease, elevated levels of mI have indeed been reported in the cerebral cortex and hippocampus of patients with mild to moderate Alzheimer's disease (Miller et al., 1993). Sleep–wake cycles are also significantly altered in Alzheimer's and other neurodegenerative diseases (Zhong, Naismith, Rogers, & Lewis, 2011), and when sleep disturbance is present, cognitive decline appears to be more pronounced (Scarmeas et al., 2007).

Although it was not our primary focus to examine depressive symptoms, we did find an association between hippocampal Cr + PCr and GDS scores. To our knowledge, such an association has not been reported previously, though an association between depressive and hippocampal brain volumes is well documented (Hickie et al., 2005; Naismith, Norrie, Mowszowski, & Hickie, 2012). Researchers conducting further hypothesis-driven studies may now wish to explore the association between neurometabolites and depressive symptoms in more detail.

Although this was an exploratory study, the findings need to be considered in light of several limitations that warrant discussion. First, although the sample size in this study was large and well-characterized clinically and medically, the findings could have been enhanced by the inclusion of more detailed measures of sleep. Polysomnographic (PSG) measures of sleep macro- and micro-architecture may help further elucidate how glial parameters relate to specific neurophysiological events. In addition, there were no records of the quality of sleep obtained the night before the MRS scan. Though there are no known data in this area, it is plausible that the quality of sleep the night before the scan, as well as the circadian rhythm, could relate to neurometabolite levels, and thus future studies may best examine sleep in close time proximity to scanning.

The current findings indicate that *local* changes in brain neurochemistry are aligned with sleep quality in healthy older people. As single voxel ^{1}H-MRS measurements are very limited by the specific focus of this technique, these results raise the question of whether changes in other regions may also occur in association with self-reported levels of sleep quality. The current study focused on only two structures within the brain. Future research is needed to expand the current findings to investigate whether other regions within the brain that are also linked to sleep, such as the reticular nuclei within the brainstem and the frontal lobes, also undergo significant metabolite changes in association with sleep quality. It is also noted as a limitation that five left-handed subjects were included in this study, as metabolite levels were obtained from the left hippocampus. This could have influenced the results, although prior MRS studies that have specifically examined regions bilaterally have not found a laterality effect (Beacher, 2005).

This study provides initial insight into the areas and processes that may be associated with declining sleep quality in older age. Although specific to a healthy sample, the current results suggest that alterations in neural networks, in particular glial processes, involving the hippocampus may underpin sleep disturbance and sleep-related cognitive decline even in healthy older people.

Future studies could provide further insights into the etiological link between glial function and sleep quality by examining neurochemical changes both prior to and after a period of sleep. Similarly, combining MRS, sleep, and cognitive measures may help elucidate the processes underlying successful memory consolidation. Finally, it would be helpful to ascertain the prognostic significance of these changes longitudinally, to determine whether glial dysfunction, with or without concomitant sleep disturbance, is predictive of cognitive decline or the emergence of neurodegenerative disease longitudinally. Since there is now considerable data suggesting that sleep is pertinent to neurogenesis and may offer neuroprotective benefits, such findings would provide invaluable opportunities for early intervention for cognitive decline (Naismith et al., 2009) and sleep disturbance in the aging population.

References

Almeida, O. P., & Pfaff, J. J. (2005). Sleep complaints among older general practice patients: Association with depression. *British Journal of General Practice, 55,* 864–866.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM–IV–TR*). Washington, DC: Author.

Beacher, F., Simmons, A., Daly, E., Prasher, V., Adams, C., Margallo-Lana, M. L., . . . Murphy, D. G. M. (2005). Hippocampal myo-inositol and cognitive ability in adults with Down syndrome: An in vivo proton magnetic resonance spectroscopy study. *Archives of General Psychiatry, 62,* 1360–1365. doi:10.1001/archpsyc.62.12.1360

Bottomley, P. A. (1987). Spatial localization in NMR-spectroscopy invivo. *Annals of the New York Academy of Sciences, 508,* 333–348.

Brand, A., Richter-Landsberg, C., & Leibfritz, D. (1993). Multinuclear NMR studies on the energy metabolism of glial and neuronal cells. *Developmental Neuroscience, 15,* 289–298. doi:10.1159/000111347

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research, 28,* 193–213. doi:10.1016/0165-1781(89)90047-4

Buzsák, G. (1998). Memory consolidation during sleep: A neurophysiological perspective. *Journal of Sleep Research, 7,* 17–23. doi:10.1046/j.1365-2869.7.s1.3.x

Carrier, J., Land, S., Buysse, D. J., Kupfer, D. J., & Monk, T. H. (2001). The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20–60 years old). *Psychophysiology, 38,* 232–242. doi:10.1111/1469-8986.3820232

Floyd, J. A. (2002). Sleep and aging. *Nursing Clinics of North America, 37,* 719–731. doi:10.1016/S0029-6465(02)00034-8

Folstein, M., Folstein, S., & McHugh, P. (1975). "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12,* 189–198.

Frank, M. G. (2011). Beyond the neuron: Astroglial regulation of mammalian sleep. *Current Topics in Medicinal Chemistry, 11,* 2452–2456. doi:10.2174/156802611797470321

Haga, K. K., Khor, Y. P., Farrall, A., & Wardlaw, J. M. (2009). A systematic review of brain metabolite changes, measured with ^{1}H magnetic resonance spectroscopy, in healthy aging. *Neurobiology of Aging, 30,* 353–363. doi:10.1016/j.neurobiolaging.2007.07.005

Hickie, I., Naismith, S., Ward, P. B., Turner, K., Scott, E., Mitchell, P., . . . Parker, G. (2005). Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *British Journal of Psychiatry, 186,* 197–202.

Jessen, F., Gur, O., Block, W., Ende, G., Frölich, L., Hammen, T., . . . Träber, F. (2009). A multicenter ^{1}H-MRS study of the medial temporal lobe in AD and MCI. *Neurology, 72,* 1735–1740. doi:10.1212/WNL.0b013e3181a60a20

Kantarci, K., Parisi, J. E., Dickson, D. W., Petersen, R. C., Boeve, B. F., Knopman, D. S., . . . Jack, C. R. (2004). Myo-inositol/creatine ratio correlates with the neuropathological involvement in Alzheimer's disease. *Neurobiology of Aging, 25,* S372. doi:10.1016/S0197-4580(04)81220-X

Magistretti, P. J., & Pellerin, L. (1999). Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging.

Philosophical Transactions of the Royal Society of London: Series B. Biological Sciences, *354,* 1155–1163. doi:10.1098/rstb.1999.0471

Marshall, L., & Born, J. (2007). The contribution of sleep to hippocampus-dependent memory consolidation. *Trends in Cognitive Sciences, 11,* 442–450. doi:10.1016/j.tics.2007.09.001

McDermott, C. M., LaHoste, G. J., Chen, C., Musto, A., Bazan, N. G., & Magee, J. C. (2003). Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. *The Journal of Neuroscience, 23,* 9687–9695.

Miller, B. L., Moats, R. A., Shonk, T., Ernst, T., Woolley, S., & Ross, B. D. (1993). Alzheimer disease: Depiction of increased cerebral myo-inositol with proton MR spectroscopy. *Radiology, 187,* 433–437.

Naismith, S. L., Glozier, N., Burke, D., Carter, P. E., Scott, E., & Hickie, I. B. (2009). Early intervention for cognitive decline: Is there a role for multiple medical or behavioural interventions? *Early Intervention in Psychiatry, 3,* 19–27. doi:10.1111/j.1751-7893.2008.00102.x

Naismith, S. L., Norrie, L. M., Mowszowski, L., & Hickie, I. B. (2012). The neurobiology of depression in later-life: Clinical, neuropsychological, neuroimaging and pathophysiological features. *Progress in Neurobiology, 98,* 99–143.

Naismith, S. L., Rogers, N. L., Hickie, I. B., Mackenzie, J., Norrie, L. M., & Lewis, S. J. G. (2010). Sleep well, think well: Sleep-wake disturbance in mild cognitive impairment. *Journal of Geriatric Psychiatry and Neurology, 23,* 123–130. doi:10.1177/0891988710363710

Naismith, S. L., Rogers, N. L., Lewis, S. J. G., Terpening, Z., Ip, T., Diamond, K., . . . Hickie, I. B. (2011). Sleep disturbance relates to neuropsychological functioning in late-life depression. *Journal of Affective Disorders, 132,* 139–145. doi:10.1016/j.jad.2011.02.027

Naismith, S. L., Terpening, Z., Shine, J. M., & Lewis, S. J. G. (2011). Neuropsychological functioning in Parkinson's disease: Differential relationships with self-reported sleep-wake disturbances. *Movement Disorders, 26,* 1537–1541. doi:10.1002/mds.23640

Oosterman, J. M., van Someren, E. J. W., Vogels, R. L. C., van Harten, B., & Scherder, E. J. A. (2009). Fragmentation of the rest-activity rhythm correlates with age-related cognitive deficits. *Journal of Sleep Research, 18,* 129–135. doi:10.1111/j.1365-2869.2008.00704.x

Petit, J. M., Tobler, I., Allaman, I., Borbely, A. A., & Magistretti, P. J. (2002). Sleep deprivation modulates brain mRNAs encoding genes of glycogen metabolism. *European Journal of Neuroscience, 16,* 1163–1167. doi:10.1046/j.1460-9568.2002.02145.x

Provencher, S. W. (1993). Estimation of metabolite concentrations from localized in-vivo proton NMR-spectra. *Magnetic Resonance in Medicine, 30,* 672–679. doi:10.1002/mrm.1910300604

Rauchs, G., Schabus, M., Parapatics, S., Françoise, B., Clochon, P., Hot, P., . . . Anderer, P. (2008). Is there a link between sleep changes and memory in Alzheimer's disease? *NeuroReport: For Rapid Communication of Neuroscience Research, 19,* 1159–1162. doi:10.1097/WNR.0b013e32830867c4

Scarmeas, N., Brandt, J., Blacker, D., Albert, M., Hadjigeorgiou, G., Dubois, B., . . . Stern, Y. (2007). Disruptive Behavior as a predictor in Alzheimer disease. *Archives of Neurology, 64,* 1755–1761. doi:10.1001/archneur.64.12.1755

Siapas, A. G., & Wilson, M. A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron, 21,* 1123–1128. doi:10.1016/S0896-6273(00)80629-7

Spencer, R. M. C., Gouw, A. M., & Ivry, R. B. (2007). Age-related decline of sleep-dependent consolidation. *Learning & Memory, 14,* 480–484. doi:10.1101/lm.569407

Talairach, J., & Tournoux, P. (1987). *Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system. An approach to cerebral imaging* (Translated from the French by Mark Rayport). New York, NY: Thieme.

Tamminen, J., Payne, J. D., Stickgold, R., Wamsley, E. J., & Gaskell, M. G. (2010). Sleep spindle activity is associated with the integration of new memories and existing knowledge. *The Journal of Neuroscience, 30,* 14356–14360. doi:10.1523/JNEUROSCI.3028-10.2010

Van Praag, H., Schinder, A. F., Christie, B. R., Toni, N., Palmer, T. D., & Gage, F. H. (2002). Functional neurogenesis in the adult hippocampus. *Nature, 415,* 1030–1034. doi:10.1038/4151030a

Walker, M. P., & Stickgold, R. (2006). Sleep, memory, and plasticity. *Annual Review of Psychology, 57,* 139–166. doi:10.1146/annurev.psych.56.091103.070307

World Medical Association. (2008). *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (6th rev.). Seoul, Korea: 59th Meeting of the World Medical Association.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M. B., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research, 17,* 37–49.

Ylinen, A., Bragin, A., Nádasdy, Z., Jandó, G., Szabó, I., Sik, A., & Buzsáki, G. (1995). Sharp wave-associated high-frequency oscillation (200-hz) in the intact hippocampus: Network and intracellular mechanisms. *The Journal of Neuroscience, 15,* 30–46.

Zhong, G., Naismith, S. L., Rogers, N. L., & Lewis, S. J. G. (2011). Sleep-wake disturbances in common neurodegenerative diseases: A closer look at selected aspects of the neural circuitry. *Journal of the Neurological Sciences, 307,* 9–14. doi:10.1016/j.jns.2011.04.020

Zimmerman, M. E., Pan, J. W., Hetherington, H. P., Katz, M. J., Verghese, J., Buschke, H., . . . Lipton, R. B. (2008). Hippocampal neurochemistry, neuromorphometry, and verbal memory in nondemented older adults. *Neurology, 70,* 1594–1600. doi:10.1212/01.wnl.0000306314.77311.be

Received January 23, 2013
Revision received June 27, 2013
Accepted July 1, 2013 ■