Running title: Sleep quality in MCI

Poor sleep quality is observed in Mild Cognitive Impairment and is largely unrelated to depression and anxiety.

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Abstract

Background: Individuals with Mild Cognitive Impairment (MCI) commonly experience a number of sleep quality related issues. However, it remains unclear if these issues are specific to MCI or are simply attributed to the elevated levels depression and anxiety symptoms frequently observed among those with MCI. The present study sought to examine group differences between participants with MCI and matched controls on self-reported measures of sleep quality while controlling for depression and anxiety levels.

Methods: Participants with MCI (N=48) and demographically-matched controls (N=48) were administered self-report measures of anxiety, depression and sleep quality. Sleep quality between both groups were first analyzed using a Multivariate Analysis of Variance, and then subsequently a Multivariate Analysis of Covariance incorporating depression and anxiety scores as covariates.

Results: The MCI group had significantly higher levels of depression and anxiety than the controls. On the sleep-related measures, the MCI group had significantly worse outcomes in sleep duration, disturbances, latency, efficiency, quality and daytime dysfunction. After controlling for depression and anxiety levels, with the exception of daytime dysfunction, all other differences remain significant, and are also associated with moderate to large effect sizes

Conclusion: The results suggest that sleep quality issues are present in MCI and are largely independent of depression and anxiety.

Keywords: Mild cognitive impairment, sleep quality, elderly, depression, anxiety

Introduction

Mild cognitive impairment (MCI) is characterized by cognitive decline that falls in between that of normal aging and dementia (Petersen et al., 1999). Unlike a healthy individual, a person with MCI presents with objective impairments in at least one cognitive domain. Despite such cognitive deficits, the level of functional impairment is minimal in MCI unlike individuals with dementia (Petersen, 2004).

Even though, normal aging is typically associated with a number of adverse changes in sleep, such as a lower proportion of rapid eye movement (REM) sleep, decreased sleep efficiency and increased sleep latency (Ohayon, 2004), individuals with MCI may experience these consequences more severely and/or experience additional sleep-related issues. Beaulieu-Bonneau & Hudon (2009) reviewed the preliminary evidence in this area, which consisted of studies that compared between MCI populations and healthy controls on sleep quality among other neuropsychiatric symptoms (i.e., sleep quality were not the focus), and concluded that sleep disturbances are a major non-cognitive symptom of MCI. Since then, there have been several studies conducted on MCI populations that focus specifically on sleep-related issues. For instance, one study which utilized self-reports measures, reported that relative to healthy controls, sleep in participants with MCI is poorer in quality (Dlugaj et al., 2014) . These findings were also complemented with studies that assessed sleep objectively. For instance, one study reported that MCI subjects had significantly shorter duration of REM sleep and greater fragmentation of slow-wave sleep relative to healthy controls. Furthermore, among MCI subjects who were tested positive for APOE-ε4 genotype , which is suggestive of an increased risk for developing Alzhiemier's disease (AD), had significantly shorter REM sleep duration when compared to their APOE-ε4 negative MCI counterparts (Hita-Yanez, Atienza, Gil-Neciga, & L. Cantero, 2012).

Reduced REM sleep in MCI subjects have also been related to and cortical thinning in regions which are typically associated with AD and increased plasma amyloid beta levels (Sanchez-Espinosa, Atienza, & Cantero, 2014). Taken together, these findings suggest that certain sleep characteristic in MCI subjects may be suggestive of AD pathophysiology.Interestingly, earlier dim light melatonin onset was also reported in MCI subjects relative to healthy controls, which may be suggestive of disturbances in the circadian and sleep-wake system (Naismith et al., 2014). The empirical support relating to sleep quality in MCI does not solely come from cross-sectional studies; there is also some evidence from longitudinal studies to suggest that sleep quality related issues precede MCI. For instance, it was found that self-reported sleep quality issues at baseline significantly predicted the incidence of MCI two years later (Lobo et al., 2008). It was also reported that older women with abnormal circadian rhythms, as indicated by wrist actigraphy, are at increased risk of developing MCI five years later (Tranah et al., 2011). Despite these significant findings, negative findings have also been reported. A few studies have failed to replicate the previously reported group differences (MCI vs. controls) in self-reported sleep characteristics and polysomnography data (Kim, Lee, Lee, Jhoo, & Woo, 2011; Terpening et al., 2015; Yu et al., 2009).

Poor sleep quality is also commonly associated with both depression and anxiety in the elderly (Chang et al., 2014; Paudel et al., 2008; Yu et al., in press). The relationship between sleep quality related issues and these psychiatric conditions may be bidirectional; these issues may exist both as a precursor (Baglioni et al., 2011; Jansson-Fröjmark & Lindblom, 2008) and as a consequence of depression and anxiety disorders (Costa, Carvalho, & Fernandes, 2013; Papadimitriou & Linkowski, 2005). There is also some evidence to suggest that depression (Panza et al., 2010) and anxiety disorders (Beaudreau & O'Hara, 2008) are more prevalent

among those with MCI as compared to the general population. Taken together, this suggests the possibility that sleep quality related issues in MCI can be accounted for by the depression and anxiety symptoms among those with MCI rather than being specifically related to MCI. Hence, it is important to take into account the severity of depression and anxiety when investigating sleep quality in MCI; clear delineation of the relationship between, sleep, MCI and, depression and anxiety is necessary. Although some of the studies mentioned above (Dlugaj et al., 2014; Kim et al., 2011; Tranah et al., 2011) have specifically controlled for the effect of depression on sleep quality in MCI, none of them controlled for anxiety symptoms. There is a possibility that differences in the level of anxiety symptoms across studies may account for the mixed findings discussed previously, especially since anxiety symptoms were previously reported to be associated with the severity of sleep disturbances in participants with MCI (Rozzini et al., 2009).

Given these shortcomings in the existing literature, there is a need for more research to clarify on the sleep quality associated with MCI and specifically to take into account the effects of depression and anxiety on sleep quality in MCI. Such research would help to optimize diagnostic markers involving sleep in MCI and highlight sleep-related issues as a target for interventions in the MCI population. To these ends, the present research adopts a case-control approach to compare the self-report of sleep quality between individuals with MCI and matched controls. Based on previous findings, it is hypothesized that participants with MCI would report significantly lower sleep quality compared to the matched controls. We also predict that, after controlling for depression and anxiety levels, some of these group differences in self-reported sleep quality may no longer remain significant.

Method

Measures

The Geriatric Depression Scale short version (GDS; Sheikh & Yesavage, 1986) was used to assess the level of depression. The GDS consist of 15 yes/no items and has demonstrated good psychometric properties in the local context; a validated cut-off score of 4/5 was also established locally (Nyunt, Fones, Niti, & Ng, 2009). The Geriatric Anxiety Inventory (GAI; Pachana et al., 2007) was used to measure the level of anxiety. It consists of 20 agree/disagree items- each worth a point, giving a maximum total score of 20. A cut-off score of 10/11 has been established in the original validation study (Pachana et al., 2007). The GAI has been validated and has demonstrated good psychometric properties in a similar Asian population (Yan, Xin, Wang, & Tang, 2014). The Pittsburgh Sleep Quality Index (PSQI) (Buysse, III, & Monk, 1989) was used to index sleep-related variables. It consists of 19 questions that assess different aspects of sleep such as its duration, latency, disturbance, efficiency and quality, daytime dysfunction and use of sleep medications. Each of these is scored from 0 to 3, and a global score is obtained by summing up the components' scores. The PSQI has been validated and has shown good psychometric properties in a similar Asian population (Tsai et al., 2005).

For these three questionnaires, higher scores reflect greater severity of problems. Both the GDS and GAI were chosen for this study because they do not include items assessing sleep related issues unlike other commonly used measures such as the Beck Depression Inventory and the Geriatric Anxiety Scale. Hence, this would avoid the possibility of high scores on the PSQI corresponding to high scores on the GDS and GAI simply because all three instruments measure very similar constructs.

Apart from these questionnaires, the Montreal Cognitive Assessment (MoCA) was also administered to the participants. The MoCA is a brief cognitive screening tool that assesses cognitive functions in the domains of visuo-executive, naming, attention, language, abstraction, delayed recall, and orientation. The MoCA is scored on a 30-point scale and higher scores correspond to better cognitive status. For the present study, a validated local adaptation of the MoCA (Liew, Feng, Gao, Ng, & Yap, 2015) was used.

Participants and procedures

The present study's participants were from the Aging in a Community Environment Study (ACES), which recruited elderly participants (aged ≥ 60 years) from geographically defined areas in Jurong, a western district in Singapore. The ACES was approved by a university's Institutional Review Board. Prior to the data collection in the ACES, nurses visited homes within the district to recruit participants. Interested participants were subsequently invited to a community research center. At the center, written informed consent was first obtained from the participants. Thereafter, the above questionnaires, MoCA, a demographics questionnaire as well as various tests necessary for the diagnosis of MCI were administered by trained nurses. These nurses were also present during the entire duration of the questionnaire administration to provide clarification to the participants if they had trouble understanding any of the items. In cases where participants were illiterate, these measures would be administered verbally by the nurses. Each participant was assigned a unique code number for identification; no personal identifiers were used in the data entry.

Within this cohort of 395 participants, 48 were diagnosed with MCI. These diagnoses were made via a consensus from a team that consists of two senior consultant psychiatrists, a

psychiatric epidemiologist and other clinical assessment team members. The Petersen's (2004) criteria of MCI was used and cognitive impairment was assessed via locally normed (age and education adjusted) neuropsychological tests such as the delayed recall and recognition subtests from the Rey Auditory Verbal Learning Test, Digit Span Backward, Block Design, Semantic Fluency and Color Trails Test 2. All MCI cases had also fulfilled the criteria of mild neurocognitive disorder in the DSM V. Those who presented with cognitive deficits severe enough to be diagnosed with dementia (N = 9) were not included. This MCI group consisted of 20 participants with single domain non-amnestic (na)MCI, 7 with multiple domain naMCI, 7 with single domain amnestic (a)MCI and 14 with multiple domain aMCI. Using propensity score matching with a match tolerance of 0.9, 48 control participants were identified based on matching criteria in age, sex, ethnicity, years of education and housing type from the remaining 338 participants. Housing type is used as a rough gauge for socio-economic status (i.e., one-two room public housing ~ lowest tier; Maisonette/Condominium/Landed Housing ~ highest tier). All participants in the MCI group were of Chinese ethnicity, despite the fact that ethnicity was not an exclusion criteria. Consequently, after the matching process, all of the 96 included participants were of Chinese ethnicity. There are no significant differences in age, years of education, number of medical conditions reported and distribution of sexes and housing types between both groups, as determined via Mann-Whitney U tests and Chi-Square tests of independence (ps > 0.5). However, relative to controls, the MCI group had significantly higher scores on the GAI (Mann-Whitney U = 921, Z = 2.3, p = 0.02) and GDS (Mann-Whitney U = 699, Z = 3.4, p = 0.001). Nevertheless, it should be noted that the mean GAI and GDS scores in the MCI group are still well below the respective clinical cut-off criteria in both instruments. Finally, as expected, the MCI group had significantly lower scores on the MoCA as compared to

the control group; Mann-Whitney U = 759, Z = 2.5, p = 0.01. Participants' characteristics and group comparison statistics are presented in Table 1.

INSERT TABLE 1 HERE

Statistical analysis

As a result of skewed distributions in the data, bootstrapping techniques were used. Bootstrapping is a re-sampling method that does not make any assumptions on the sample's distribution (Chen & Peng, 2015) and is robust to violations of normality and sphericity (Berkovits, Hancock, & Nevitt, 2000). Group differences in the sleep variables were tested using a bootstrapped multivariate analysis of variance (MANOVA) and subsequently a bootstrapped multivariate analysis of covariance (MANCOVA) with GAI and GDS scores as covariates. Bootstrapping was carried out using the Bias-Corrected and Accelerated approach with 5000 bootstrap samples. Effect sizes for the MANOVA and MANCOVA analyses were calculated using partial η^2. Statistical significance was set at $p < 0.05$. All analyses were carried out using Statistical Package for the Social Sciences (SPSS version 22) software.

Results

INSERT TABLE 2 HERE

The descriptive statistics and the results of the MANOVA and MANCOVA are reported in Table 2. The MANOVA yielded significant F-statistics in all outcome variables (ps < 0.01) except 'use of sleep medication' ($p > 0.05$); the MCI group had scored significantly higher than the controls in these outcomes. These group differences were also associated with moderate to large effect sizes ($0.09 \leq$ Partial $\eta^2 \leq 0.51$). Next, after including GAI and GDS scores as covariates in the MANCOVA, 'Daytime dysfunction' scores were no longer significantly different between

groups ($p > 0.05$). Nevertheless, group differences in sleep duration, disturbance, latency, efficiency, quality and global PSQI score remained significant ($ps < 0.01$) and were also associated with moderate to large effect sizes ($0.13 \leq \text{Partial } \eta^2 \leq 0.45$). A post-hoc MANOVA analysis was conducted to determine if there were significant group differences between participants with naMCI (N=27) and aMCI (N=21) in the sleep variables, GAI and GDS scores, and demographics (i.e., age and years of education). The results suggest that there were no significant group differences in any of these variables.

Discussion

The present study sought to investigate differences in self-reported sleep quality between participants with MCI and matched controls. In the current report, clear differences, as reflected by the moderate to large effect sizes, were observed between the MCI group and matched controls in a number of areas, such as sleep duration, disturbances, latency, efficiency, quality and daytime dysfunction; the MCI group had poorer outcomes in these areas. This is consistent with the findings of previous studies that utilized subjective self-reports (Dlugaj et al., 2014; Hita-Yañez, Atienza, & Cantero, 2013; Terpening et al., 2015) as well as objective measurements (Hita-Yanez et al., 2012). Taken together with previous findings, the weight of the evidence suggests that individuals with MCI have poorer sleep quality compared to their cognitively healthy counterparts.

Additionally, the current report has also presented some new findings. The results showed that most of these sleep-related issues among participants with MCI, such as decreased sleep duration, efficiency and quality, and increased sleep disturbance and latency, could not be attributed to depression and anxiety levels. Only the group differences in ‘daytime dysfunction’

could be accounted for by depression and anxiety levels. It is possible that depression and anxiety, in addition to sleep and cognitive decline, may also contribute to the daytime dysfunctions component. This is especially so given that the PSQI component of 'daytime dysfunction' is assessed with items querying one's motivational state (i.e., being able to stay awake and keep up enthusiasm while performing various tasks). It is not surprising that these dysfunctions may be accounted for by anxiety and depression, since both are significantly related to motivational deficits (Dickson & MacLeod, 2004).

The finding that participants with MCI were significantly more depressed and anxious, and experienced a lower quality of sleep fits well with the frontal lobe hypothesis of sleep and cognition (Jones & Harrison, 2001). As reviewed by Durmer and Dinges (2005), sleep deprivation- one possible sleep quality related issue, implicates the frontal lobe functioning, as seen from the reduced cognitive task performance that is mediated by atypical levels of pre-frontal cortex (PFC) activation in sleep deprived participants, relative to undeprived controls. Likewise, this PFC region is also crucially involved in emotional regulatory processing that is associated with both depression and anxiety symptoms (Laeger et al., 2012). Taken together, these research on sleep deprivation and atypical emotional regulation points to abnormalities associated with frontal lobe functioning- specifically those related to the PFC region , which are in line with structural (Medina et al., 2006) and functional (Saykin et al., 2004) neuroimaging findings in the MCI population.

Even though it was not the primary goal of the current report to investigate differences in self-reported sleep quality between MCI subtypes, the results showed that the level of sleep quality reported was similar across both subtypes. This null result remained even after depression and anxiety levels were controlled for. This finding is limited by the small sample sizes of the

subgroups. Nevertheless, this is consistent with earlier findings as reviewed by Beaulieu-Bonneau and Hudon (2009). In general, the accumulated evidence thus far does not provide strong support for differing severity and profiles of sleep quality related issues across MCI subtypes. Despite this, future research may want to re-examine such differences between MCI subtypes using objective measurements such as polysomnography since these earlier findings (Beaulieu-Bonneau & Hudon, 2009) and those of the current report were all based on subjective self-reports.

The current findings present two important implications in the clinical context. Firstly, given the clear differences between the MCI group and matched controls on a number of sleep-related issues and the fact that such differences were largely independent of depression and anxiety levels suggest poor sleep quality can potentially be used as a marker for cognitive decline. This is of major significance in the Asian mental health context. Perhaps as a result of the stigma associated with cognitive impairment in the Asian context (Liu, Hinton, Tran, Hinton, & Barker, 2008), afflicted individuals may avoid reporting or choose to downplay symptoms associated with cognitive deficits and instead may emphasize on reporting somatic symptoms (Zaroff, Davis, Chio, & Madhavan, 2012). Hence, among Asian elderly, self-reported sleep difficulties, a major somatic symptom associated with cognitive decline, may be even more crucial for the detection of MCI. Secondly, the current report also highlighted the need for intervention work to address the low sleep quality among individuals with MCI. As suggested by longitudinal evidence, resolving such sleep-related issues would help to prevent further cognitive decline (Lobo et al., 2008; Tranah et al., 2011) and reduce their risks of developing psychiatric illness (Asarnow, Soehner, & Harvey, 2013).

One notable strength of this study relates to the good control of potential confounding variables; as many as five different demographic variables (i.e., age, sex, ethnicity, years of education and housing type) were controlled for in the present study. This study is, however, limited by the use of self-report measurements of depression, anxiety and sleep without any objective assessments to corroborate these subjective reports.There may be some accuracy concerns relating to the use of these measures with a cognitively impaired population. For instance, discrepancies in sleep fragmentation and latency between subjective and objective measures have been noted in MCI subjects(Hita-Yañez et al., 2013). Additionally, we did not test for AD risk factors and biomarkers such as ApoE genotypes and amyloid-beta levels in our MCI participants; these AD-related parameters could have confounded sleep outcomes in MCI subjects (Hita-Yanez et al., 2012; Sanchez-Espinosa et al., 2014). Finally, this study is also limited by the use of a cross-sectional design in which causal inferences cannot be made.

In conclusion, the current report has shown that poor sleep quality is clearly observed among participants with MCI. Furthermore this is largely unrelated to the elevated levels of depression and anxiety commonly associated with MCI. These findings suggest that sleep quality related issues can be used as a potential non-cognitive marker in the detection of MCI. Additionally, they also highlight the need for intervention work to address sleep-related issues that commonly afflict those with MCI to better their outcomes.

Disclosure statement

The authors have no conflicts of interest to declare

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Table 1

Participants' characteristics

			Between group comparison	
	Control	**MCI**	*Z* *(Mann-Whitney U)*	χ^2
Mean Age (SD)	68.1 (5.6)	67.9 (4.9)	0.15	
Gender				
Male	16	8		3.6
Female	32	40		
Mean years of education (SD)	5.8 (4.0)	5.4 (4.6)	0.49	
Housing Type				
1 to 3-room PH	6	8		
4 to 5-room PH	33	30		0.5
Maisonette/Condominium/Landed housing	9	10		
Mean No. of Medical Conditions (SD)	2.21 (2.6)	2.31 (1.5)	1.16	
Mean MoCA score (SD)	26.2 (3.5)	24.2 (3.6)	2.5*	
Mean GDS score (SD)	0.9 (1.0)	2.1 (1.9)	3.4*	
Mean GAI score (SD)	0.4 (1.1)	1.5 (2.8)	2.3*	

MCI = Mild Cognitive Impairment; SD = Standard Deviation; PH = Public Housing; MoCA = Montreal Cognitive Assessment; GDS = Geriatric Depression Scale; GAI = Geriatric Anxiety Inventory. *P <0.05

Table 2

Descriptive statistics, MANOVA and MANCOVA on sleep variables between groups

	Control		**MCI**		**MANOVA**			**MANCOVA***		
	Mean	SD	Mean	SD	$F_{1,91}$	P	Partial η^2	$F_{1,88}$	P	Partial η^2
Sleep duration	0.10	0.31	0.83	0.91	29.56	<.0001	0.25	19.72	<.0001	0.18
Sleep disturbance	0.31	0.47	0.83	0.52	29.91	<0.001	0.25	23.19	<0.001	0.21
Sleep latency	0.10	0.31	1.08	1.23	30.11	<0.001	0.25	18.84	<0.001	0.18
Daytime dysfunction	<0.01	<0.01	0.25	0.60	8.53	0.004	0.09	3.57	0.062	0.04
Sleep efficiency	0.02	0.15	0.65	0.87	23.78	<0.001	0.21	13.43	<0.001	0.13
Sleep quality	0.02	0.14	0.85	0.58	93.99	<0.001	0.51	71.44	<0.001	0.45
Use of sleep medication	<0.01	<0.01	0.13	0.61	2.09	0.152	0.02	2.58	0.112	0.03
Global PSQI Score	0.56	0.50	4.61	3.40	72.14	<0.001	0.44	50.87	<0.001	0.36

MCI = Mild Cognitive Impairment; PSQI = Pittsburgh Sleep Quality Index; SD = Standard Deviation. *Geriatric Anxiety Inventory and Geriatric Depression Scale scores are included as covariates.