Comparison of Cognitive Functioning Among Individuals With Treated Restless Legs Syndrome (RLS), Untreated RLS, and No RLS

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Restless legs syndrome (RLS) is a common neurological sensory-motor condition. High prevalence of comorbid depression and anxiety has been reported, but the few available data on the impact of RLS on cognition have been conflicting. The authors compared 91 participants (No-RLS group: N=37; Untreated RLS group: N=23; Treated RLS group: N=31) on cognitive performance and depression ratings. There were minimal observed group differences in cognitive performance, but the untreated RLS group had significantly higher depressive symptoms than the treated RLS and the no-RLS groups. RLS does not appear to affect cognition, but there does appear to be a strong association between untreated RLS and depression.

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Restless Legs Syndrome (RLS) is a common neurosensory motor disorder that affects 1.9%−4.6% of the general adult population.[1] Previously subsumed under Dysomnia, Not Otherwise Specified, in the 4th Edition of the Diagnostic and Statistical Manual of Mental disorders (DSM-IV), RLS has been elevated to a full diagnosis in the DSM-5.[2] As a result, the evaluation and treatment of RLS in psychiatric practice are likely to become more common.

Although population- and clinic-based studies have established close associations between RLS and noncognitive psychiatric conditions, such as depression and anxiety,[3] few available studies have examined the impact of RLS or RLS treatment on cognition. At least two variables could theoretically link RLS to cognitive performance. First, RLS-related sleep loss might result in cognitive deficits, such as those observed in studies of sleep deprivation.[4] Insomnia symptoms are also associated with an increased risk of depressive symptoms,[5] which have been linked to cognitive decline.[6] Individuals with RLS commonly have insomnia complaints; therefore, depressive symptoms might moderate an RLS–cognition association.

However, the empirical literature includes inconsistent findings for the impact of RLS symptoms on cognitive performance. Two previous studies that compared the cognitive functioning of RLS patients to RLS-free control subjects have reported impairment primarily in executive functioning among RLS patients.[7,8] In contrast, Gamaldo et al.[9] reported superior performance in letter and category fluency among untreated RLS patients as compared with sleep-restricted controls. Findings from population-based studies have also been inconsistent. Celle et al.[10] found that individuals with RLS exhibited lower performance on the Stroop task and verbal fluency, whereas Driver-Dunckley et al.[11] found no differences in multiple domains of cognitive functioning between those with mild RLS as compared with those without RLS.

Treatment of moderate-to-severe RLS appears to reduce RLS symptoms and improve quality of life. However, no previous study has examined whether or not treatment status is associated with improved cognitive performance among RLS patients. Also, with the

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important exception of the study by Fulda et al.,[8] most studies have examined the impact of RLS on a specific cognitive domain (e.g., verbal fluency) only. Therefore, it remains unclear whether RLS patients have one or two specific cognitive deficits or whether the findings extend to other cognitive domains.

In this study, we compared the cognitive performance and depressive symptoms of three participant groups: individuals with treated RLS, untreated RLS, and no RLS. We hypothesized that individuals with treated RLS would perform better than individuals with untreated RLS on measures of executive functioning because their sleep would be improved. Furthermore, we hypothesized that the untreated RLS participant group would have a higher depression rating than the no RLS group.

METHODS

Study Sample

A total of 105 individuals consented to participate in this study. Participants with untreated RLS and without RLS were recruited from the RLS in Baltimore ECA (RiBECA) Study. Details of the RiBECA Study have been described previously.[12] Briefly, RiBECA was an ancillary study to Wave IV of the Baltimore Epidemiologic Catchment Area follow-up study, in which 1,028 community-dwelling Baltimore residents completed the RiBECA−7Q, a questionnaire with 7 items mirroring the National Institutes of Health/International Restless Legs Syndrome Study Group (NIH/IRLSSG) diagnostic criteria for RLS.[13] Of the 1,028 participants in the RiBECA Study, 41 screened positive for RLS on the RiBECA−7Q. All 41 reported that they were not being treated for their RLS symptoms, and they were invited to participate in this follow-up study. Of the 41 participants with RLS, 6 could not be reached. The remaining 35 with positive RiBECA−7Q screens consented to participate. We then recruited 35 age-, gender- and race-matched participants who screened negative on the RiBECA−7Q from the RiBECA Study. Also, we recruited a group of individuals with RLS who were receiving treatment (N=35) from the Johns Hopkins Center for RLS who were prescribed medication for relief of their RLS symptoms. An RLS diagnosis of these participants was confirmed by the study clinician on the basis of the same diagnostic procedure as the other two groups.

Of these 105 subjects, we excluded those with dementia (N=6) or a history of stroke (N=1). Dementia status was determined by review of the neuropsychological battery test scores by a neuropsychologist (CAM), who was blind to RLS-group status, based on the DSM-IV definition of dementia—specifically, those participants who had significant cognitive deficits in memory and at least one other cognitive domain. Deficient scores were those that were judged to be lower than expected, given the educational and occupational level of the participant. Because of the wide age range (34 to 98 years), we also excluded those with an age more than two standard deviations (SD) above or below the mean age of 67.4 (N=7). Also, of those (N=35) who screened positive on the RiBECA−7Q, 6 who did not have RLS, based on detailed examination, were categorized to the No-RLS group. The final sample for this study consisted of 91 adults (mean age: 67.1 years; SD: 10.5; 75.8% women; 67% White). Of the 91 participants, 23 had untreated RLS; 31 had treated RLS; and 37 participants had no RLS. This ancillary study was approved by the Johns Hopkins School of Medicine Institutional Review Board.

RLS Assessment

All participants were assessed for RLS by an RLS expert clinician (HBL) who conducted a full neurologic examination and in-person administration of the Hopkins Telephone Diagnostic Interview (HTDI). The HTDI assesses the four key diagnostic features of RLS and factors that provoke and relieve symptoms while also identifying those individuals with "RLS mimics" (e.g., restlessness due to anxiety).[14] Participants with RLS also completed the 10-item International RLS Study Group RLS Rating Scale (IRLSSG Rating Scale),[15] which is a measure of RLS disease severity and the impact of RLS symptoms on a participant's daily life, sleep, and mood. Higher scores on the IRLSSG indicate more severe RLS symptoms. RLS participants also completed the 17-item RLS Quality of Life Instrument (RLS-QLI),[16] which measures four factors (Daily Function, Social Function, Sleep Quality, and Emotional Well-Being). Higher scores on the RLS-QLI indicate a lower quality of life. Those who were treated for RLS were asked to rate their pretreatment RLS symptoms and quality of life, based on the IRLSSG and RLS-QLI.

Cognitive Assessment

This study's neuropsychological battery included the following tests: 1) National Adult Reading Test, to estimate verbal IQ (NART); 2) the Boston Naming Test;

TABLE 1. Sociodemographic Characteristics for No-RLS, Untreated RLS, and Treated RLS (Restless Legs Syndrome), mean (standard deviation)

	No RLS (N=37)	Untreated RLS (N=23)	Treated RLS (N=31)	*F*[df]; p
Sociodemographic				
Age	68.1 (8.9)	69.6 (12.5)	64.2 (10.3)	*F*[2, 88]=2.06; NS
Education	12.1 (3.1)‡	11.7 (2.7)‡	15.71 (2.8)*†	*F*[2, 88]=9.01; p <0.01
				t; p
RLS variables				
RLS Quality of Life	N/A	67.48 (13.86)‡	49.68 (15.25)†	*t*=4.28; p <0.01
RLS Symptom Severity	N/A	18.67 (8.80)‡	29.23 (6.60)†	*t* = –4.94; p <0.01
	N (%)	**N (%)**	**N (%)**	**χ^2; p**
Sex				
Men	9 (24.3)	2 (8.7)	11 (35.5)	χ^2=5.17, p=0.08
Women	28 (75.7)	21 (91.3)	20 (64.5)	
Race				
White	21 (56.8)‡	11 (47.8)‡	29 (93.5)*†	χ^2=15.47, p <0.01
African American	16 (43.2)	12 (52.2)	2 (6.5)	
Health				
Self health rating (good)	24 (66.7)	18 (85.7)	22 (73.3)	χ^2=2.48; NS
Heart disease	2 (8.7)	4 (28.6)	6 (21.4)	χ^2=2.57; NS
Diabetes	8 (22.2)	7 (31.8)	2 (7.1)	χ^2=4.97; p=0.08
Hypertension	11 (50.0)	6 (42.9)	15 (50.0)	χ^2=0.22; NS
Cancer	3 (13.0)	1 (7.1)	6 (20.0)	χ^2=1.34; NS
Osteoporosis	6 (16.7)	7 (31.8)	7 (24.1)	χ^2=1.80; NS
Asthma	7 (19.4)	7 (31.8)	3 (10.0)	χ^2=3.88; NS
Arthritis	26 (70.3)	15 (68.2)	17 (56.7)	χ^2=1.47; NS
Health insurance	29 (80.6)	18 (81.8)	26 (89.7)	χ^2=1.08; NS

*Significant (p <0.01) difference with No-RLS group.
†Significant (p <0.01) difference with Untreated RLS group.
‡Significant (p <0.01) difference with Treated RLS group.

3) the Trail-Making Test; 4) the Brief Test of Attention (BTA[17]); 5) The Hopkins Verbal Learning Test, Revised Edition (HVLT-R); 6) the Brief Visuospatial Memory Test, Revised Edition (BVMT-R); 7) the Grooved Pegboard Test; 8) the Clock-Drawing Test (CLOX); 9) the Rey-Osterrieth Complex Figure Test (Rey Copy); and 10) letter and category verbal fluency tasks.

Depression Assessment

Participants also completed the 30-item Geriatric Depression Scale (GDS)[18] to assess their current level of depressive symptoms. Higher scores on the GDS indicate more severe depressive symptoms.

Statistical Analyses

We compared the three groups with respect to sociodemographic and health-related variables by use of chi-square tests for categorical variables and a multivariate analysis of covariance (MANCOVA) for continuous variables. Independent-samples *t*-tests were used to compare the treated and untreated RLS groups on RLS quality of life and RLS symptom severity. Participants with treated RLS were asked to rate their symptoms, based on their memory of their symptoms at a time when they were not receiving treatment. We used a MANCOVA, with education and age as covariates, to compare the three groups on cognitive performance variables. Mean substitution within groups was used for participants who had partial cognitive data-points. We selected an alpha cut-off of <0.01 for statistical significance so as to reduce potential Type I error due to multiple comparisons. All statistical analyses were performed with SPSS 19.0.

RESULTS

Table 1 shows that we found no significant group differences on the health variables across the three groups, indicating that group differences in cognition are not likely to have been due to a comorbid medical condition. There were significant differences in RLS quality of life, with treated RLS participants reporting worse quality of life and more severe symptoms before treatment than untreated RLS participants. There were significant group differences across all three groups on race and education, with the treated RLS group being primarily White and highly-educated. Education and

TABLE 2. Psychological Variables for No-RLS, Untreated RLS, and Treated RLS, mean (standard deviation)

	No RLS (N=37)	Untreated RLS (N=23)	Treated RLS (N=31)	*F*[df]; p
Cognition				
Estimated Verbal IQ	94.51 (14.82)	95.45 (11.20)	106.39 (10.55)	*F*[2, 86]=0.47; NS
Boston Naming Test	26.00 (4.47)	26.45 (3.70)	28.87 (2.68)	*F*[2, 86]=0.54; NS
Trails A Time	67.06 (60.82)	62.05 (38.96)	39.61 (14.28)	*F*[2, 86]=0.97; NS
Trails B Time	165.67 (127.11)	171.29 (118.54)	95.42 (64.57)	*F*[2, 86]=0.11; NS
Brief Test of Attention	13.36 (4.96)	12.00 (4.05)	14.94 (3.66)	*F*[2, 86]=0.54; NS
HVLT, Learning	20.94 (5.90)	21.23 (4.67)	23.16 (5.27)	*F*[2, 86]=0.13; NS
HVLT, Trial 4	6.66 (3.23)	6.86 (2.49)	8.65 (2.43)	*F*[2, 86]=1.77; NS
HVLT, Discrimination	9.26 (1.88)	9.59 (1.67)	9.35 (1.91)	*F*[2, 86]=1.21; NS
BVMT, Total Recall	16.89 (8.09)	13.41 (7.10)	18.40 (6.29)	*F*[2, 86]=1.84; NS
BVMT, Trial 4	6.71 (3.52)	5.45 (2.81)	8.10 (2.37)	*F*[2, 86]=1.20; NS
BVMT, Discrimination	5.20 (1.31)	5.14 (1.06)	5.33 (0.79)	*F*[2, 86]=0.27; NS
BVMT, Copy	10.80 (1.81)	10.95 (1.02)	10.79 (1.14)	*F*[2, 86]=1.80; NS
Pegboard Test, Dominant Average	111.79 (53.20)	126.89 (64.70)	85.73 (19.11)	*F*[2, 86]=0.1.59; NS
Pegboard Test, Nondominant Average	128.41 (54.85)	130.61 (55.28)	89.46 (21.32)	*F*[2, 86]=1.91; NS
Letter Fluency, Correct	24.80 (12.17)	26.27 (10.20)	29.74 (9.14)	*F*[2, 86]=0.53; NS
Category Fluency, Correct	37.23 (11.22)	35.43 (10.62)	44.19 (10.95)	*F*[2, 86]=0.72; NS
Clock-Drawing	7.77 (1.86)‡	8.32 (1.79)	9.26 (1.37)*	*F*[2, 86]=4.48; p=0.01
Clock Copy	9.06 (1.00)‡	8.95 (0.93)‡	9.94 (0.25)*,†	*F*[2, 86]=9.39; p <0.01
Rey Copy	25.36 (8.21)	25.00 (6.04)	30.43 (4.10)	*F*[2, 86]=0.94; NS
Depression				
Geriatric Depression Scale score	5.19 (4.98)†	10.50 (8.07)*	7.39 (6.27)	*F*[2, 86]=5.21; p <0.01

HVLT: Hopkins Verbal Learning Test; BVMT: Brief Visuospatial Memory Test.
*Significant (p <0.01) pairwise difference with No RLS group.
†Significant (p <0.01) pairwise difference with Untreated RLS group.
‡Significant (p <0.01) pairwise difference with Treated RLS group.

age were entered as covariates in the MANCOVA to avoid misattributing group cognitive differences to treatment status, rather than education or age differences.

Table 2 shows between-group differences on the cognitive variables after the adjustment for education and age. Before we controlled for education, significant group differences were observed in estimated verbal IQ, Boston Naming Test, Category Fluency, and the Clock-Drawing test. However, after adjusting for education, there were no significant group differences on cognitive performance except for the Clock tasks. Treated RLS patients performed better (p <0.01) on the Clock-Drawing and Clock Copy tests than untreated RLS patients or no-RLS participants, but the difference in group mean scores among them were not clinically significant. Notably, however, untreated RLS patients reported more symptoms of depression on the GDS than participants with no RLS (p <0.01).

DISCUSSION

Consistent with other, previous studies,[3] we found that the untreated RLS group had a higher depression rating than the no-RLS group. However, after adjusting for education, we found no significant group differences in cognitive performance among participants with treated RLS, untreated RLS, and no RLS. Therefore, our study did not support our hypothesis that treatment status of RLS symptoms would be associated with cognitive performance. In fact, RLS diagnosis seems to have little impact on cognitive performance in general; we found no difference in cognitive performance among the three groups.

Our finding is consistent with the Gamaldo et al. study results,[9] but in conflict with Fulda and colleagues' findings.[8] Our study built on previous studies by adjusting for education and age, which can skew results on cognitive performance if earlier group differences exist. The present study also included a comparison of individuals with untreated RLS and those without RLS from the same community in order to reduce potential referral bias.

An important strength of our study is the availability of an untreated RLS group. Previous studies, in order to examine the impact of untreated RLS symptoms on cognition, weaned participants off RLS-related medications before assessment. Severe RLS patients can rarely tolerate being off RLS medications for an extended period of time, and rebound RLS symptoms and/or the

sudden cessation of RLS treatment make the true impact of RLS symptoms on cognition difficult to assess. Our study chose to recruit untreated RLS patients so that we could examine the role of RLS treatment status on cognitive performance. However, this cross-sectional aspect of our study is also a methodological limitation. The treated RLS group had substantially higher baseline RLS symptom severity level and endorsed more severe sleep disturbance and fatigue caused by sleep disturbance on the IRLSSG rating scale than the untreated RLS group. Also, retrospective rating of the pretreatment RLS symptoms and related quality of life among treated RLS subjects adds to imprecision of their ratings due to recall bias. Perhaps more severe RLS symptoms associated with sleep disturbance would have led to more of an impact on cognitive performance, if left untreated. Additional measures of sleep quality (e.g., actigraphy) and daytime sleepiness would have enhanced our study design.

A double-blind, placebo-controlled trial of treatment-naïve RLS patients with cognitive deficits before and after RLS treatment could provide more definitive data for the impact of RLS treatment on cognition among RLS patients. However,, the mean IRLSSG Severity rating scale score (mean: 18.67; SD: 8.80) of the untreated RLS group was still in the clinically significant range. The fact that there was no difference in cognitive performance between the Untreated RLS and No-RLS groups indicates that RLS likely has little-or-no impact on cognitive performance.

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