The Relationship Between Cognitive Function and Physical Function in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To examine the relationship between cognitive impairment and functional limitations and disability in persons with rheumatoid arthritis (RA).

Methods. Individuals from a longitudinal cohort study of RA participated in study visits that included physical, psychosocial, and biological metrics. Cognitive function was assessed using a battery of 12 standardized neuropsychological measures yielding 16 indices covering a range of cognitive domains. On each test, subjects were classified as "impaired" if they performed 1 SD below age-based population norms. Total cognitive function scores were calculated by summing the number of tests on which individuals were classified as "impaired" (higher scores = greater impairment). Performance-based and self-reported functional limitations were assessed with the Short Physical Performance Battery (SPPB) and the Health Assessment Questionnaire (HAQ), respectively. Self-reported disability was measured with the Valued Life Activities (VLA) scale. Multiple regression analyses controlling for sex, race, education, cardiovascular comorbidity, disease duration, disease severity, and depression were conducted to identify whether cognitive impairment was independently associated with physical function difficulties.

Results. There were 122 subjects with mean (SD) age of 58.4 (± 10.8) years; 62% were female and 80% were white. In multivariate regression models, total cognitive function score was significantly associated with greater functional limitations (SPPB: $\beta = -0.24$, $p = 0.014$; HAQ: $\beta = 0.24$, $p = 0.003$) but not with disability (VLA: $\beta = 0.10$, $p = 0.207$).

Conclusion. Cognitive impairment was significantly associated with greater functional limitations in patients with RA, suggesting that cognitive impairment may play a role in poor functional status in persons with RA. (First Release Jan 15 2013; J Rheumatol 2013;40:236–43; doi:10.3899/jrheum.120871)

Key Indexing Terms:
COGNITIVE IMPAIRMENT
FUNCTIONAL LIMITATIONS
DISABILITY
RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease that is characterized by pain, joint stiffness/swelling, and subsequent functional limitations and disability[1]. The proportion of persons living with RA-attributable adverse outcomes, such as functional limitations and disability, has increased over time because of longevity and disease chronicity[2]. Understanding the risk factors that aggravate functional status is essential for developing effective interventions to minimize these outcomes.

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Supported by the US National Institutes of Health (NIH)/US National Institute of Arthritis and Musculoskeletal and Skin Diseases Grant P60AR053308 and the NIH/US National Center for Research Resources, University of California San Francisco – Clinical and Translational Sciences Institute Grant UL1RR024131.

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Accepted for publication November 19, 2012.

For persons with chronic diseases such as RA, intact cognitive function is crucial for performing daily activities and maintaining disease management skills, including adhering to medication regimens, planning and initiating activities based on one's current condition, changing plans if pain unexpectedly worsens, and limiting behaviors that worsen pain or health status[3]. Although several mechanisms may influence cognitive function in persons with RA, cognitive function has not been extensively studied in these patients[4].

Two primary studies have evaluated cognitive function in well characterized cohorts of patients with RA using a comprehensive neuropsychological test battery that extends beyond general mental status screening examinations. In a study by Bartolini, *et al*[5], cognitive dysfunction was observed to be common in patients with RA, with prevalence rates ranging from 38% (attention and mental flexibility) to 71% (visuospatial and planning functions). In this cohort, cognitive dysfunction was also associated with neuroimaging findings, including hypoperfusion on brain single-photon-emission computed tomography and increased white-matter alterations on magnetic resonance imaging. Additionally, Appenzeller and colleagues[4]

observed cognitive impairment in 30% of the RA cohort as compared to 8% of healthy controls. Patients with RA had significantly worse outcomes in verbal fluency and episodic memory. These few studies have important implications in that they highlight the potential burden of cognitive impairment and its adverse effect on functioning in patients with RA.

Because RA is a chronic, incurable disease, persons with RA may have the increased burden of both age-related and disease-related cognitive decline as they age. A number of studies have assessed cognitive dysfunction as one of many predictors that might exacerbate functional limitations or disability in large samples of community-dwelling individuals with various chronic health conditions[1,6,7,8,9]. For example, Greiner, *et al*[8] found that low cognitive function was significantly associated with the subsequent loss of physical function in daily activities. Wang, *et al*[9] also found a significant relationship between cognitive function and functional limitations in older adults.

Considering the lifelong disabling symptoms of RA, persons with RA may be at even greater risk for physical function difficulties compared to the general aging population. However, no study has examined the relationship between cognitive function and physical function in persons with RA. Our purpose was to explore that relationship. The hypothesis was that cognitive impairment would be independently related to higher levels of physical function difficulties (functional limitations and disability) in persons with RA after controlling for sociodemographic and disease-related factors.

MATERIALS AND METHODS

Sample and setting. Subjects were drawn from the University of California, San Francisco (UCSF) RA Panel, begun in 1982. Details about enrollment and data collection have been described[10]. Briefly, a random sample of rheumatologists practicing in Northern California recruited participants with RA presenting in their offices over a 1-month period. Between 1982 and 1983, 822 persons were enrolled, supplemented with 4 additional recruitments from 1989 to 2003. Trained interviewers conducted structured annual telephone interviews that included questions on sociodemographic characteristics, general health status, disease-related symptoms, medication use, psychological health status, physical function, and disability.

At the end of the telephone interviews in study years 2007-2009, participants who lived in the San Francisco Bay Area and were willing to travel to UCSF were recruited for in-person assessments at the UCSF Clinical and Translational Science Institute Clinical Research Services (CRS) facility. In 2009, an additional 44 subjects were recruited from the UCSF rheumatology clinic and from individuals who had participated in another study of RA and had agreed to be contacted for other studies. In total, 144 individuals participated in the CRS visits, 60% of those who were recruited and eligible.

The CRS visits included a range of physical, psychosocial, cognitive, and biological measures. Data from the CRS visits were merged with data collected during the standardized telephone interviews. Finally, 122 subjects who had complete data on all outcomes and covariates of interest were included in our study; of participants who were excluded, the majority were missing data on neuropsychological performance (n = 9) and cardiovascular comorbidity index (n = 7; Figure 1).

The research protocol was approved by the UCSF Committee on Human Research, and all subjects gave their informed consent to participate.

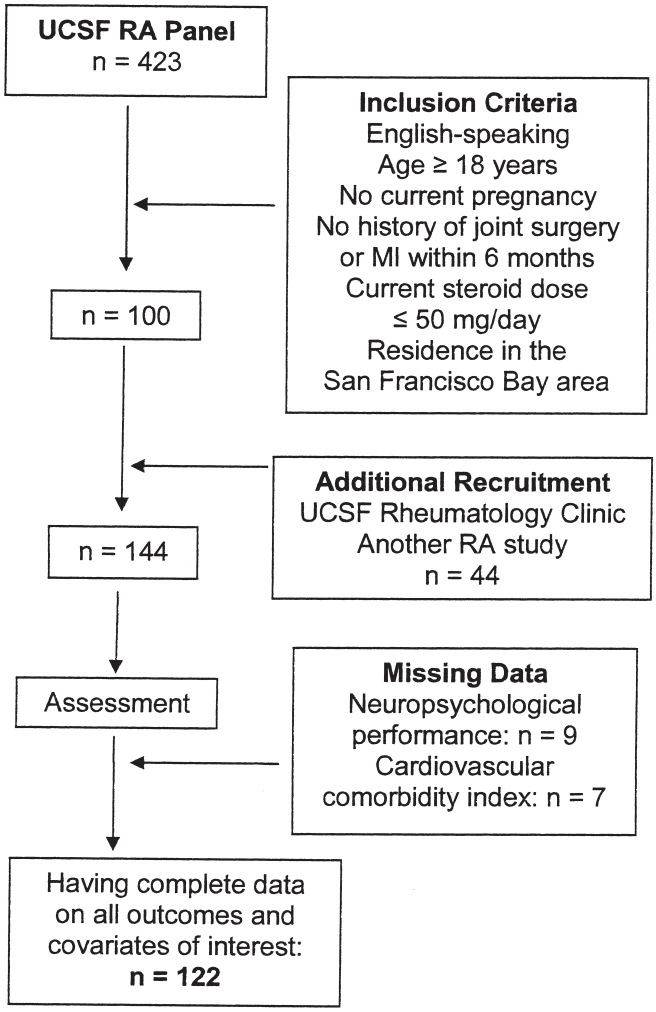

Figure 1. Selection criteria of study subjects. UCSF RA Panel: University of California, San Francisco Rheumatoid Arthritis Panel; MI: myocardial infarction.

Measures. Our assessment of functioning was based on the Disablement Process Model (DPM) proposed by Verbrugge and Jette[11], in which functional limitations and disability are clearly differentiated. Functional limitations are restrictions in performing fundamental physical *actions* (e.g., mobility, motion, and strength), while disability reflects difficulty or inability to perform *activities*. Performance of activities requires physical actions, but may also require personal or environmental adaptations. According to the DPM[11,12], functional limitations are precursors of disability. We examined 3 measures of physical functioning to tap both functional limitations and disability. We also used both performance-based (observed) and self-reported measures of functional limitations (observed measures of disability as conceived by the DPM are not available; the construct is inherently self-perceived). This selection of measures permitted us to examine possible dissimilar relationships of cognitive function with 2 types of physical function difficulties and with observed versus self-reported functional limitations.

Functional limitations: performance-based. The Short Physical Performance Battery (SPPB)[13] was used as an observed measure of functional limitations. The SPPB has been used as a reliable and valid

performance-based measure of physical function in many disability studies[14,15,16]. Components include standing balance, 4-m gait speed, and chair rising tasks. A single summary performance score is calculated, ranging from 0 to 12 (lower scores = greater functional limitations)[13,17].

Functional limitations: self-reported. The Health Assessment Questionnaire (HAQ)[18], one of the most widely used measures of functioning in RA research, was used as a self-reported measure of functional limitations. The HAQ includes 20 items covering physical actions in 8 domains: dressing and grooming, arising, eating, walking, personal hygiene, reaching, gripping, and outdoor activities. HAQ scores range from 0 to 3 with higher scores reflecting greater functional limitations[19,20].

Disability: self-reported. The Valued Life Activities (VLA) scale[21,22] was administered to assess self-reported disability in daily activities. The 33-item VLA scale assesses a wide range of activities, ranging from obligatory activities (e.g., self-care) to discretionary activities (e.g., recreation and social participation). Activities that were not applicable to a subject (e.g., "taking care of children" if the subject had no children) or were not important to the subject (e.g., "household maintenance" if the spouse did all the household maintenance work) were not included in scoring the scale. Difficulty was rated on the same scale as the HAQ (0–3, higher scores = greater disability). The VLA was scored as the mean difficulty for all rated items.

Cognitive function. Cognitive function was assessed using a standardized neuropsychological battery that was modified from the American College of Rheumatology neuropsychological battery[23]. It is primarily recommended for systemic lupus erythematosus (SLE), and has been deemed reliable and valid[24,25]. We modified it for use in RA to minimize or control for the effects of hand-motor dysfunction.

Neuropsychological tests included the California Verbal Learning Test-II[26] Learning, Short Delay, and Long Delay Recall; the Rey-Osterrieth Complex Figure Test[27] Copy Trial, Immediate Delay, and Long Delay Recall; the Controlled Oral Word Association Test and the Animal Naming Test[28]; the oral version of the Symbol Digit Modalities Test[29]; the Delis-Kaplan Executive Function Scale, including the Card Sorting Test (Total Correct), Design Fluency Test (Total Correct), Trail Making Test (Timing for Sequencing/Shifting Condition), and Color Word Inference Test[30] Inhibition and Switching Conditions; the Wechsler Adult Intelligence Scale-III Digit Span Backwards Test[31]; and the short-form Judgment of Line Orientation Test[32,33]. The duration of the neuropsychological battery was about 60–80 min.

Neuropsychological tests were scored to yield z-scores based on age-stratified population norms, and 16 neuropsychological indices were derived. Using conventional cutpoints, subjects were classified as "impaired" if they performed 1 SD below age-stratified population norms for each cognitive index[24,34]. A total cognitive function score was calculated by summing the number of tests on which individuals were classified as "impaired," ranging from 0 to 16 (higher scores = greater impairment). Subjects who completed at least 80% of the 16 subtests (≥ 13) were included in the analyses.

For additional analyses, total executive and memory function scores were created by using 9 and 6 test results, respectively. A total executive function score was calculated by summing the number of tests on which individuals were classified as "impaired" out of 9 tests assessing fluency, executive function, and working memory and speed processing, ranging from 0 to 9 (higher scores = greater impairment). A total memory function score was calculated by summing the number of tests on which individuals were classified as "impaired" on 6 tests assessing verbal learning and memory and visuo-spatial learning and memory, ranging from 0 to 6 (higher scores = greater impairment).

Covariates. Self-reported information on sociodemographics and disease characteristics were assessed as covariates. Blood samples for measurement of cholesterol levels were collected during the CRS visit and sent to a commercial laboratory for analysis.

A cardiovascular (CV) comorbidity index was generated based on variables in the CV disease risk score profiles from the Framingham Heart Study[35,36]. The CV comorbidity index was calculated as the total number of the following CV risk factors that were present: hypertension, systolic blood pressure > 140 mm Hg, antihypertensive medication use, total cholesterol > 200 mg/dl, high-density lipoprotein < 60 mg/dl, current smoking, and obesity (body mass index > 30). CV comorbidity index ranged from 0 to 6, with higher scores indicating greater CV-related comorbidities.

Depression was assessed using the Mini International Neuropsychiatric Interview (MINI)[37,38], a short diagnostic structured interview corresponding to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria for the Axis I psychiatric disorders. The MINI was administered by study clinical evaluators trained and supervised by a clinical psychologist (LJ). The MINI has been deemed reliable and valid across many populations[37,38].

Severity of RA was assessed using the Rheumatoid Arthritis Disease Activity Index (RADAI)[39,40], a patient-assessed measure of RA disease activity covering global disease activity in the past 6 months; current joint pain, tenderness, and swelling; and current duration of morning stiffness. RADAI scores range from 0 to 10, with higher scores reflecting greater disease activity. It has been shown to be reliable and valid[39,40].

Statistical analyses. T test, Mann-Whitney U test, or chi-square were used to assess whether there were significant differences between subjects from the UCSF RA panel and subjects from the additionally recruited group. Multiple linear regression analyses were used to identify the relationship between total cognitive function score and 3 physical function test scores, controlling for covariates (sex, race, education level, CV comorbidity, disease duration, disease severity, and depression). Three separate multiple regression analyses were conducted (1 for each dependent variable) to examine the independent contribution of cognitive impairment to physical function difficulties, controlling for other covariates. The same statistical methods were used for analyses of the executive and memory function scores. The limit for significance was set at 2-tailed $\alpha = 0.05$. All analyses were conducted using the IBM SPSS software, version 19.0.

RESULTS

Subject characteristics are presented in Table 1. Mean (SD) age of 122 subjects was 58.4 years (± 10.8). Sixty-two percent were female, 80% were white, and 62% were married/living with partners. Eight percent met the criteria for major depressive disorder. Mean education level was 15.3 years (± 2.2) and disease duration was 19.7 years (± 11.3). Mean CV comorbidity was 2.0 (± 1.7). Mean scores of the SPPB, HAQ, and the VLA difficulty were 9.3 (± 2.4), 1.0 (± 0.7), and 0.6 (± 0.5), respectively. Subjects from the UCSF RA panel were more likely to be female, white, have longer disease duration, and less disability measured by the VLA than subjects from the additionally recruited group. Except for these 4 variables, there was no significant difference between the 2 groups.

Mean total cognitive function score was 2.5 (± 2.1), and ranged from 0 to 9 (Tables 2 and 3). The proportion of persons who were classified as cognitively impaired on each test ranged from 8% (semantic fluency test) to 29% (design fluency test). The proportion of persons cognitively impaired on 4 or more tests was 30%. Mean total executive function score was 1.3 (± 1.3) and ranged from 0 to 6; mean total memory function score was 1.1 (± 1.4) and ranged from 0 to 5. The proportions of persons cognitively impaired on 2 or more of executive function and memory tests were 35% and 30%, respectively.

Table 1. Characteristics of subjects (n = 122).

Characteristics	N (%)	Mean ± SD (range)
Sociodemographic		
Age, yrs		58.4 ± 10.8 (25, 87)
Female	76 (62.3)	
White	97 (79.5)	
Education level, yrs		15.3 ± 2.2 (10, 20)
Married/living with partner	75 (61.5)	
Family income		
Below $20,000 (US)	9 (7.4)	
$20,000–$40,000	19 (15.6)	
$40,000–$60,000	15 (12.3)	
$60,000–$80,000	13 (10.7)	
$80,000–$100,000	21 (17.2)	
Above $100,000	40 (32.8)	
Cardiovascular comorbidity		2.0 ± 1.7 (0, 6)
Disease-related		
Duration of RA, yrs		19.7 ± 11.3 (0, 56)
RADAI score (severity of RA)		2.4 ± 1.6 (0, 6.7)
Depression	10 (8.2)	
Physical function		
Valued Life Activity difficulty		0.57 ± 0.46 (0, 2.2)
Health Assessment Questionnaire		0.95 ± 0.66 (0, 2.4)
Short Physical Performance Battery		9.30 ± 2.44 (0, 12)

RADAI: RA Disease Activity Index.

Relationship between total cognitive function score and physical function measures. In bivariate regression models, total cognitive function score was significantly associated with all 3 physical function measures (SPPB: β = –0.26, p = 0.004; HAQ: ß = 0.33, p < 0.001; VLA: β = 0.25, p = 0.006; Table 4). All 3 multivariate regression models were statistically significant and the 8 variables in the model accounted for 17%, 43%, and 49% of the variance in physical function measures (i.e., SPPB, HAQ, and VLA, respectively). Total cognitive function score was significantly associated with greater functional limitations on both performance-based and self-reported tests (SPPB: β = –0.24, p = 0.014; HAQ: β = –0.24, p = 0.003) even after controlling for sex, race, education level, CV comorbidity, duration of RA, severity of RA, and depression. For each 1 SD increase in total cognitive function score, the SPPB decreased by 0.24 SD, holding all other variables constant. With a 1 SD increase in total cognitive function score, the HAQ increased by 0.24 SD, holding all other variables constant. However, total cognitive function score was not significantly associated with greater self-reported disability (VLA: β = 0.10, p = 0.207), controlling for all other variables in the model. Among disease-related factors, longer duration of RA was significantly associated with all 3 physical function measures (SPPB: β = –0.22, p = 0.015; HAQ: β = 0.33, p < 0.001; VLA: β = 0.23, p = 0.002). Greater severity of RA was significantly associated with worse physical function measured by the HAQ (β = 0.39, p < 0.001) and the VLA (β = 0.50, p < 0.001). CV comorbidity was found to be significantly associated with greater VLA disability only (β = 0.18, p = 0.013). Depression appeared to be associated with the VLA disability, although the relationship was not statistically significant (β = 0.13, p = 0.087).

Table 2. Characteristics of performance on individual neuropsychological tests.

Characteristics	Mean ± SD (range) of Raw Z Scores	N (%) ≤ 1 SD	N (%) ≤ 1.5 SD	N (%) ≤ 2 SD
Verbal learning and memory impairment				
CVLT Learn	0.6 ± 1.2 (–4, 3.2)	12 (9.8)	5 (4.1)	2 (1.6)
CVLT Short Delay Free Recall	0.3 ± 1.2 (–4.5, 2)	24 (19.7)	8 (6.6)	6 (4.9)
CVLT Long Delay Free Recall	0.1 ± 1.2 (–5, 1.5)	23 (18.9)	13 (10.7)	10 (8.2)
Visuospatial learning and memory impairment				
Rey-O Complex Figure Test Copy	–0.6 ± 1.6 (–5.9, 1)	35 (28.7)	27 (22.1)	21 (17.2)
Rey-O Immediate Delay	0.4 ± 1.2 (–2.5, 4.4)	16 (13.1)	7 (5.7)	2 (1.6)
Rey-O Long Delay	0.4 ± 1.3 (–2.9, 4.2)	19 (15.6)	7 (5.7)	3 (2.5)
Fluency impairment				
Phonemic fluency	0.4 ± 1.2 (–2.4, 5.2)	11 (9.0)	6 (4.9)	2 (1.6)
Semantic fluency	0.5 ± 1.1 (–1.9, 3.3)	10 (8.2)	2 (1.6)	0 (0)
Design fluency	–0.4 ± 0.9 (–3, 1)	35 (28.7)	12 (9.8)	11 (9.0)
Executive function impairment				
Color-Word Inhibition	0.2 ± 0.9 (–2.3, 2.3)	17 (13.9)	4 (3.3)	3 (2.5)
Color-Word Switching	0.3 ± 0.9 (–3, 2.7)	13 (10.7)	4 (3.3)	3 (2.5)
Card Sorting	0.2 ± 0.9 (–2.3, 3)	15 (12.3)	7 (5.7)	4 (3.3)
Trail Making Condition 4	–0.3 ± 0.7 (–2.3, 1.7)	25 (20.5)	7 (5.7)	3 (2.5)
Visuospatial impairment				
Judgment of Line Orientation	0.2 ± 0.9 (–3.1, 1.4)	14 (11.5)	5 (4.1)	2 (1.6)
Working Memory and Speed Processing Impairment				
Symbol Digit Modalities	–0.2 ± 0.9 (–2.2, 2.3)	22 (18.0)	8 (6.6)	3 (2.5)
Digit Span Backward	0.1 ± 1 (–3.7, 2.2)	13 (10.7)	3 (2.5)	2 (1.6)

CVLT: California Verbal Learning Test.

Table 3. Cognitive function summary scores.

Types of Scores	Mean ± SD (range)	N (%)
Global cognitive function		
Total cognitive function score	2.5 ± 2.1 (0, 9)	
At least 4 (25%) of cognitive tests impaired		37 (30.3)
Executive function		
Total executive function score*	1.3 ± 1.3 (0, 6)	
At least 2 (25%) of executive tests impaired		43 (35.2)
Memory function		
Total memory function score**	1.1 ± 1.4 (0, 5)	
At least 2 (25%) of memory tests impaired		37 (30.3)

* Total executive function score = fluency impairment + executive function impairment + working memory and speed processing impairment. ** Total memory function score = verbal learning and memory impairment + visuospatial learning and memory impairment.

Table 4. Relationship between cognitive function scores and physical function measures.

Score and Function	Bivariate Std. ß**	p	Multivariate* Std. ß**	p
Global cognitive function				
Regression 1: SPPB†	–0.26	0.004	–0.24	0.014
Regression 2: HAQ	0.33	< 0.001	0.24	0.003
Regression 3: VLA difficulty	0.25	0.006	0.10	0.207
Executive function				
Regression 1: SPPB†	–0.14	0.125	–0.07	0.458
Regression 2: HAQ	0.29	0.001	0.16	0.046
Regression 3: VLA difficulty	0.22	0.016	0.04	0.603
Memory function				
Regression 1: SPPB†	–0.24	0.008	–0.25	0.009
Regression 2: HAQ	0.21	0.022	0.18	0.029
Regression 3: VLA difficulty	0.17	0.055	0.11	0.163

* Covariates: sex, race, education level, duration of rheumatoid arthritis (RA), severity of RA, cardiovascular comorbidity, and depression. ** Std. ß are for the effect of the independent variable (cognitive function scores) on each physical function measure (SPPB, HAQ, and VLA). † On SPPB, lower scores reflect worse functioning; on HAQ and VLA, higher scores reflect worse functioning. SPPB: Short Physical Performance Battery; HAQ: Health Assessment Questionnaire; VLA: Valued Life Activities.

Additional analyses. In bivariate regression models, total executive function score was significantly associated with the HAQ (β = 0.29, p = 0.001) and the VLA (β = 0.22, p = 0.016; Table 4). All 3 multivariate regression models were statistically significant and the 8 variables in the model accounted for 12%, 40%, and 49% of the variance in physical function measures (i.e., SPPB, HAQ, and VLA, respectively). Total executive function score was significantly associated with greater functional limitations measured by the HAQ after controlling for other covariates in the model. In bivariate regression models, total memory function score was significantly associated with the SPPB (β = –0.24, p = 0.008) and the HAQ (β = 0.21, p = 0.022; Table 4). All 3 multivariate regression models were statistically significant and the 8 variables in the model accounted for 17%, 41%, and 49% of the variance in physical function measures (i.e., SPPB, HAQ, and VLA). Total memory function score was significantly associated with greater functional limitations measured by the SPPB (β = –0.25, p = 0.009) and the HAQ (β = 0.18, p = 0.029) after controlling for other covariates in the model.

DISCUSSION

In our study, we sought to identify the relationship between cognitive impairment and physical function difficulties (functional limitations and disability) in persons with RA. It is possible that cognitive function is associated with actual performance of physical functioning, with perceptions of that performance (i.e., with self-reports), or with both. In bivariate regression models, total cognitive function score was significantly associated with all 3 physical function measures. But in multivariate regression models, after controlling for covariates, cognitive impairment was significantly associated with greater functional limitations on both performance-based and self-reported tests, but not with greater self-reported disability.

The hypothesis of our study was supported — that cognitive impairment would be independently related to increased functional limitations in persons with RA even after controlling for other covariates. Decreased cognitive function was found to be significantly associated with increased functional limitations assessed with both performance-based and self-reported measures. These results are consistent with previous studies in the general population with or without various health conditions[8,9].

In contrast, cognitive function was not significantly associated with our self-reported measure of disability in VLA after controlling for covariates. The major question arising from this result is why self-report of disability would not be associated with cognitive function while self-report of functional limitations was associated. This finding suggests that other factors, such as psychological symptoms, may be more influential in determining VLA disability. Depression may play a larger role in self-reports of disability than of functional limitations, and may supplant the effects of cognitive impairment. Many previous studies that found depression to be a significant factor of disability and poor health outcomes support this explanation. For example, Mella, *et al*[41] found that more than 50% of patients with RA had depressive symptoms, and depressed subjects had greater disability than nondepressed subjects. Morris and colleagues[42] found that longterm patterns of depression, both intermittent and chronic, had significant adverse effect on disability and perceived health status in RA even after controlling for demographics, disease-related factors, and physical limitations.

It might be expected that cognitively impaired persons

would be inaccurate reporters of their functioning. Our results suggest that, for functional limitations, this may not be true, based on the correspondence between findings from the observed and self-reported measures of functional limitations. Because self-reports of functional limitations may be quite concrete (e.g., items query a very specific task, such as opening a car door), responses may be less affected by cognitive impairments. On the other hand, items to assess disability may be more complex and require consideration of more elements [e.g., how much difficulty do you have opening a car door (functional limitation) vs how much difficulty do you have traveling in a car (disability)]. More study is required to clarify both these associations and the measurement issues they raise.

Nearly one-third of subjects in our study were classified as cognitively impaired on 4 or more out of 16 subtests. About 20%–30% of subjects were found to be cognitively impaired in domains evaluating executive function; specifically, 29% in the nonverbal fluency test and 21% in the sequencing and set shifting test. Similarly, 20% and 29% of subjects were classified as cognitively impaired in domains evaluating verbal learning/memory and visuospatial learning/memory, respectively. The prevalence rates of this population were lower than those of other populations, for example, SLE or multiple sclerosis. In a study by Baumstarck-Barrau and colleagues[43], 37%–78% of patients with multiple sclerosis were classified as cognitively impaired. The prevalence of cognitive impairment in patients with SLE has been found to be 13%–81%, depending on the methodology used[44,45,46]. However, our results are analogous to the few previous studies of cognitive functioning in patients with RA. For example, Appenzeller and colleagues[4] found cognitive impairment in 30% of their well-characterized RA cohort. We found slightly lower prevalence rates in comparison to another study by Bartolini, *et al*[5], who observed cognitive dysfunction in 38%–71% of their cohort of patients with RA. Although direct comparisons among studies may not be made because of the different classifications of cognitive impairment, diverse assessment methods used, and differences in subject characteristics, our results coupled with these previous studies imply the significance of cognitive problems in RA. Further studies are needed to assess cognitive function with standardized criteria and methodologies in patients with RA.

A similar proportion of subjects was impaired on executive function (35%) and memory function (30%) when compared to global cognitive function (30%). In multivariate regression analyses, unexpectedly, total executive function test score was significantly associated only with the HAQ. Total memory function test score was significantly associated with the SPPB and the HAQ. Because executive function tests included motor planning assessment, we expected a stronger relationship between total executive function score and physical function measures. This somewhat counterintuitive finding might be due to using only 1 type of motor planning test (Trail Making Test), the limited number of subjects, or the characteristics of our cohort, which was more impaired on memory function tests than on executive function tests. This finding also suggests that in patients with RA, an overall burden of cognitive impairment affects functioning, rather than specific types of cognitive impairment. Further study is needed of the relationship between specific subdomains of cognitive function and physical functioning.

Several mechanisms have been hypothesized to influence cognitive function in persons with RA, including the systemic inflammatory process, chronic pain, psychological distress, and longterm glucocorticoid use[4]. Regardless of the source, our findings suggest that cognitive impairment should be considered in clinical settings as a significant factor that may affect functional status among persons with RA and may place them at risk for disability. Prevention strategies to avoid further functional decline could be targeted toward these individuals. For example, the Restorative Care Intervention for the Cognitively Impaired[47], a motivational intervention for both nursing staff and clients emphasizing restoration and/or maintenance of physical function, can be an effective intervention for older adults with cognitive impairment to improve depressive symptoms and disturbing behaviors. The improvement of psychological status and behavioral symptoms in persons with cognitive impairment can in turn lead to preserving and/or promoting functioning.

Our study has limitations. The sample for our study may not be representative of all patients with RA for several reasons. Many subjects were participants in a longterm prospective study of RA (active since 1983) and may be relatively healthy survivors. Only persons who lived in the San Francisco Bay Area who were able to travel to the UCSF clinical research center were included in the study, perhaps also biasing the sample toward healthier individuals. Subjects were primarily white with relatively advanced education and high income, which might limit the generalization of the study findings to certain groups. High education status is potentially protective against cognitive impairment or dementia. Therefore, RA patients with low education status may have more severe cognitive impairment and physical function difficulties.

The classification criterion of cognitive impairment in our study (i.e., if subjects performed 1 SD below age-adjusted population norms) may be less conservative than some other studies, but it is comparable in stringency to other studies in rheumatic disease[24,34]. It was our intent to evaluate the spectrum of cognitive impairment in this condition, because even mild levels of impairment can disrupt daily functioning. Additionally, this cohort was highly educated, and we wanted to minimize the risk of

false-negatives in our criteria selection. Some studies found that neuropsychologically healthy individuals might produce abnormal scores depending on the number of tests performed and the cutoff point used to define cognitive impairment[48,49,50,51]. For example, Schretlen and colleagues[50] found that 35% of subjects obtained 2 or more abnormal adjusted T scores out of 10 tests when using the cutoff point of 1 SD below the population mean. In another study, by Axelrod and Wall[51], 29% of healthy young adults produced impaired scores on 3 or more of 7 measures. Therefore, the findings of our study should be cautiously interpreted.

Individuals who are cognitively impaired may be inaccurate reporters of their functioning. However, our use of a performance-based measure served to at least partially mitigate this limitation. A cross-sectional study cannot provide causal information about the variables. In spite of statistically significant findings regarding the relationship between the 2 variables of interest, whether cognitive impairment caused physical function difficulties or the reverse could not be determined in this cross-sectional study. A longitudinal study design is required to identify the causal relationship between the independent and dependent variables.

Our study has several strengths. Cognitive function was assessed using a standardized neuropsychological battery covering a wide spectrum of cognitive domains that provided richer information compared with bedside mental status screening tests. To our knowledge, this is the first study that has identified the relationship between cognitive function and physical function in persons with RA. Using both subjective and objective measures, our study provided unique and comprehensive information about physical function difficulties in daily life and minimized potential bias that could be produced by use of self-report measures only.

Our study has significant implications for clinical practice. Intact cognitive function in patients with chronic diseases is important for performing fundamental daily activities and managing complex health conditions such as RA. Identifying factors that exacerbate or enhance physical function is an initial step in health management and may support the continued development of effective interventions for patients. Our results emphasize the risk of cognitive impairment in patients with RA, and the importance of assessing cognitive status in clinical settings to identify risk factors of functional decline. Some persons with RA may benefit from interventions modified for cognitively impaired patients or designed to improve cognitive function; such interventions may, in turn, be effective in enhancing or maintaining physical function and ultimately in promoting quality of life.

ACKNOWLEDGMENT

We thank Dr. Shin's adviser, Dr. Margaret Wallhagen, for her encouragement, guidance, and support.

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