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The Relationship between Perceived Cognitive Dysfunction and Objective Neuropsychological Performance in Persons with Rheumatoid Arthritis

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Abstract

OBJECTIVE—Research shows a gap between perceived cognitive dysfunction and objective neuropsychological performance in persons with chronic diseases. We explored this relationship in persons with rheumatoid arthritis (RA).

METHODS—Individuals from a longitudinal cohort study of RA participated in a study visit that included physical, psychosocial, and biological metrics. Subjective cognitive dysfunction was assessed using the Perceived Deficits Questionnaire (PDQ; 0–20, higher scores = greater perceived impairment). Objective cognitive impairment was assessed using a battery of 12 standardized neuropsychological measures yielding 16 indices. 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 transformed scores (0–16, higher scores = greater impairment). Multiple linear regression analyses determined the relationship of total cognitive function score with PDQ score, controlling for gender, race, marital status, income, education, disease duration, disease severity, depression, and fatigue.

RESULTS—120 subjects (mean ± SD age: 58.5 ± 11.0 years) were included. Mean ± SD scores of total cognitive function and PDQ were 2.5 ± 2.2 (0–10) and 5.8 ± 3.8 (0–16), respectively. In multivariate analysis, there was no significant relationship between total cognitive function score and PDQ score. However, depression and fatigue ($\beta = 0.31$, $p < 0.001$; $\beta = 0.31$, $p = 0.001$) were significantly associated with PDQ score.

CONCLUSION—The findings emphasize the gap between subjective and objective measures of cognitive impairment and the importance of considering psychological factors within the context of cognitive complaints in clinical settings.

INTRODUCTION

For persons with chronic diseases such as rheumatoid arthritis (RA), intact cognitive function is critical for performing daily activities and adhering to self-management regimens (1). Few studies have examined cognitive function in RA using methods that extend beyond conventional bedside mental status screening exams. In one study, cognitive dysfunction

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was observed to be common in RA patients with prevalence rates ranging from 38% to 71% (2). Appenzeller and colleagues (3) found cognitive impairment in 30% of a Brazilian RA cohort as compared to 8% of healthy controls. These studies have important implications in that they highlight the potential burden of cognitive impairment and its possible risk factors in RA patients who have not been widely investigated.

In clinical settings, evaluating cognitive function using objective measures holds particular challenges including the limited access to neuropsychological services, length of examinations, and costs (4). One method of screening for cognitive impairment that has been especially appealing is the administration of self-reported assessments of perceived cognitive functioning. However, in some populations, research generally has shown a gap between self-reported cognitive dysfunction (i.e., subjective measure) and neuropsychological performance (i.e., objective measure). Although there are mixed findings, some studies have observed no significant relationship between subjective and objective measures of cognitive dysfunction (4–6). Instead, they found that psychological distress, depression or fatigue, was significantly correlated with perceived cognitive dysfunction.

To our knowledge, no study has explored the relationship between perceived cognitive dysfunction and objective neuropsychological performance in persons with RA. This question seems particularly important to address in RA given the increasing appreciation of the burden of cognitive impairment in RA combined with high levels of psychological distress (e.g., depression and fatigue) commonly observed in this health condition. Therefore, the purpose of this study was to explore the relationship between perceived cognitive dysfunction and objective neuropsychological performance in persons with RA, with particular consideration of symptoms of depression and fatigue as confounding factors.

METHODS

Sample and Setting

Subjects were drawn from the University of California, San Francisco (UCSF) RA Panel, which was initiated in 1982. Details about enrollment and data collection have been described previously (7). Briefly, a random sample of rheumatologists practicing in Northern California recruited participants with RA presenting in their offices over a one month period. Eight hundred twenty two persons were enrolled between 1982 and 1983, supplemented with four additional recruitments from 1989 to 2003. Trained interviewers have 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 the UCSF were recruited for in-person assessments at the UCSF Clinical Research Services (CRS) facility. In 2009, 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 research visits, 60% of those who were recruited and deemed 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, 120 subjects who had complete data on all outcomes and covariates of interest were included in this study. The research protocol was approved by the

UCSF Committee on Human Research, and all subjects gave their informed consent to participate.

Measures

Subjective measure of cognitive function—Perceived cognitive dysfunction was assessed using the Perceived Deficits Questionnaire-5 item version (PDQ) (8, 9), which has been utilized as a reliable and valid tool in patients with chronic health conditions (10, 11). The PDQ determines how often people have experienced perceived cognitive problems during the past four weeks, and covers four domains: attention/concentration, retrospective memory, prospective memory, and planning/organization. It includes five items such as "how often did you have trouble getting things organized" and "how often did you have trouble concentrating on things like watching a television program or reading a book," each of which is scored on a five-point scale (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = almost always). Total PDQ score can be calculated by summing raw scores, ranging from 0–20 (higher scores = greater perceived impairment).

Objective measure of cognitive function—Cognitive function was objectively assessed using a standardized neuropsychological battery that was modified from the American College of Rheumatology (ACR) neuropsychological battery (12). It was initially developed and recommended for patients with systemic lupus erythematosus, and has been deemed reliable and valid (13, 14). We modified it for use in RA to minimize or control for the effects of hand-motor dysfunction in these patients.

Neuropsychological tests included the California Verbal Learning Test-II (15) Learning, Short Delay, and Long Delay Recall; the Rey-Osterrieth Complex Figure Test (16) Copy Trial, Immediate Delay, and Long Delay Recall; the Controlled Oral Word Association Test and the Animal Naming Test (17); the oral version of the Symbol Digit Modalities Test (18); the Delis Kaplan Executive Function Scale, including Card Sorting Test (Total Correct), Design Fluency Test (Total Correct), Trail Making Test (Timing for Sequencing/Shifting Condition), and Color Word Inference Test (19) Inhibition and Switching Conditions; the Wechsler Adult Intelligence Scale-III Digit Span Backwards Test (20); and the short form Judgment of Line Orientation Test (21, 22). The duration of the neuropsychological battery was approximately 60 to 80 minutes in length.

Neuropsychological tests were scored to yield z-scores based on age-stratified population norms, and sixteen neuropsychological indices were derived. Using conventional cut points, subjects were classified as "impaired" if they performed 1 SD below age-stratified population norms for each cognitive index (13, 23). Total cognitive function score was calculated by summing the transformed scores, ranging from 0 to 16 (higher scores = greater impairment). For subjects who completed at least 80% of the 16 subtests (≥13), but did not complete up to three of the subtests, the mean z-score of the subtests that they did complete was substituted as the scores for the missing subtests before the total cognitive function score was created.

Covariates—Self-reported information on sociodemographics and disease characteristics were assessed as covariates. Severity of RA was assessed using the Rheumatoid Arthritis Disease Activity Index (RADAI) (24, 25), a patient-assessed measure of disease activity in RA, covering global disease activity in the past 6 months; current joint pain, tenderness, and swelling; and current duration of morning stiffness. RADAI score ranges from 0 to 10, with higher scores reflecting greater disease activity. It has been shown to be reliable and valid (24, 25).

Depression was assessed using the Mini International Neuropsychiatric Interview (MINI) (26, 27), a short diagnostic structured interview corresponding to the Diagnostic and Statistical Manual (DSM)-III-R 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 (26, 27).

Fatigue was assessed using the Multidimensional Assessment of Fatigue (MAF) scale consists of 16 items assessing four dimensions of fatigue for the past week, including severity, distress, degree of interference in activities of daily living, and timing (28, 29). The MAF has been tested to be reliable and valid in many chronic conditions including RA(30–32). For these analyses, we used the fatigue severity score, which ranges from 0–10 with higher scores indicating greater fatigue.

ANALYSES

Bivariate and multivariate linear regression analyses were conducted to identify the relationship between total cognitive function and PDQ scores, controlling for other covariates (gender, race, marital status, income, education, disease duration, disease severity, depression, and fatigue). We also identified covariates that were significantly associated with PDQ scores. The limit for significance was set at two-tailed $\alpha = .05$. All analyses were conducted using the Statistical Package for the IBM SPSS Statistics, version 19.0.

RESULTS

Subject characteristics are presented in Table 1. Mean ± SD age of 120 subjects was 58.5 ± 11.0 years. Sixty four percent were female, 82% were white, and 63% were married/living with partners. Mean ± SD educational level was 15.3 ± 2.2 years and disease duration was 19.9 ± 11.1 years. Mean ± SD MAF score was 4.7 ± 2.5 (range: 0.5–10), and 7% met the criteria for major depressive disorder. Mean ± SD PDQ score was 5.8 ± 3.8 (range: 0–16). Mean ± SD total cognitive function score was 2.5 ± 2.2 (range: 0–10). 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 classified as cognitively impaired on four or more out of 16 subtests was 31% (Table 2).

In bivariate regression models, total cognitive function score was significantly associated with PDQ score ($\beta = .26$, $p = 0.004$). Psychological factors, depression and fatigue, were also strongly correlated with PDQ score ($\beta = .42$, $p < 0.001$; $\beta = .40$, $p < 0.001$) (Table 3). Multivariate regression model with 10 covariates was statistically significant and accounted for 31% of the variance in perceived cognitive dysfunction. Total cognitive function score was not significantly associated with PDQ score ($\beta = .104$, $p = 0.250$) after controlling for gender, race, marital status, income, education, disease duration, disease severity, depression, and fatigue. When examining the regression results for factors that were associated with perceived cognitive dysfunction, both depression and fatigue were significantly associated with PDQ score ($\beta = .308$, $p < 0.001$; $\beta = .316$, $p = 0.001$).

DISCUSSION

In this study, we explored the relationship between perceived cognitive dysfunction and objective neuropsychological performance in persons with RA. Almost one-third of subjects had cognitive impairment as determined by performance significantly below age-based population norms on a comprehensive neuropsychological battery. The proportion of persons who were classified as cognitively impaired on each subtest ranged from 8% to 29%. In multivariate model, there was no significant relationship between subjective and

objective measures of cognitive impairment controlling for sociodemographics, disease characteristics, depression, and fatigue. This finding suggests that self-reported cognitive function may not be an adequate substitute for performance-based cognitive function.

The cognitive subdomains that were most commonly affected were design fluency (29%) and visuo-spatial learning/memory (28%). These results are analogous to previous studies by Appenzeller and colleagues (3) who found cognitive impairment in 30% of the RA cohort, with worse outcomes in domains evaluating verbal fluency and episodic memory. We found slightly lower prevalence rates in comparison to another study by Bartolini et al. (2), who observed cognitive dysfunction in 38% (divided/sustained attention and mental flexibility) to 71% (visuo-spatial and planning functions) of their cohort of RA patients.

Discrepancies between subjective and objective measures of cognitive impairment have been reported in several other groups of patients, including persons with multiple sclerosis (4, 6), cancer (33, 34), and epilepsy (35). Our findings extend these previous results to RA patients. Although the criteria and measures used to assess cognitive function were different, the gap between subjective and objective cognitive dysfunction was consistently found across the studies. Further studies evaluating these relationships in more diverse and representative subjects are warranted.

Depression and fatigue were both significantly associated with perceived cognitive dysfunction in this study. This result is analogous to the aforementioned studies (4–6, 33–35) observing similar correlations of depression or fatigue with perceived cognitive complaints, and emphasizes the potential role of other factors that may influence the perceptions and reports of cognitive dysfunction in persons with RA.

A routine neuropsychological evaluation would be beneficial for most patients with cognitive complaints or suspected cognitive impairment. However, this method is not always available in clinical settings due to limited access to neuropsychological services, high costs, and time constraints (4). Therefore, there may be value in using self-reported measures, which are brief and cost-effective as screening approaches to detect cognitive impairment efficiently. However, our study suggests some caution in using these approaches in RA and confirms previous studies observing stronger associations with other psychological factors including depression and fatigue as compared to objective neuropsychological performance. Therefore, these factors should be considered when interpreting the results of self-reported measures of cognitive dysfunction. Using measures of perceived cognitive impairment in combination with consideration of other factors that may contribute to a patient's reported cognitive functioning may help to identify patients who would benefit from a more comprehensive neuropsychological assessment and/or a mental health screening examination (36).

This study has significant implications for clinical practice. While self-reported measures of cognitive dysfunction may have limitations, they may still have a clinical usability and a patient's report of cognitive impairment should be considered as clinically meaningful. These measures can capture a patient's experience of his/her cognitive performance and may have the potential to identify very mild cognitive changes noticeable to the patient but not yet detected on the conventional neuropsychological assessment (36). In addition, a comparison of self-reported measures to proxy-reported measures and objective neuropsychological performance can provide important information about a patient's insight into his/her own functioning.

This study may have some limitations. The sample for this study may not be representative of all patients with RAfor several reasons. Many subjects were participants of a long-term prospective study of RA (active since 1983) and may be relatively healthy survivors who

have been able to participate in long-term research studies. Only persons who lived in the San Francisco Bay Area and were able to travel to the UCSF CRS visit were included in the study, perhaps also biasing the sample toward more healthy individuals. Subjects were primarily white with relatively high education and income, which might limit the generalization of the study findings to certain groups. Lack of a matched control group limits out ability to attribute findings to RA specifically.

The classification criteria of cognitive impairment in this study (i.e., performance 1 SD below age-adjusted population norms on each neuropsychological test) may be less conservative than some other studies, but also is comparable in stringency to other studies in rheumatic disease (13, 23). It was our intent to evaluate the spectrum of cognitive impairment in this condition, as even mild levels of impairment can disrupt daily functioning. Additionally, this cohort was highly educated and we wanted to minimize risk of false negatives in our criteria selection.

A cross-sectional study could not provide causal information among the variables. In spite of statistically significant findings, whether depression and fatigue caused perceived cognitive dysfunction could not be determined. A longitudinal study design is required to identify the causal relationship between the variables of interest.

CONCLUSION

There was no significant relationship between perceived cognitive dysfunction and objective neuropsychological performance in patients with RA, after controlling for covariates. Depression and fatigue, however, were significantly associated with perceived cognitive dysfunction. The findings of this study emphasize the gap between subjective and objective measures of cognitive impairment and the importance of considering depression and fatigue within the context of cognitive complaints in clinical settings.

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SIGNIFICANCE & INNOVATION

- Intact cognitive function is critical for performing daily activities and adhering to self-management regimens for persons with chronic diseases such as rheumatoid arthritis (RA).
- This is one of the few studies that assessed a wide spectrum of cognitive domains in RA patients using both subjective and objective neuropsychological tests.
- The findings of this study emphasize the gap between subjective and objective measures of cognitive impairment, and the importance of considering depression and fatigue within the context of cognitive complaints in clinical settings.

Table 1

Characteristics of Subjects (N = 120)

	N (%)	Mean ± SD (Range)
Age in years		58.5 ± 11.0 (25–87)
Female	77 (64.2)	
White	98 (81.7)	
Education less than 12 years	18 (15)	
Married/living with partner	75 (62.5)	
Family income below $20,000	10 (8.3)	
Duration of RA in years		19.9 ± 11.1 (0–56)
Severity of RA(RADAI)		2.4 ± 1.6 (0–6.7)
Depression (MINI)	8 (6.7)	
Fatigue (MAF)		4.73 ± 2.48 (0.5–10)
Total cognitive function score		2.53 ± 2.18 (0–10)
Perceived cognitive dysfunction (PDQ)		5.83 ± 3.83 (0–16)

Table 2

Characteristics of Neuropsychological Test Performance

	Mean ± SD (Range) or N (%)
Verbal Learning and Memory Impairment	
CVLT Learn	12 (10.0)
CVLT Short Delay Free Recall	24 (20.0)
CVLT Long Delay Free Recall	23 (19.2)
Visuo-spatial Learning and Memory Impairment	
Rey-O Complex Figure Test Copy	33 (27.5)
Rey-O Immediate Delay	16 (13.3)
Rey-O Long Delay	18 (15.0)
Fluency Impairment	
Controlled Oral Word Association (Phonemic Fluency)	12 (10.0)
Animal Naming (Semantic Fluency)	10 (8.3)
Design Fluency	35 (29.2)
Executive Function Impairment	
Color-Word Inhibition	15 (12.5)
Color-Word Switching	12 (10.0)
Card Sorting	16 (13.3)
Trail Making Condition 4	25 (20.8)
Visuo-spatial Impairment	
Judgment of Line Orientation	13 (10.8)
Working Memory and Speed Processing Impairment	
Symbol Digit Modalities	22 (18.3)
Digit Span Backwards	14 (11.7)
At least 4 of cognitive tests impaired	37 (30.8)
Total Cognitive Function Score	2.5 ± 2.2 (0–10)

Table 3

The Relationship between Objective Cognitive Impairment and Subjective Cognitive Deficit

	Bivariate		Multivariate	
	Std. β	**p**	**Std. β**	**p**
Total cognitive function score	.26	.004	.104	.250
Depression (MINI)	.42	<.001	.308	**< .001** *
Fatigue (MAF)	.40	<.001	.316	**.001** *

* Covariates: Gender, race, marital status, family income, educational level, duration of RA, and severity of RA

* Significant at $p < 0.05$