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Cognition, mood, and purpose in life in neuromyelitis optica spectrum disorder

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1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare neurological condition that affects an estimated 4000–8000 people in the United States, making it about 100 times less prevalent than multiple sclerosis (MS) [1]. The criteria for a diagnosis of NMOSD, newly developed by the International Panel for NMOSD diagnosis, requires either the presentation of at least one core clinical characteristic of NMOSD and aquaporin-4 (AQP4)-IgG positivity in the absence of alternative diagnoses, or the presentation of at least two disseminated core clinical characteristics (one being optic neuritis, acute myelitis with longitudinally extensive transverse myelitis lesions, or area postrema syndrome) and fulfillments of MRI requirements in the case of optic neuritis acute myelitis, area postrema syndrome, and acute brainstem syndrome if the patient has a negative or unknown AQP4-IgG status [2].

Until recently it was assumed that the brain is largely spared in NMOSD, which led to the conclusion that higher cortical functions also remain unaffected by the disease. However, more recent studies report highly selective brain injury in NMOSD. The regions and extent of damage vary depending on the report, with some reporting damage to white matter but no loss of gray matter [3], while others report that white matter is spared but normal appearing gray matter is compromised in NMOSD [4]. Others account damage to both white and gray matter in NMOSD [5].

Cognition has only recently been studied in NMOSD, with the first report of impairments in cognitive function in the disease published in 2008 [6]. In two limited studies on cognition in NMOSD, the rates of cognitive impairment in NMOSD are similar to those observed in patients with MS, with approximately half of all NMOSD and MS patients displaying impaired cognitive performance [3,7]. Significant impairments in speed of information processing and sustained attention occur in NMOSD, and the degree of impairment is also similar to that observed in MS [6].

Few studies have characterized features of depression in NMOSD, with the first case of depression related to NMOSD reported in 2004 [8]. Similar to MS [9,10], rates and severity of depression are higher in NMOSD as compared to the general population [11]. In fact, two studies comparing depressive symptoms in NMOSD and MS reported more severe depression in NMOSD versus MS [12,13]. Depression has been linked to cognition in NMOSD, with more severe depression associated with worse cognitive function, while disease duration and EDSS scores do not appear to be related to mood in NMOSD [13].

The Purpose in Life (PIL) test was developed by Crumbaugh and Maholick based on the teaching of Dr. Viktor Frankl [14]. Dr. Frankl survived life in a concentration camp during the Holocaust, and during this time he noticed that those who seemed to have a higher purpose in life were more likely to survive. The PIL covers three dimensions of life purpose: the will to find meaning in existence, the freedom to create meaning in daily activities, and the will to find meaning in future challenges [15]. Higher life purpose has been linked to decreased incidence of a variety of physical ailments, including Alzheimer's disease (AD) [16], incident disability in the elderly [17], stroke [18], and myocardial infarction [19,20]. High purpose in life is also associated with increased participation in physical activity [21], not smoking [22], and use of

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Table 1
Summary of DANA cognitive tests.

Cognitive test	Structure	Targets
Code Substitution	9 symbol-digit pairs are shown in a key and one combination is displayed, subject determines if the combination matches the key.	Executive capacity, immediate memory, and attention
Spatial Processing	Pairs of 4-bar histograms are presented, one rotated 90°, subject determines if they are the same or different	Executive capacity and spatial manipulation
Simple Reaction Time	Subject taps on the location of an asterisk symbol as soon as it appears	Reaction time
Procedural Reaction Time	One of 4 numbers is displayed, subject must select if the number is a "2 or 3", or "4 or 5"	Executive functioning with decision making capabilities
Finger tapping test	Subject taps the screen with pointer finger of dominant hand as many times as possible within a given time	Motor function

preventative health care services [23]. PIL in NMOSD has not yet been studied.

Here, we sought to measure the relationship between cognition, mood, and PIL in NMOSD. This is the first study to assess PIL in NMOSD. Here, we compare PIL in NMOSD to non-NMOSD control subjects, and we examine the relationships between PIL, mood, and cognition in both cohorts.

2. Material and methods

2.1. Participants

Subjects were recruited from attendees of the Johns Hopkins Hospital NMO Patient Day, held on October 5, 2014. Attendees came from across the United States to attend a series of lectures, and numerous research studies were conducted in conjunction with the lectures. Family or friends of NMOSD patients also attending NMO Patient Day served as control subjects. Only willing participants were recruited into the study, and those attending NMO Patient Day who did not wish to participate in research studies could do so without penalty. 20 control subjects and 23 individuals with NMOSD completed a DANA battery of cognitive assessment tests (see description below), with an additional 1 NMOSD patient completing the Patient Health Questionnaire (PHQ-9) test and the PIL test, and another NMOSD patient completing the PIL test (total NMOSD n = 25). All participants provided general personal information, including age, gender, and highest level of education. NMOSD participants provided information related to their disease, including date of NMOSD onset, date of NMOSD diagnosis, number of relapses, time since last relapse, and current mobility status. Three of the 25 NMOSD subjects are AQP4-IgG seronegative, but all 25 meet the diagnostic criteria for NMOSD. All protocols were approved by the Johns Hopkins Institutional Review Board.

2.2. DANA cognitive assessment battery

Study subjects underwent a battery of cognitive tests on the neurocognitive assessment tool Defense Automated Neurobehavioral Assessment (DANA), developed by AnthroTronix, Inc. (Silver Spring, MD) [24]. The DANA tests are conducted on Samsung Galaxy tablets. The cognitive tests included in the current study were the Simple Reaction Time (SRT) test, Procedural Reaction Time (PRT) test, Spatial Processing (SP), and Code Substitution (CS) (Table 1). The primary outcome for cognitive tests was throughput, calculated as [(% correct) / (Reaction Time for correct responses) × 60,000]. In addition to the cognitive tests, the DANA battery also included a finger tapping test (FTT) to assess tapping motor function and the PHQ-9 to assess mood. In the FTT, the patient taps the tablet screen as many times as he or she can in a 10-second interval. Three consecutive trials were conducted with the dominant hand used to complete the cognitive test battery. The PHQ-9 is a standard and valid 9-question test to evaluate depression severity based on symptoms within the last two weeks [25].

2.3. Purpose in life

A subset of participants additionally completed a modified Purpose in Life (PIL) survey. The PIL survey consists of 20 Likert-style items, in which the patient self-ranks himself or herself on a scale of 1–7 with anchors to each question or statement [14]. For example, question 1 reads, "I am usually: 1(completely bored), 2, 3, 4 (neutral), 5, 6, 7 (exuberant, enthusiastic)", and the subject circles the number corresponding to his or her usual state.

2.4. Statistical analyses

Regression analyses were conducted using Stata 13.1 (College Station, TX). Univariate analyses were conducted for DANA cognitive tests, followed by multivariate analyses. Independent variables factored into the multivariate analyses included age, gender, highest level of education, mood (as determined by PHQ-9 test), and the reported number of hours of sleep the previous night. Data are presented as Mean ± SEM. P values less than 0.05 are considered statistically significant.

3. Results

Study participant information is presented in Table 2. The control group had a nearly equal ratio of males and females. Females were significantly overrepresented in the NMOSD group (n = 23/25, 92%, $P < 0.01$), in line with the 6.5:1 female predominance of NMOSD in American patients [26]. Mean age of participants was higher in controls versus NMOSD (50.97 ± 3.48 versus 44.03 ± 2.86 years, respectively), but this difference did not reach statistical significance (P = 0.13). Participants attained equivalent levels of education (Control = 14.7 ± 0.6, NMOSD = 14.96 ± 0.5).

DANA cognitive test responses require a finger tap from the participant. Because NMOSD subjects can have motor impairments that might

Table 2
Study Sample Characteristics.

	NMOSD n = 25	Control n = 20	P value
Gender (female)	23 (92%)	11 (55%)	0.004
Mean age (years)	44.03 ± 2.86	50.97 ± 3.48	0.128
Level of education (years)	14.96 ± 0.50	14.70 ± 0.59	0.736
Hours sleep, previous night	5.89 ± 0.39	6.58 ± 0.29	0.173
Disease duration (months)	65.09 ± 11.84		
# of days since last relapse	413.6 ± 131.0		
Total # of relapses	4.25 ± 0.82		
Mobility impairment			
Fully mobile	14 (56%)		
Occasional walking aid (e.g. cane)	3 (12%)		
Walking aid required	1 (4%)		
Occasional wheelchair	3 (12%)		
Wheelchair-bound	4 (16%)		

Data are presented as mean ± SEM or number of participants (% total).