



Quality of Life of HIV-negative, previously healthy individuals following cryptococcal meningoencephalitis: a cross-sectional study.



Owen Dean¹, Seher Anjum¹, Terri Scott¹, Lillian Ham², Katherine Traino², Jing Wang³, Sally Hunsberger³
John H Powers III⁴, Joseph Snow², Peter R Williamson¹

¹Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD USA

²National Institute of Mental Health, National Institutes of Health, Bethesda, MD USA

³Biostatistics Research Branch, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD USA

⁴Clinical Research Directorate, Frederick National Laboratory for Cancer Research, Frederick, MD USA

Background: Cryptococcal meningoencephalitis (CM) causes significant morbidity and mortality in HIV-negative, previously healthy populations. This group has significant disease sequelae including a fronto-subcortical syndrome, hearing loss, vision loss, and spinal arachnoiditis. However, the health-related quality of life (HRQOL) of this group of patients following microbial recovery from infection has not been reported.

Methods: We cross-sectionally defined the HRQOL of previously healthy individuals with CM seen at the NIH Clinical Center since 2013 using the Quality of Life in Neurological Disorders (Neuro-QoL) project. This includes forms which assess domains such as anxiety, fatigue, depression, dexterity and mobility in patients with chronic neurological disease. Form scores were calculated for each domain at least one year after diagnosis and centered to a general or clinical United States population reference. Impairment was considered a subject score of at least one half a standard deviation (SD) lower than the population reference average.

Results: Of 46 subjects with CNS disease (mean age 51.2 years, 59% male, mean time to survey from diagnosis 5.4 years), we identified moderate or severe self-reported impairment in at least one QOL domain in 61% of subjects at least one year following diagnosis. Self-reported cognitive impairment was noted in 52% and sleep disturbance was noted in 55%.

Conclusion: Moderate or severe HRQOL deficits were found in more than half of previously healthy individuals following microbial recovery from CM. These data reinforce and quantify the long-term morbidity of this disease and identify patient-centered outcomes for future interventional trials.

Table 1: Patient Demographic and Clinical Characteristics

| | CNS disease, n=46 | non-CNS disease, n=10 |
|--|-----------------------|-----------------------|
| Age at Diagnosis, median years [IQR] | 51.2 [37.2-60.4] | 42.9 [34.0-53.3] |
| Diagnosis to HRQOL survey, median years [IQR] | 5.4 [2.4-8.4] | 8.3 [4.8-8.6] |
| Gender, male/female (% male) | 27/19 (59) | 3/7 (30) |
| Race, n (%) | | |
| White | 36 (78) | 7 (70) |
| Black/African American | 3 (7) | 1 (10) |
| Asian | 3 (7) | 1 (10) |
| American Indian/Alaska Native | 1 (2) | 0 (0) |
| Multiracial or other | 3 (7) | 1 (10) |
| Ethnicity, n (%) Hispanic | 4 (4) | 1 (2) |
| Cryptococcal Isolate | | |
| <i>C. neoformans</i> | 16 (35) | 3 (30) |
| <i>C. gattii</i> | 12 (33) | 2 (20) |
| unknown | 18 (39) | 5 (50) |
| CSF glucose at diagnosis, median [IQR] mg/dL n=22 | 30 [19-51] | N/A |
| CSF Cryptococcal Antigen titer at diagnosis, median [IQR] n=22 | 1:1236 [1:448-1:2048] | N/A |
| Neurosurgical Intervention during hospitalization*, no. (%) | 19 (44) | N/A |

CSF: cerebrospinal fluid; *18/19 with neurosurgical intervention (95%) had a ventriculoperitoneal shunt placement, 1 (5%) had a lumbar drain placement

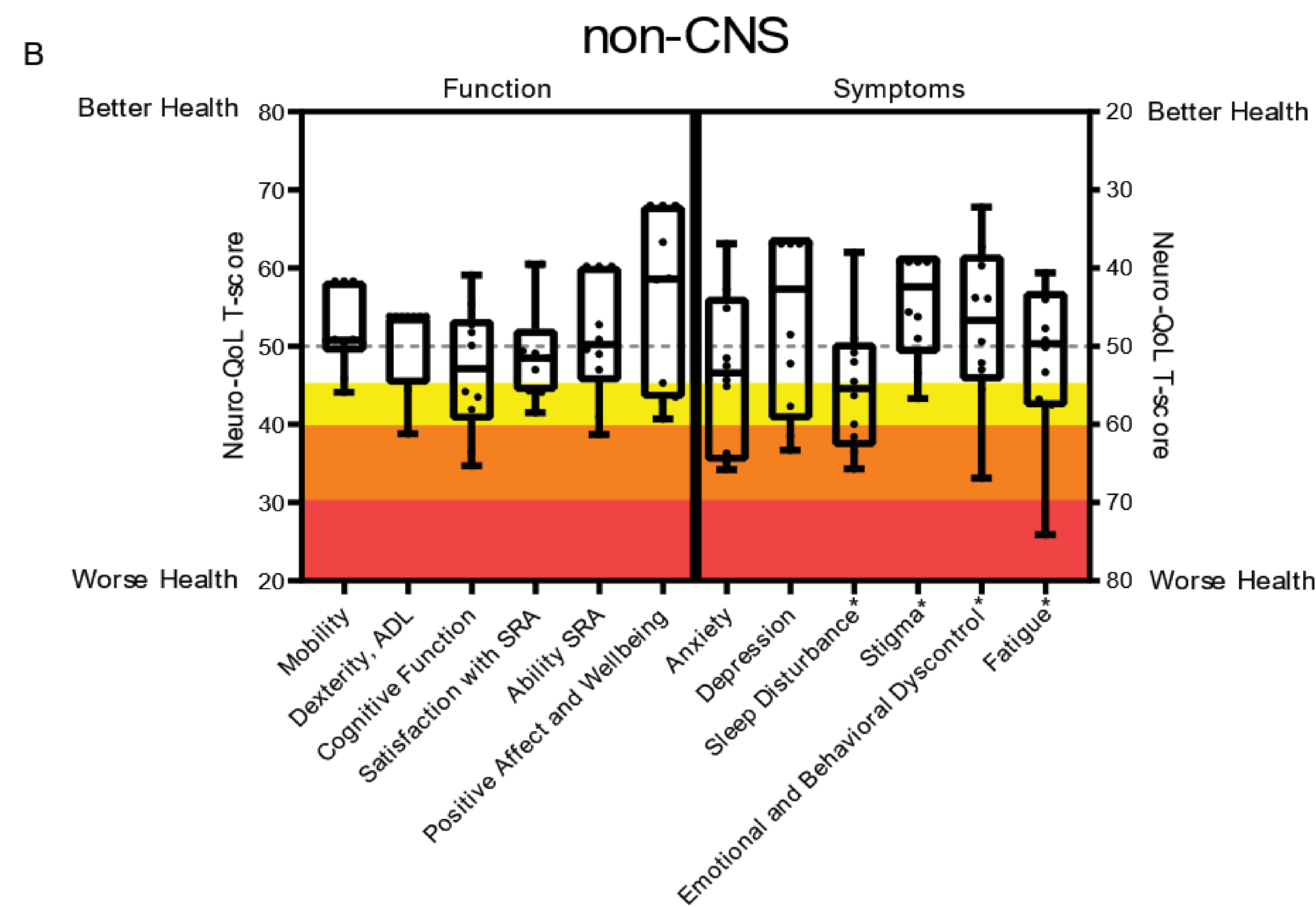
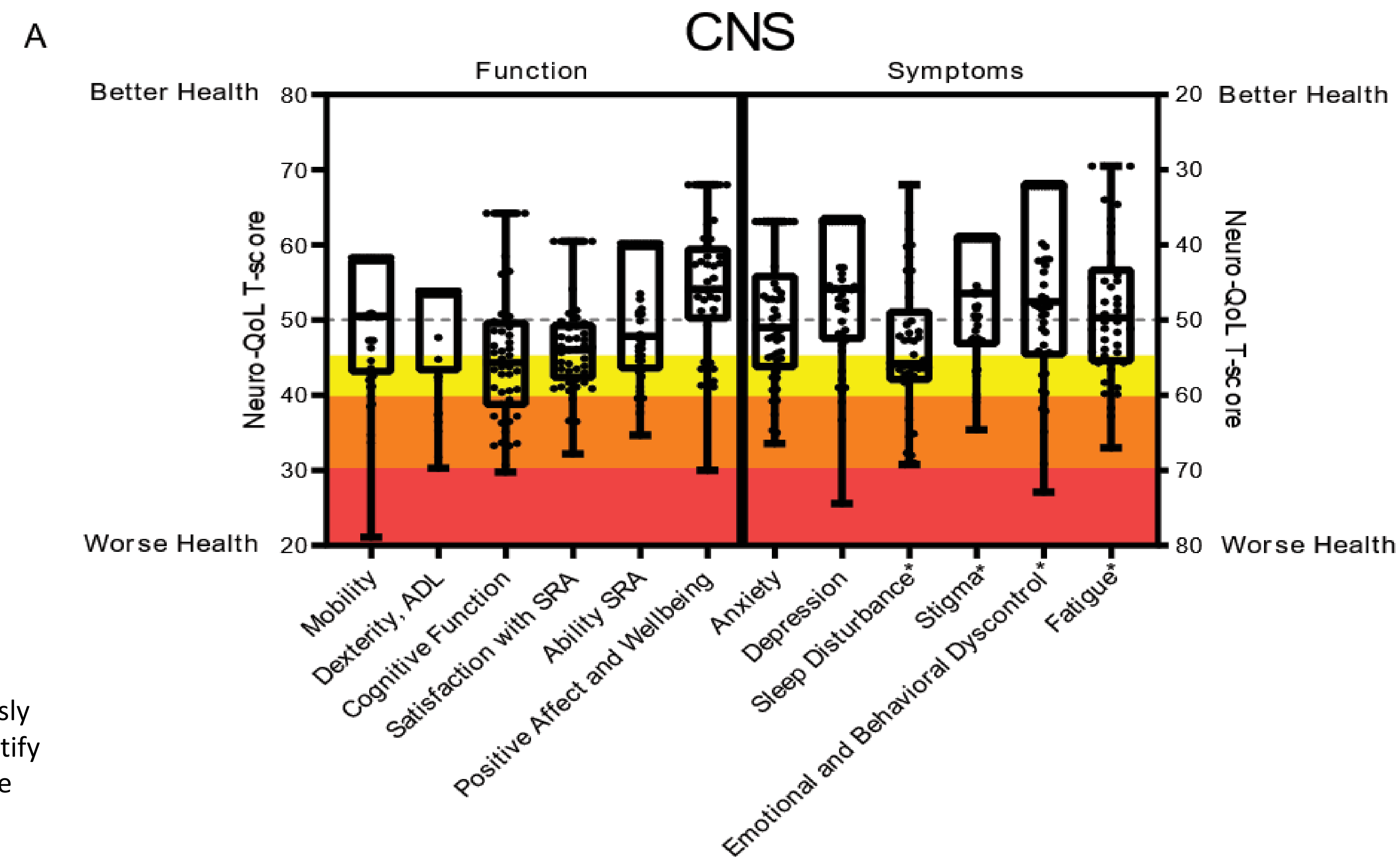


Figure 1: Patient reported quality of life following microbial recovery from cryptococcosis by population scaled Neuro-QoL domains. **A:** subjects with CNS cryptococcosis (n=46). **B:** non-CNS cryptococcosis subjects (n=10). Box plots show median, 25th, and 75th percentiles. The yellow region designates mild symptoms or impairment, orange, moderate, and red, severe. The gray dotted line represents the mean T-score (50) of the U.S. population reference for each Neuro-QoL domain. The asterisk* indicates measures that were centered to U.S. clinical reference population. All other domains were centered to a U.S. general population reference. Abbreviations: CNS, central nervous system, ADL, activities of daily living, SRA, social roles and activities

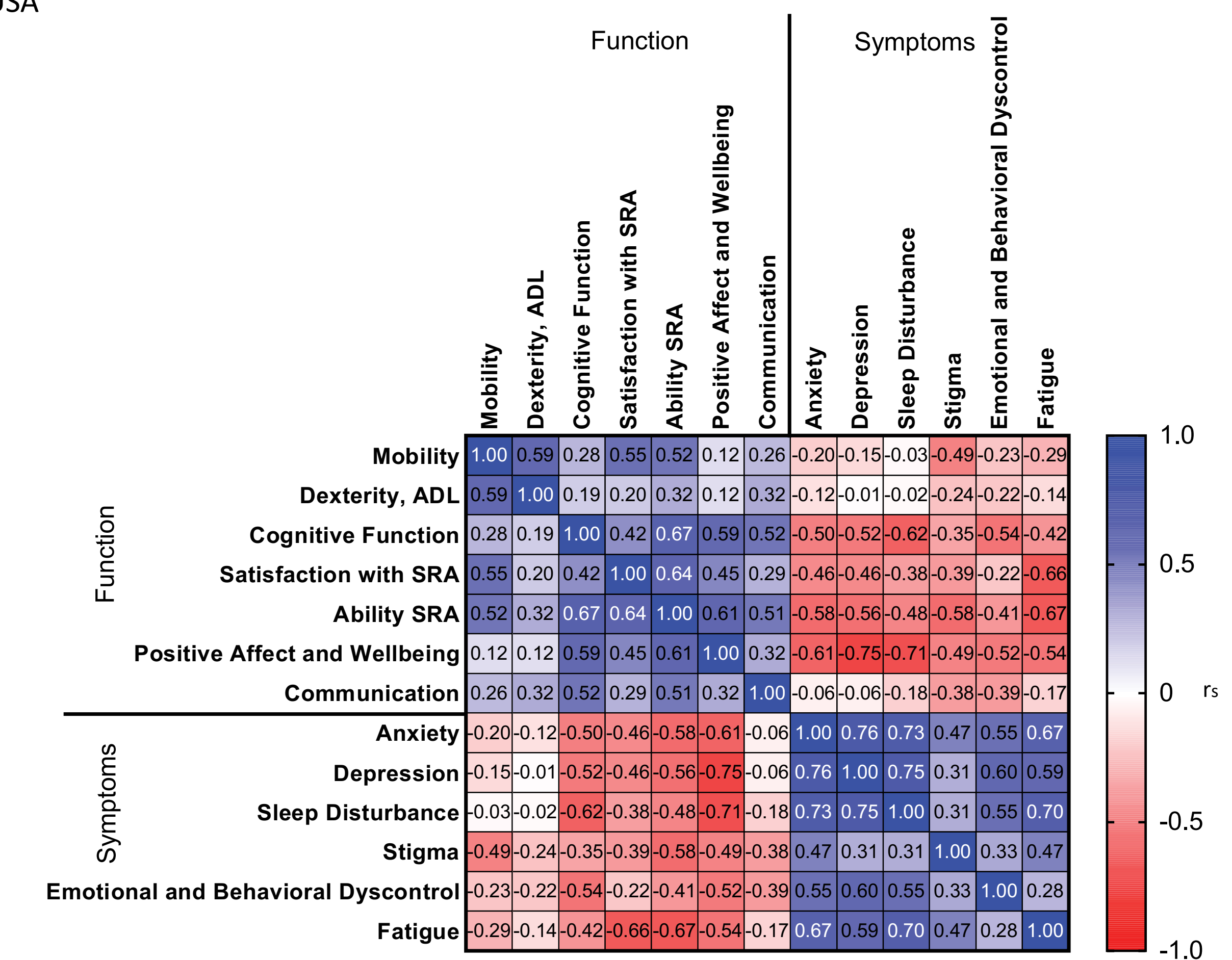


Figure 2: Correlation matrices of Neuro-QoL Domain T-scores for CNS subjects (n=45). rs=Spearman correlation coefficient.

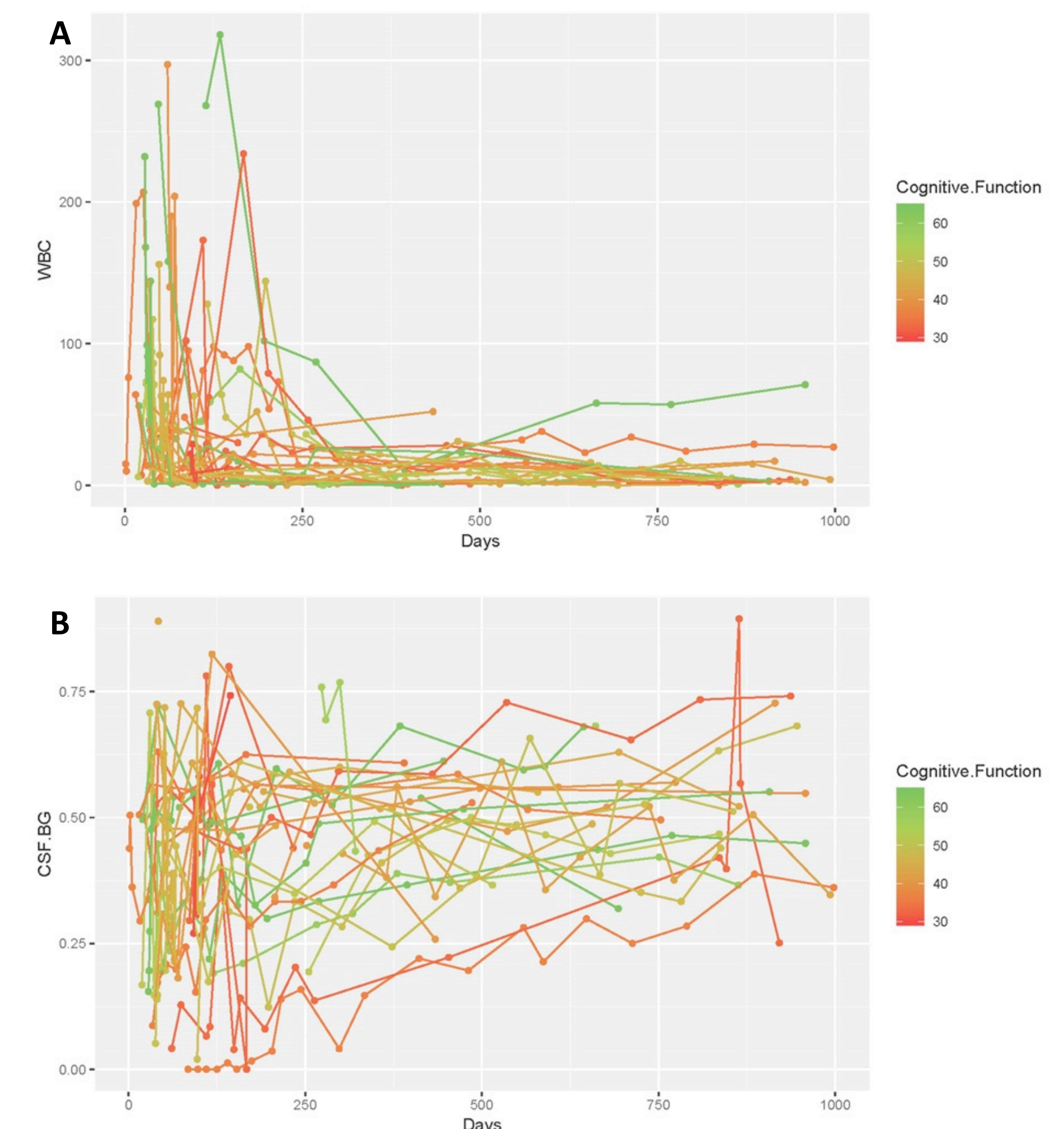


Figure 3: Longitudinal cerebrospinal fluid (CSF) profiles of CNS cryptococcosis subjects with overlaid long-term Neuro-QoL cognitive function T-score (n=43). **A:** CSF white blood cell (WBC) count versus days past diagnosis. **B:** CSF glucose: blood glucose (BG) ratio versus days past diagnosis. Individual subject data points are connected by lines. Subject data points and lines are colored by the Neuro-QoL cognitive function T-score with green being better scores, red being worse. All data points are representative of lumbar punctures (LP) performed at the NIH Clinical Center. All Neuro-QoL data was surveyed after the representative LP points shown on the diagram. Not all subjects had the same number of LPs performed. The timing of LPs was based on clinical condition and necessity.