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Effects of Illness Severity and Alcohol Use on Cognition in End Stage Liver Disease after Controlling for General Intelligence and Mood

——Cognition in End Stage Liver Disease

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ABSTRACT

Background: While neuropsychological deficits are common in patients with end stage liver disease (ESLD) evaluated for transplantation, the determinant factors are not clear. **Methods:** Towards that end, we examined data from 108 patients who completed neuropsychological tests as part of their liver transplantation evaluation. First, controlling for estimated premorbid ability and mood, multiple regression analyses were used to examine the effects of illness severity on cognition. Second, we compared neuropsychological functioning of patients with vs. without a history of excessive alcohol use, independent of primary liver disease diagnosis. **Results:** Severity of illness was associated with the extent of psychomotor slowing. Excessive alcohol use was associated with lower scores on tests of memory. Furthermore, worse memory was not explained by lower estimated premorbid ability, lower concurrently measured general intelligence, or greater illness severity. **Conclusions:** Our findings illustrate the importance of controlling for estimated premorbid ability in assessing the effect of illness variables on cognition. Another implication is that measures of psychomotor speed are important in assessing cognition in patients with ESLD, and especially for patients with a history of excessive alcohol use, a broader range of domains, including memory, should be examined.

Keywords: Liver Disease; Cognition

1. Introduction

Liver disease is a major cause of death in the United States. For example, in 2007 it was the fourth leading cause of death in people ages 45 to 54 years [1]. The most common causes of liver disease are heavy alcohol consumption and hepatitis C. Other etiologies include hepatitis B, nonalcoholic fatty liver disease, autoimmune hepatitis, diseases that damage or destroy the bile ducts, inherited diseases, and fulminant liver failure due to toxicity.

Cognitive impairment, affective symptoms, and compromised quality of life are common consequences of chronic liver disease [2,3]. Cognitive impairment from liver disease, furthermore, is associated with increased socioeconomic (employment, finances) and caregiver burden [2]. Hepatic encephalopathy (HE) is characterized by deficits in multiple cognitive domains and may progress to acute confusion or coma. While HE typically responds to treatment targeting the suspected underlying metabolic causes, it can lead to neurobehavioral dysfunction that does not completely resolve after liver transplantation [4-6]. Many patients experience milder cognitive dysfunction, commonly referred to as minimal hepatic encephalopathy (MHE). MHE is primarily characterized by a deficit in cognitive processing speed that is apparent on select neuropsychological tests rather than standard mental status exam (for review, see Randolph *et al*. [7]). Early detection and management of patients with MHE is important because of the increased risk of developing overt hepatic encephalopathy and gross cognitive impairment.

Recently, the International Society on Hepatic Encephalopathy and Nitrogen Metabolism convened a group of experts to recommend approaches for the routine neuropsychological assessment of patients with liver disease. In their practice guidelines [7] the commission recommended two specific batteries, the PSE-Syndrom-Test [8] and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [9]. The PSE-Syndrom-Test consists of five measures of psychomotor speed.

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The RBANS measures several cognitive domains and has been validated for use with a variety of patient groups that evidence neurobehavioral dysfunction.

Patients with ESLD exhibit a range of deficits on the RBANS. Sorrell *et al*. [10] examined cognitive functioning in 300 consecutive outpatients presenting for liver transplantation evaluation using the RBANS and the Trail-Making Test (TMT), a measure of psychomotor speed requiring executive function (attentional shifting). Worse test scores were associated with greater severity of liver disease as measured by MELD (measure of end-stage liver disease) score. The authors identified the pattern of deficits on RBANS Index scores as being consistent with subcortical brain dysfunction. After controlling for the severity of liver disease, patients with a history of alcohol abuse or dependence performed more poorly on the RBANS and TMT than those patients without such a history. However, group differences were only examined for the RBANS Total score and not the five Index scores. In a similar study, Mooney *et al*. [11] found that patients with ESLD performed below expectation on the RBANS compared to the healthy standardization sample [9]. Consistent with Sorrell *et al*. [10] they identified a subcortical pattern of impairment on the RBANS. However, there were no significant differences among diagnostic groups, including those that varied by alcohol etiology, in analyses which controlled for estimated premorbid verbal intelligence. This study did not examine cognitive performance as a function of illness severity.

Both of the above studies demonstrated neuropsychological deficits in patients with ESLD, but neither study examined the effect of illness severity on cognition after controlling for estimated premorbid ability and symptoms of depression and anxiety. Both studies focused on patient groups classified by primary diagnosis (e.g., alcoholic liver disease, hepatitis C with or without alcoholic liver disease, cholestatic liver disease). The findings regarding the importance of alcohol history were inconsistent, and the cognitive domains from the RBANS most likely to differentiate those patients with vs without a history of alcohol abuse or dependence remains unclear.

While the etiology of liver disease is important, the extent of prior alcohol consumption may be a more critical determinant of cognitive status among patient with ESLD. Chronic excessive alcohol consumption is associated with decreased cortical gray matter volume, shrinkage of select subcortical regions (e.g., thalamus, hippocampus, mammillary bodies), demyelination, and axonal degeneration [12]. Longitudinal MRI studies have shown that with abstinence brain volume loss is partially reverseble, especially in frontal and temporal regions, although one factor that diminishes recovery is concurrent hepatic disease [13].

The RBANS is sensitive to deficits in memory, psychomotor speed, verbal fluency and visuospatial ability in moderate to heavy active alcohol users [14]. Persistent cognitive deficits following abstinence include memory and executive dysfunction [12]. Because the RBANS does not assess executive function, the TMT is often included in assessments of patients with ESLD who have a history of alcohol abuse [10].

To the extent that chronic excessive alcohol consumption causes cognitive impairment independent of liver disease, the pattern of dysfunction in liver disease patients with vs. without a history of alcohol abuse or dependence will likely differ. For this reason, it is useful to assess neuropsychological functioning in ESLD patients by alcohol status independent of the primary liver disease diagnosis. Such information, in turn, may inform assessment and management practices for these different liver disease populations.

In this study we examined the neuropsychological functioning of patients being evaluated for liver transplantation as a function of illness severity, after controlling for estimated premorbid ability, depression, and anxiety. We also expanded on prior research by including a brief measure of general intelligence as well as the RBANS and TMT as dependent variables. Our principal aim was to compare patient groups classified by the presence vs. absence of a history of alcohol abuse or dependence, independent of the primary liver disease diagnosis. We hypothesized that patients with a history of alcohol abuse or dependence would exhibit greater neuropsychological dysfunction than those without such a history. Given the well-known effects of alcoholism on cognition, we anticipated that RBANS memory would be particularly sensitive to group differences.

2. Methods

2.1. Participants

Participants were 108 adults who were being evaluated for orthotopic liver transplantation at a large, urban medical center in central Virginia. They were mostly male (70.4%) and Caucasian (82.4%), with 13.7% African American and 3.7% Hispanic. Mean age was 53.3 (SD = 7.5) and mean education level was 12.8 years (SD = 2.4). About 32% of patients were actively employed, 42% disabled, 10% retired, and the remainder unemployed or not actively working. All participants completed a comprehensive multidisciplinary evaluation by a hepatologist, transplant surgeon, clinical psychologist and social worker. Medical history, physical exam, laboratory studies, clinical interview and mental status exam were used to identify etiology and severity of liver disease, comorbid medical conditions, psychiatric disorders, history of substance use,

cognitive impairment, current health behaviors and treatment status. Individuals were excluded from this study if cognitive impairment was attributed to neurologic disorders (e.g., traumatic brain injury), acute medical illness other than liver disease, or poorly managed psychiatric disorders. Individuals were also excluded if English was not their primary language. Liver diagnoses in our sample were: 40.7% Hepatitis C, 25% alcoholic cirrhosis, and 34.3% other (e.g., sarcoidosis, cryptogenic, biliary cirrhosis). This study was approved by the Virginia Commonwealth University Institutional Review Board.

2.2. Measures and Procedures

All patients completed a clinical interview, self-report inventory, and neuropsychological tests, as described below. Tests were administered by a doctoral level psychologist (second author) or a doctoral trainee under the supervision of the psychologist. The MELD score [15] was used to assess severity of liver disease. The diagnosis of alcohol abuse or dependence was made after the clinical interview, using criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition [16].

Neuropsychological tests. General intellectual ability was assessed using the Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI) [17]. These two subtests have a high factor loading on g (general intelligence factor) and yield an estimated Full Scale IQ (FSIQ) score. The Wechsler Test of Adult Reading (WTAR) [18] demographic formula was used as an estimate of premorbid FSIQ. Neuropsychological functioning was assessed using the RBANS [9] and the TMT. The RBANS and TMT were selected because of the important cognitive domains assessed, length of time for administration that minimizes effects of fatigue, and demonstrated utility in detecting and characterizing cognitive impairment in patients with ESLD. The RBANS yields a summary score and separate age-adjusted index scores for immediate memory, delayed memory, visuospatial-construction, attention and language. The TMT is a well-established test requiring visuomotor speed and attention [19]. In part A the individual draws lines to connect consecutively numbered circles, and in part B is required to connect the same number of consecutively numbered and lettered circles in an alternating sequence. An age-corrected time score for part B was used in the present study.

Millon Behavioral Medicine Diagnostic (*MBMD*). The MBMD [20] is an inventory composed of statements answered true or false that is designed to identify psychosocial assets and liabilities which may affect an individual's response to treatment. It includes a validity indicator and response pattern scales, and norms for a general medical population. The scores from two scales, Anxiety-Tension and Depression, were used in the present study.

2.3. Analyses

After descriptive analyses, Pearson's correlations between study variables were calculated (WTAR, Anxiety, Depression, MELD, WASI FSIQ, RBANS Total and Index Scores, TMT-B). We then examined the relationship between severity of liver disease and cognitive function with three hierarchical multiple regression analyses, controlling for premorbid ability and mood. The independent variables were: WTAR (Step 1), MBMD Depression and Anxiety (Step 2), and MELD (Step 3). The dependent variables were WASI FSIQ (Model 1), RBANS Total (Model 2), and TMT-B time (Model 3). All neurocognitive scores were age-corrected. Next, to explore the hypothesis that cognitive function was significantly impaired due to history of alcohol abuse or dependence, independent samples (*i.e.*, positive vs negative alcohol status) t-tests examined differences in the RBANS Total and Index Scores, TMT-B, and WASI FSIQ. T-tests also examined differences by alcohol status in covariates of WTAR, MELD and MBMD Depression and Anxiety. SPSS v. 18.0 (Chicago, IL) was used in analyses. All tests were 2-tailed with $p < 0.05$ set to indicate signifycance.

3. Results

The mean MELD score was 14.6 (SD = 4.9). Sixty-two (57%) of participants reported a history of alcohol abuse or dependence. **Table 1** displays the correlations among study variables. As shown, higher estimated premorbid ability (WTAR) was associated with better performance on all cognitive measures (*r's* = 0.20 – 0.63). Neither mood nor MELD scores was associated with premorbid ability, and MELD was also not significantly correlated with depression or anxiety ($p > 0.05$). Anxiety was significantly negatively associated with overall cognitive functioning (RBANS Total), immediate and delayed memory, and language (*r's* = –0.19 to –0.27) and positively associated with TMT-B time ($r = 0.19$), suggesting greater anxiety is associated with poorer functioning on these measures. Similarly, greater depression was associated with lower scores on FSIQ, RBANS Total, immediate memory and language (*r's* = –0.19 to –0.22), and longer time to complete TMT-B ($r = 0.21$).

Results of regression analyses (see **Table 2**) suggested that MELD was not significantly associated with FSIQ or RBANS Total. The association of MELD with TMT-B approached significance ($p = 0.081$). In Models 1 and 2,

Table 1. Correlation matrix among cognitive, mood, and severity of illness variables of patients presenting for liver transplantation evaluation.

	1	2	3	4	5	6	7	8	9	10	11	12
1. WTAR[a]	-	0.21†	–0.15	–0.13	0.63***	0.44***	0.38***	0.31**	0.30**	0.29**	0.31**	–0.20*
2. MELD[b]		-	0.02	0.10	0.05	0.06	0.04	0.18	0.01	–0.05	0.00	0.16
3. Anxiety[c]			-	0.47***	–0.18	–0.25*	–0.24*	–0.14	–0.19*	–0.08	–0.27**	0.19*
4. Depression[c]				-	–0.22*	–0.22*	–0.19*	–0.13	–0.21*	–0.16	–0.16	0.21*
5. FSIQ[d]					-	0.62***	0.43***	0.50***	0.50***	0.52***	0.40**	–0.48***
6. RBANS Tot[e]						-	0.81***	0.70***	0.69***	0.74***	0.80***	–0.58***
7. RBANS- IM[f]							-	0.36***	0.44***	0.51***	0.66***	–0.46***
8. RBANS-VC[g]								-	0.41***	0.34***	0.43***	–0.35***
9. RBANS-Lang[h]									-	0.45***	0.44***	–0.43***
10. RBANS-Attn[i]										-	0.50***	–0.49***
11. RBANS-DM[j]											-	–0.50***
12. Trails B[k]												-

Note: [a]WTAR = Wechsler Test of Adult Reading; [b]MELD = Measure for End Stage Liver Disease; [c]Anxiety and Depression measured with Millon Behavioral Medicine Diagnostic; [d]FSIQ = Wechsler Full Scale Intelligence Quotient; [e]RBANS Tot = Repeatable Battery for the Assessment of Neuropsychological Status Total Score; [f]RBANS-IM = Immediate Memory; [g]RBANS-VC = Visuo-constructional; [h]RBANS-Lang = Language; [i]RBANS-Attn = Attention; [j]RBANS-DM = Delayed Memory; [k]Trails B is a measure of visuomotor speed and attention. $N = 108$ for all variables, except for MELD score where $n = 92$ due to missing data. Higher scores reflect better functioning on all measures except for Trails B and MELD: higher MELD is associated with worse liver disease and higher Trials B is associated with greater impairment. $^{\dagger}p = 0.05$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 2. Multiple regression analyses examining the relationship among severity of liver disease and cognitive functioning; *n* = 92.

Variable	Model 1 FSIQ[d]				Model 2 RBANS[e]				Model 3 Trails B[k]			
	R^2	ΔR^2	B (SE)	β	R^2	ΔR^2	B (SE)	*β*	R^2	ΔR^2	B (SE)	*β*
Step 1 WTAR[a]	0.39	0.39***	1.23 (0.16)	0.62***	0.21	0.21***	0.78 (0.16)	0.46***	0.05	0.05*	–0.10 (0.05)	–0.22*
	F (1, 89) = 56.6, $p < 0.001$				F (1, 89) = 24.0, $p < 0.001$				F (1, 89) = 4.52, $p < 0.05$			
Step 2 WTAR[a]			1.19 (0.17)	0.61***			0.73 (0.16)	0.43***			–0.08 (0.05)	–0.18
Depression[c]	0.40	0.01	–0.06 (0.06)	–0.10	0.24	0.02	–0.05 (0.06)	–0.10	0.11	0.07	0.03 (0.02)	0.20
Anxiety[c]			–0.02 (0.06)	–0.03			–0.04 (0.06)	–0.08			0.01 (0.02)	0.07
	F (3, 87) = 19.4, $p < 0.001$				F (3, 87) = 8.94, $p < 0.001$				F (3, 87) = 3.42, $p < 0.05$			
Step 3 WTAR[a]			1.22 (0.17)	0.62***			0.74 (0.16)	0.44***			–0.10 (0.05)	–0.22*
Depression[c]	0.40	0.00	–0.05 (0.06)	–0.09	0.24	0.00	–0.05 (0.06)	–0.09	0.14	0.03$^{\div}$	0.02 (0.02)	0.18
Anxiety[c]			–0.02 (0.06)	–0.03			–0.04 (0.06)	–0.08			0.01 (0.02)	0.07
MELD[b]			–0.21 (0.29)	–0.06			–0.06 (0.28)	–0.02			0.14 (0.08)	0.18$^{\div}$
	F(4, 86) = 14.6, $p < 0.001$				F (4, 86) = 6.65, $p < 0.001$				F (4, 86) = 3.40, $p < 0.05$			

Note: All scores are age-corrected, thus age is not included as a covariate. Analyses include 92 patients with MELD scores available. No differences were found between patients with and without recorded MELD scores. [a]WTAR = Wechsler Test of Adult Reading; [b]MELD = Measure for End Stage Liver Disease; [c]Anxiety and Depression measured with Millon Behavioral Medicine Diagnostic; [d]FSIQ = Wechsler Full Scale Intelligence Quotient; [e]RBANS = Repeatable Battery for the Assessment of Neuropsychological Status-Total score used in analyses; [k]Trails B is a measure of visuomotor speed and attention. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{\div}p = 0.081$.

estimated premorbid ability was the only variable significantly associated with FSIQ and RBANS Total, explaining 62% and 44% of the variance, respectively. The addition of depression and anxiety (Step 2) and MELD (Step 3) did not increase the explanatory power of the models (nonsignificant ΔR^2). In Model 3 premorbid ability was

significantly negatively associated with TMT-B time (β = –0.26), suggesting better performance with higher premorbid ability. Thus in each model, higher premorbid ability was associated with better performance on the tests of cognitive function, explaining the majority of the variance in the outcomes. Severity of liver disease only explained a marginally significant amount of the variance (18%) in psychomotor speed (*i.e.*, TMT-B) and was not associated with either overall intellectual functioning (WASI FSIQ) or overall neuropsychological functioning (RBANS Total). Depression and anxiety explained a small but nonsignificant amount of the variance in each outcome.

Table 3 displays liver diagnoses, MELD scores, and cognitive and mood variables by history of alcohol abuse/dependence. Patients with a history of alcohol use/dependence were more likely to have Hepatitis C as well as alcoholic cirrhosis, compared with other diagnoses. Estimated premorbid ability and MELD scores were similar on the two groups. Patients with a history of alcohol use reported greater depression and had lower scores on measures of immediate and delayed memory than patients without a history of alcohol abuse/dependence.

4. Discussion

Results of this study underscore the importance of assessing alcohol history in patients presenting for liver transplantation evaluation. Specifically, those individuals with a history of excessive alcohol use scored lower on RBANS measures of memory. Lower memory scores were not explained by lower estimated premorbid intelligence or lower WASI FSIQ, which were similar for the alcohol and non-alcohol groups. This finding is consistent with well-known effects of alcoholism on brain function. That is, impaired explicit memory, especially on tests of free recall, is a salient persistent deficit associated with alcoholism [12]. Patients with vs without a history of excessive alcohol use did not differ in illness severity, as measured by MELD scores (see **Table 3**). However, it remains possible that the relation between alcohol and illness severity was mitigated by self-report bias at the time of the transplant evaluation. Depression may also have been a contributing factor. Depression was associated with worse performance on several cognitive tests and those individuals with a history of alcohol abuse or dependence reported higher levels of depression.

Severity of liver disease was marginally associated with psychomotor speed, consistent with the findings of Sorrell *et al.* [10]. The relationship between illness severity and psychomotor speed was independent of the effects of premorbid ability and mood. Specifically, liver disease severity explained 18% of the variance on TMT-B scores,

Table 3. Liver diagnosis and cognitive functioning by alcohol abuse/dependence status.

Variable	Alcohol n = 62	No Alcohol n = 46
Diagnosis		
Hepatitis C (%)	43.5	37.0
Alcoholic Cirrhosis (%)	41.9	2.2
Other (%)	14.5	60.9
MELD Score[b]	14.9 (5.0)	14.1 (4.7)
Premorbid IQ-WTAR[a]	101.6 (8.4)	101.6 (7.8)
WASI-FSIQ[d]	95.0 (16.3)	95.8 (16.4)
RBANS-Total[e]	81.2 (13.7)$^{\pm}$	86.4 (14.1)
Immediate Memory	83.2 (15.9)**	92.0 (16.2)
Visuo-constructional	84.6 (18.9)	85.8 (15.8)
Language	89.7 (9.8)	92.2 (12.5)
Attention	84.7 (14.6)	86.2 (15.7)
Delayed Memory	85.5 (14.8)*	92.2 (15.0)
Trails B (z-score)[k]	2.4 (3.7)	1.49 (3.3)
MBMD Anxiety[c]	46.9 (27.1)	38.6 (25.6)
MBMD Depression[c]	53.6 (27.3)*	41.1 (27.5)

Note: Data are Mean (SD), unless otherwise indicated. Scaled scores of measures are reported. Significance tests indicate differences on variable by alcohol abuse/dependence vs no alcohol abuse/dependence, calculated with independent samples t-tests or one-way ANOVAs. [a]WTAR = Wechsler Test of Adult Reading; [b]MELD = Measure for End Stage Liver Disease; [c]Anxiety and Depression measured with Millon Behavioral Medicine Diagnostic; [d]FSIQ = Wechsler Full Scale Intelligence Quotient; [e]RBANS Total = Repeatable Battery for the Assessment of Neuropsychological Status Total Score; [k]Trails B is a measure of visuomotor speed and attention. $^{\pm}p = 0.055$, $^{*}p < 0.05$, $^{**}p < 0.01$.

after controlling for estimated premorbid intelligence and self-reported depression and anxiety. In contrast, severity of liver disease was not associated with measures of generalized cognitive impairment (*i.e.* RBANS Total score and WASI FSIQ). Sorrell *et al*. [10] did find a correlation between MELD and RBANS Total score, but the association was weak (Pearson correlation = –0.20). Furthermore, a strength of our study is that we controlled for depression, anxiety, and estimated premorbid ability, the latter of which was significantly related to performance on all the dependent variables in our regression analyses.

Our findings illustrate the importance of taking into account estimated premorbid ability in assessing the effect of illness variables on cognitive test performance. Estimated premorbid ability was the only variable associated with not only WASI FSIQ but also RBANS Total score, explaining 62% and 44% of the variance, respectively. Estimated premorbid ability also explained 22% of the variance on TMT-B scores.

Individuals with MHE and HE often report symptoms of depression and anxiety. While simple correlations showed that both depression and anxiety were negatively associated with cognitive performance, in regression analyses depression and anxiety explained only small, non-significant amount of the variance in each outcome measure. Also, greater illness severity was not associated with higher levels of anxiety or depression.

Limitations of our study include the use of a demographic formula to estimate premorbid intelligence without the concurrent measure of reading skills on the WTAR. However, both demographic indices and reading achievement tests are commonly used without the other to estimate premorbid intelligence, and the demographic formula used in this study was the only variable reliably related to all three neuropsychological measures in the regression analyses. Current intellectual ability was assessed using two WASI subtests and the obtained score is only an estimate of FSIQ. While about 14% of the sample was African-American, it was not otherwise representatve of the diversity of the US population. In order for our findings to be as generalizable as possible to the population of liver disease patients evaluated for orthotopic liver transplantation, we did not exclude individuals with comorbid medical disorders unless there was an acute illness felt to be the cause of observed cognitive dysfunction. Nevertheless, the relationship between MELD scores and cognitive test scores may have been attenuated by the presence of comorbid medical disorders. However, this study has multiple strengths including control for estimated premorbid ability and mood in regression analyses, inclusion of a concurrent measure of general intelligence, and the comparison of patient groups classified by alcohol status independent of primary liver disease diagnosis.

In summary, our findings suggest a negative relationship between illness severity and psychomotor speed, and between excessive alcohol use and memory, in patients with ESLD. One important implication of these findings is that different neuropsychological tests might be used to efficiently screen cognitive abilities in individuals being evaluated for liver transplantation, depending on their history of alcohol use. Tests such as the RBANS are particularly important in assessing those individuals with known or suspected history of excessive alcohol use, regardless of the primary liver disease diagnosis. In those individuals without a significant drinking history, measures of psychomotor or information processing speed may have greater utility. The sensitivity of such speed tests to the effects of liver disease of various etiologies is an important area of ongoing research, especially for individuals at risk for MHE who may be more amendable to treatment with lactulose and other therapies.

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