Neuropsychological functioning among individuals infected with hepatitis C: a comparison of pre- and post-transplant performance

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Abstract

It is well established that patients with end stage liver disease (ESLD) experience cognitive and mood problems; however, little is known about changes in cognitive and emotional functioning following liver transplantation, especially over the past decade with the epidemic of hepatitis C virus (HCV) infection taking over as the leading indication for liver transplantation. Seventeen patients with ESLD secondary to chronic HCV were assessed pre- and post-liver transplantation using a comprehensive neuropsychological battery. After an average of four years post-transplant, patients demonstrated significant improvements in most cognitive functioning and depressive symptoms. However, 18% of liver recipients continued to exhibit mild cognitive impairment mainly in areas of attention/executive functioning, motor speed, and learning. Liver

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transplantation is a life-extending surgery that reverses most, but not all, cognitive and mood difficulties. It is crucial to evaluate cognition after liver transplantation, especially in these three domains, and to consider the effect on daily functioning.

Keywords: Hepatitis C; Liver transplantation; Cognitive impairment; Depressive symptoms; End stage liver disease

1. Introduction

Chronic liver disease and its complications are the 12th leading cause of death in the U.S. (Murphy, Xu & Kochanek, 2013). Approximately 5.5 million Americans suffer from cirrhosis (Zacks, 2002), and liver transplantation is the treatment of choice for those with end stage liver disease (ESLD) (Campagna, Biancardi, Cillo, Gatta & Amodio, 2010; Roberts, Angus, Bryce, Valenta & Weissfeld, 2004; Wiesner et al., 2003). Cognitive deficits are commonly observed in patients with ESLD (Collie, 2005; Mooney et al., 2007; Pantiga, Rodrigo, Cuesta, Lopez & Arias, 2003; Sorrell, Zolnikov, Sharma & Jinnai, 2006). Although clinical presentation and pathogenesis seen in patients with ESLD may depend on the types of liver failure (i.e., fulminant vs. chronic), hyperammonemia is considered to be a major factor leading to hepatic encephalopathy and cognitive deficits (Dbouk & McGuire, 2006; Quero Guillen, Carmona Soria, Garcia Montes, Jimenez Saenz & Herrerias Gutierrez, 2003). As severity of liver dysfunction increases, the liver is less able to convert ammonia absorbed from gut resulting in chronic hyperammonemia (Blei & Cordoba, 2001; Mooney et al., 2007). The chronic hyperammonemia causes changes in neural transmission that increases ammonia blood-brain barrier permeability (Butterworth, 2001; Quero Guillen et al., 2003). This condition leads to reduction of bold flow especially in subcortical brain regions, such as basal ganglia and cerebellum (Ahl et al., 2004), and as a result, cognitive deficits manifest.

However, it is unclear whether or not these deficits improve and clear post-liver transplantation. Given that more than 70% of adult liver transplant recipients survive more than 10 years (Bramhall, Minford, Gunson & Buckels, 2001) and many hope to return to productive lives, it is essential to assess ESLD patients' cognitive functions as an important aspect of transplant recovery as well as long-term everyday functions (Bravata & Keeffe, 2001; Campagna et al., 2010; Goff, Glazner & Bilir, 1998; Hunt et al., 1996).

While patients with ESLD tend to demonstrate learning and memory problems, visuospatial deficits, attention/executive dysfunction, and psycho-

motor slowing, their intellectual ability, such as verbal intelligence, is often preserved (Collie, 2005; Mooney et al., 2007; Pantiga et al., 2003; Sorrell et al., 2006). However, cognitive functioning post-liver transplant is less well characterized. A handful of studies assessed cognitive functions of liver transplant recipients (Commander, Neuberger & Dean, 1992; Elliott, Frith, Pairman, Jones & Newton, 2011; Hockerstedt et al., 1992; Ishihara et al., 2013; Lewis & Howdle, 2003; Mattarozzi et al., 2004; Mechtcheriakov et al., 2004; Miller-Matero et al., 2014; Moore, Mc & Burrows, 2000; Pantiga et al., 2003; Riether, Smith, Lewison, Cotsonis & Epstein, 1992; Sotil, Gottstein, Ayala, Randolph & Blei, 2009; Tarter, Switala, Arria, Plail & Van Thiel, 1990); however, only seven examined changes between pre- and post-transplant functioning using objective cognitive measures (Hockerstedt et al., 1992; Ishihara et al., 2013; Mattarozzi et al., 2004; Mechtcheriakov et al., 2004; Moore et al., 2000; Riether et al., 1992; Tarter et al., 1990). With the exception of one (Mechtcheriakov et al., 2004), these studies reported significant improvements in most cognitive domains studied, but four out of seven found that cognitive functioning of transplant recipients did not return to the level of the healthy controls (Hockerstedt et al., 1992; Mechtcheriakov et al., 2004; Moore et al., 2000; Tarter et al., 1990).

Although primary findings are fairly consistent across these studies, half of these studies were conducted more than 10 years ago; moreover, none of these studies focused on the hepatitis C virus (HCV) infection as a primary underlying cause of liver disease. Research over the past decade now indicates that chronic infection with HCV is the most common reason for liver transplantation in the U.S. (El-Serag, 2002; Poynard, Yuen, Ratziu & Lai, 2003; World Health Report, 2002), and a high recurrence of HCV post transplant is well reported (Berenguer et al., 2000; Prieto et al., 1999; Sanchez-Fueyo et al., 2002). Additionally, the typical age range of liver transplant recipients is between 50 and 64 years old (United Network for Organ Sharing, 2014), a decade older than transplant recipients in all but one of the prior studies (Mechtcheriakov et al., 2004).

Thus, given the limited information about cognitive functioning in liver transplant recipients and changes in the demographics of liver disease over the past 10 years, the primary purpose of the current study was to update this literature by examining pre- and post-transplant cognitive functioning in patients whose primary etiology of liver disease was HCV. In addition, although depressive symptoms are commonly seen in patients with ESLD (Campagna et al., 2010; Santos et al., 2008; Sotil et al., 2009), very few studies have examined change in depressive symptoms post-transplant. It is important to assess whether or not liver transplantation significantly reduces depressed mood among patients with ESLD. It was hypothesized

that there would be significant improvements in cognitive functioning post-transplant in all domains except verbal intelligence. In addition, this study sought to characterize cognitive functioning in these patients by examining proportion impaired and the magnitude of cognitive impairment pre- and post-transplant, as well as change in depressive symptoms.

2. Methods

2.1. Participants and procedures

This study was approved by the university human research protection program, and all patients were informed about the nature of the study and provided written informed consent. Participants were 17 liver transplant recipients (12 men and five women) who completed neuropsychological tests prior to liver transplant as a part of their standard pre-transplant psychiatric evaluation. After transplant, they were asked to participate in a study examining changes in functioning using the same neuropsychological tests. There were 33 liver recipients identified as potential participants for a post-transplant evaluation; however, 16 people did not participate in the present study due to moving away (6), other medical reasons (3), refusal (4), death (1), or unable to contact (2). All participants were provided $10 as compensation. Average age of the participants prior to transplant was 53 ± 7 years, and average level of education was 11 ± 2 years. Average age of participants post-transplant was 58 ± 6 years; evaluations were conducted an average of 49 ± 37 months post-transplant (range = 5 to 110). The time elapsed between pre- and post-transplant evaluations was 68 ± 39 months (range = 13 to 116), which is long enough for most participants that a significant practice effect was not anticipated (Dikmen, Heaton, Grant & Temkin, 1999). Ten participants (59%) were Caucasian, five (29%) were Hispanic/Latino, and two (12%) were of other ethnic backgrounds. Regarding etiology, 15 had HCV only and two had both HCV and alcohol-related liver disease. None were co-infected with human immunodeficiency virus. Thirteen participants (77%) experienced hepatic encephalopathy prior to transplant, but none were overtly encephalopathic at the time of evaluation. Eight participants (47%) had histories of substance use disorders.

2.2. Neuropsychological (NP) and depression measures

NP measures used in the present study included *The Peabody Picture Vocabulary Test - 3rd revision* (PPVT-III) (Dunn & Dunn, 1997), *The Repeatable Battery for the Assessment of Neuropsychological Status* (RBANS) (Randolph, 1998), *Trail Making Test* (TMT) (Reitan & Wolfson, 1993), *Controlled Oral Word Association Test* (COWAT) (Benton & Hamsher, 1989), *Animal Naming Test* (Strauss, Sherman & Spreen, 2006), and *Grooved Pegboard Test* (GPT) (Klove, 1963). The PPVT-III was administered as an estimate of participants' verbal intelligence. The raw scores from all NP measures, except the RBANS and PPVT-III, were converted to a T-score adjusted for age, education, gender, and ethnicity (Heaton, Miller, Taylor & Grant, 2004). Index scores of the RBANS and PPVT-III were calculated based on their manuals. In addition to the NP measures, *The Beck Depression Inventory - 2nd edition* (BDI-II) (Beck, Steer & Brown, 1996) was also used to assess participants' mood.

2.3. Statistical analysis

To test our primary hypothesis that patients would show significant improvements in all cognitive domains, pre- and post-transplant index scores for the PPVT-III and RBANS and T-scores for the TMT, COWAT, Animal Naming, and GPT were compared using paired-samples t-tests. A paired samples t-test also was used to examine changes in BDI-II scores pre- and post-transplant. To control for multiple comparisons, Bonferroni correction was applied and a significance level was set at ≤ 0.003 (0.05/14 comparisons). To characterize proportion of overall cognitive impairment and pattern of impairment, a 6-point deficit rating scale was applied to demographically corrected standard scores as follows: T ≥ 40 = 0 (Normal), T 35-39 = 1 (Mild), T 30-34 = 2 (Mild to Moderate), T 25-29 = 3 (Moderate), T 20-24 = 4 (Moderate to Severe), and T ≤ 19 = 5 (Severe). A Global Deficit Score (GDS) was then computed by adding the deficit points of the component test measures and dividing by the total number of measures. GDS ≥ .50 were considered impaired as this cut point reflects an average of at least mild impairment on at least half of the measures and has been shown to yield the optimal balance of sensitivity, specificity, positive predictive value, and negative predictive value when compared to the gold standard clinical rating approach (Carey et al., 2004). In a similar manner, deficit scores were computed for the following six cognitive domains: attention/executive functioning (RBANS Digit Span and Coding and TMT Parts A

and B), learning (RBANS List Learning and Story Memory), recall (RBANS List Recall, Story Recall, and Figure Recall), visuospatial construction (RBANS Figure Copy and Line Orientation), language (RBANS Picture Naming and Semantic Fluency, COWAT, and Animal Naming), and motor speed (GPT dominant and non-dominant hands). Pre- and post-transplant GDS and domain deficit scores were compared using paired samples t-tests. For these analyses, a significance level was set at ≤ 0.007 using Bonferroni correction (0.05/7 comparisons). Additionally, the proportion of impaired participants overall and by domain was calculated both pre- and post-transplant, as was proportion of participants obtaining BDI-II scores in the mild range of severity and above (i.e., raw score of 14 or greater). Related samples McNemar's test was used to investigate differences in proportions pre- and post-transplant with p set at ≤ 0.007 following Bonferroni correction (0.05/7 comparisons). Because all of our hypotheses were directional (i.e., that improvement would be apparent post-transplant), one-tailed tests of significance were used in all cases.

3. Results

As shown in *Table 1*, statistically significant improvements were seen on RBANS Immediate and Delayed Memory, RBANS Visuospatial/Construction, RBANS Total, COWAT and Animal Naming, and BDI-II. PPVT-III, RBANS Attention and Language, TMT, and GPT did not reach statistical significance, although all but RBANS Attention showed improvement. Analyses of GDS and domain deficit scores revealed significant improvement overall and in all domains, except Attention/Executive Functioning and Visuospatial/Construction (see *Table 2*). Pre-transplant, participants exhibited the highest deficit scores in motor speed followed by learning, attention/executive functioning, language, visuospatial/construction, and recall. Given that a GDS of .50 or greater is indicative of cognitive impairment (Carey et al., 2004), participants, on average, exhibited impairment in all six cognitive domains. Post-transplant, attention/executive functioning was the domain with the highest deficit score followed by motor speed, learning, visuospatial/construction, language, and recall. Learning, recall, language, and visuospatial/construction were no longer in the impaired range, while attention/executive functioning and motor speed remained impaired.

Table 1. Means (Standard Deviations) of neuropsychological test scores pre- and post-liver transplantation

	Pre-Transplant	Post-Transplant			
	M (SD)	*M (SD)*	*t*	*p*	*d*
PPVT-III†	100.4 (31.9)	105.5 (28.7)	-2.74	0.02	0.17
RBANS Attention†	85.4 (15.4)	85.9 (17.3)	-0.13	0.45	0.03
RBANS Immediate Memory†	81.7 (18.8)	97.1 (13.7)	-3.95	< 0.001*	0.94
RBANS Delayed Memory†	90.3 (17.6)	104.1 (11.3)	-3.15	0.003*	0.93
RBANS Visuospatial/Construction†	91.1 (17.5)	105.1(14.7)	-3.44	0.002*	0.87
RBANS Language†	89.0 (16.9)	99.7 (8.9)	-2.64	0.009	0.79
RBANS Total†	82.3 (17.2)	97.2 (13.0)	-4.25	< 0.001*	0.98
TMT-A††	40.7 (11.7)	46.1 (10.3)	2.13	0.02	0.49
TMT-B††	37.8 (11.7)	48.7 (9.7)	2.47	0.01	1.01
COWAT††	38.5 (12.0)	52.8 (8.0)	-4.43	< 0.001*	1.40
Animal Naming††	40.1 (8.3)	54.1 (7.1)	-5.57	< 0.001*	1.81
GPT dominant hand††	34.9 (8.4)	42.9 (8.6)	2.68	0.008	0.94
GPT non-dominant hand††	33.8 (9.2)	44.1 (8.2)	1.26	< 0.02	1.18
BDI-II†††	14.3 (9.7)	6.1 (6.3)	3.45	0.002*	1.00

Note: PPVT-III = The Peabody Picture Vocabulary Test - 3rd revision; RBANS = The Repeatable Battery for the Assessment of Neuropsychological Status; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; COWAT = Controlled Oral Word Association Test; GPT = Grooved Pegboard Test; BDI-II = The Beck Depression Inventory - 2nd edition.

† = index scores; †† = T-scores; ††† = raw scores; *d* indicates Cohen's *d* (effect size).

Significance was set at ≤ 0.003.

Table 2. Means (Standard Deviations) of global and domain deficit scores pre- and post-liver transplantation

	Pre-Transplant	Post-Transplant			
	M (SD)	*M (SD)*	*t*	*p*	*d*
Global Deficit Score	1.07 (.81)	.32 (.42)	4.14	< 0.001*	1.16
Attention/Executive Functioning	1.16 (1.12)	.63 (.75)	2.05	0.03	0.56
Learning	1.29 (1.50)	.38 (.76)	2.89	0.006*	0.77
Recall	.71 (.83)	.06 (.24)	3.36	0.002*	1.06
Visuospatial/Construction	.82 (1.24)	.18 (.61)	2.52	0.01	0.65
Language	.94 (.91)	.06 (.24)	4.36	< 0.001*	1.32
Motor Speed	1.68 (1.54)	.53 (.84)	3.23	0.003*	0.93

Note: d indicates Cohen's *d* (effect size). Significance was set at ≤ 0.007.

Table 3. Number (%) of impaired global and domain deficit scores pre- and post-transplant

	Pre-Transplant	Post-Transplant
Global Deficit Score	10 (59)	3 (18)
Attention/Executive Functioning	11 (65)	8 (47)
Learning	10 (59)	6 (35)
Recall	8 (47)	1 (6)
Visuospatial/Construction	6 (35)	2 (12)
Language*	11 (65)	3 (18)
Motor Speed	12 (71)	7 (41)

Note: $*p = 0.004$. Significance was set at ≤ 0.007.

As shown in *Table 3*, almost 60% of ESLD patients demonstrated global cognitive impairment prior to transplant. The highest percentage of impairment occurred in the domain of motor speed (i.e., 71%), and the lowest occurred in the domain of visuospatial/construction (i.e., 35%). Following transplant, attention/executive and motor functioning remained the domains impaired in the highest percentage of individuals (47% and 41%, respectively), while recall was the domain impaired in the lowest percentage of individuals (6%). The number of individuals with an impaired GDS before liver transplantation decreased from 10 (59%) to 3 (18%) after the transplant, which was not statistically significant after Bonferroni correction (p = .02) likely due to small sample size. Similarly, the percentages of impaired individuals dropped from pre- to post-transplant in all cognitive domains, but only the drop in percentage with language impairment reached statistical significance after Bonferroni correction (p = .004) (see *Table 3*).

In terms of emotional status as measured by the BDI-II, participants showed a significant reduction in depressive symptoms post- versus pre-liver transplant (see *Table 1*). Five patients (29%) endorsed clinically significant levels of depressive symptoms before the transplant, while only two (12%) indicated clinically significant depressive symptoms after the transplant. However, this reduction did not reach statistical significance (p = .13). Specifically, pre-transplant, three patients were categorized in the moderate range and two were in the severe range. Post-transplant, one was in the mild range, one was in the moderate range, and no one was in the severe range.

4. Discussion

This study examined changes in cognitive functioning and depressive symptoms in 17 ESLD patients who underwent neuropsychological testing both pre- and post-liver transplantation. As previous studies paid little attention to HCV as the primary underlying cause of liver disease and were less representative of the current population who are undergoing liver transplantation, this study represents a significant update in the demographics of ESLD. The current study employed a sample composed exclusively of patients whose etiology of liver disease was HCV and who were approximately a decade older (i.e., mid to late 50s) than patient samples in previous studies. Results revealed that global cognitive functioning improved significantly post-transplant as did functioning in all cognitive domains measured in this study. Receiving a new healthy liver seems to reverse hyperammonemia and hepatic encephalopathy that likely contributed significantly to cognitive deficits in

patients with ESLD pre-transplant. These findings are consistent with most prior studies, showing significantly improved cognitive functioning, overall, post-transplant.

Another goal of the study was to characterize percentage and magnitude of cognitive impairment, which had not been done previously. Pre-transplant, 59% of the sample showed at least mild global cognitive impairment. The most significant deficits were in motor speed (i.e., GDS = 1.68), which were exhibited by 71% of the sample. Attention/executive functioning, language, and learning were the next most frequently impaired domains, with 65% of patients classified as impaired in the former two domains and 59% classified as impaired in the latter. All three of these domains were close in magnitude of impairment with GDS scores of 1.29, 1.16, and 0.94 in learning, attention/executive functioning, and language, respectively. The similar level of impairment in these domains may be explained by the role of executive functions in learning and verbal fluency tasks utilized in this study (Brooks, Weaver & Scialfa, 2006; Elderkin-Thompson, Mintz, Haroon, Lavretsky & Kumar, 2007).

Visuospatial/construction and recall were similarly impaired at a milder level (i.e., GDS = .82 and .71, respectively) and affected fewer patients pre-transplant (i.e., 35% and 47%, respectively). The pattern of findings are consistent with previous studies of cognitive functioning in liver transplant candidates indicating that primarily the frontal-subcortical circuitry that mediates these cognitive functions may be impaired (Collie, 2005; Mooney et al., 2007; Pantiga et al., 2003; Sorrell et al., 2006). This study however is the first to demonstrate the breadth and severity of impairment by cognitive domain and to illustrate that the majority of ESLD patients exhibit mild global cognitive impairment.

Post-transplant, language, particularly verbal fluency, significantly improved the most followed by recall, motor speed, and learning. Notably, learning, language, visuospatial/construction, and recall were no longer in the impaired range post-transplant, with only 35%, 18%, 12%, and 6% of participants exhibiting impaired learning, language, visuospatial/constructional abilities, and recall, respectively. On the other hand, attention/executive functioning and motor speed remained impaired, on average, with 47% and 41% of post-transplant patients, respectively, performing in the impaired range. Thus, findings suggest that liver transplant recipients continue to demonstrate frontal-subcortical dysfunction after receiving a new liver, which is supportive of earlier studies showing that liver transplant recipients did not improve to the level of healthy controls (Hockerstedt et al., 1992; Mechtcheriakov et al., 2004; Moore et al., 2000; Tarter et al., 1990). Reasons for continued mild cognitive impairment in some post-transplant

patients are unclear but may be related to residual effects of chronic immune system activation associated with years of HCV infection pre-transplant, recurrence of HCV infection post-transplant, and/or continued immune system dysregulation post-transplant (Brydon, Harrison, Walker, Steptoe & Critchley, 2008; Hilsabeck, Perry & Hassanein, 2002).

With regard to depressive symptoms, there was a significant reduction in BDI-II scores and a near statistically significant reduction in the percentage of patients reporting clinically significant symptomatology. Before the transplant, almost 30% of patients endorsed clinically significant depressive symptoms ranging from moderate to severe, while after the transplant, only 12% endorsed clinically significant symptoms in the mild to moderate range. This finding is consistent with previous studies reporting significantly improved depressive mood and QOL post-transplant (Hockerstedt et al., 1992; Moore et al., 2000; Riether et al., 1992). It is well known that liver disease and depression are highly comorbid since patients' QOL is greatly decreased due to physical limitations and/or medical complications caused by liver disease (Carithers, Sugano & Bayliss, 1996; Singh, Gayowski, Wagener & Marino, 1997). While it is possible that improved mood and physical health post-transplant contributed to improved cognition, it is unlikely that these factors alone can account for the magnitude of improvement found in the current study. Attention and psychomotor speed tend to be the most affected cognitive domains by depressed mood; however, attention did not show significant improvement after liver transplantation in the present study. It is also possible that improvement in physical aspects of health post-transplant contributes to a reduction in depressive symptoms (Belle, Porayko, Hoofnagle, Lake & Zetterman, 1997; Levy et al., 1995; Moore et al., 2000). However, since HCV reoccurrence after transplantation is common and liver transplant recipients with recurrent HCV tend to exhibit depression again (Singh, Gayowski, Wagener & Marino, 1999), it is crucial for clinicians to monitor mood status.

The current study findings must be interpreted within study limitations. The post-transplant evaluations in this study were conducted, on average, four years after the surgery, and there was a large range in time between pre- and post-transplant evaluations (i.e., 0.5-9 years). Since previous studies examined liver transplant recipients' cognitive functions up to 15 months post-transplant, it is possible that attention/executive functioning and motor speed might improve for a while but then decline over time, particularly if HCV recurs. Regretfully, the exact percentage of liver transplant recipients who had recurrence of HCV in the current study was not available but it was close to 100%. It will be helpful for future studies to assess liver transplant recipients' cognitive status at regular time intervals, perhaps at annual visits,

so that their changes, if any, can be characterized more consistently. Although all patients with ESLD had the same underlying cause of liver transplant (HCV), other etiology, such as the presence of substance disorders and hepatic encephalopathy prior to transplant, was not uniform. It is ideal for future studies to have a more homogeneous sample to better capture the role of HCV, although we acknowledge that comorbid disorders are the rule, not the exception, for individuals with HCV, and it may be difficult to recruit a large enough homogenous sample. In addition, this study did not include healthy controls or other disease comparison groups, so we cannot draw conclusions about relative deficit areas, although use of GDS and domain deficit scores allows for interpretation of severity of impairment based on normative samples. Finally, the sample size was relatively small which may have limited the ability to detect statistically significant differences in some areas when actually present (i.e., Type II error).

In summary, the present study confirmed significant improvements in cognitive functioning and depressive symptoms four years post-transplant in a sample of HCV-infected patients in their mid to late 50s. Unlike previous studies, this study focused on HCV infection as the primary underlying etiology of liver disease and provided a more representative age range of the majority of ESLD patients currently receiving liver transplantation. Before the transplant, almost 60% of patients exhibited mild global cognitive impairment across all domains and 30% endorsed clinically significant depressive symptoms. In contrast, after transplant, only 18% continued to exhibit global cognitive impairment primarily in the areas of attention/executive functioning and motor speed, and only 12% reported clinically significant depressive symptoms. While these findings are positive and demonstrate that liver transplantation is a life expanding treatment that improves cognitive function and depressive symptoms, it is important for clinicians to be aware that some liver transplant recipients may still have cognitive difficulties. Given that a high rate of recurrence of HCV post-transplant is well documented, it is possible that liver transplant recipients' cognitive function may again decline. These cognitive deficits in attention, executive function and motor speed can affect patients' everyday functioning including employment, driving, cooking, and managing medications (Albert et al., 1995; Benedict, Mezhir, Walsh & Hewitt, 2000; Gorman, Foley, Ettenhofer, Hinkin & van Gorp, 2009; Hinkin et al., 2002). It is therefore crucial to assess cognition, especially these three domains, as well as depression after liver transplantation on a regular, preferably annual, basis.

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