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Improvement of Neurocognitive Function in Responders to an Antiviral Therapy for Chronic Hepatitis C

Michael R. Kraus,[1,2]* Arne Schäfer,[1]* Gerlinde Teuber,[3] Heiner Porst,[4] Kathrin Sprinzl,[3] Sven Wollschläger,[4] Christian Keicher,[1] and Michael Scheurlen[1]

Earlier studies have suggested neurocognitive impairment in patients with chronic hepatitis C virus (HCV) infection even before liver cirrhosis has developed. Since these deficits might be reversible after successful antiviral therapy, we analyzed the long-term course of neurocognitive parameters in HCV patients with and without successful virus elimination by an interferon-based antiviral treatment. In a multicenter study including 168 HCV patients receiving antiviral therapy (peginterferon alpha-2b and ribavirin) we performed a long-term follow-up of neurocognitive performance before and after treatment. Neurocognitive function was psychometrically assessed using the computer-aided TAP (Test Battery of Attentional Performance). When tested at least 12 months after termination of antiviral treatment, patients with sustained virologic response (SVR) had improved significantly as compared to their pretreatment performance in three of five TAP subtasks (vigilance, $P < 0.001$; shared attention: optical task, $P < 0.001$; working memory, $P < 0.001$). Patients who failed to eradicate the virus, however, showed no significant long-term changes in neurocognitive performance in all five subtasks assessed ($0.194 < P < 0.804$). In the post-treatment evaluation, neurocognitive function was significantly better in responders to the antiviral therapy as compared to nonresponders. *Conclusion:* Successful eradication of HCV leads to a significant improvement of relevant aspects of attentional and neurocognitive performance, indicating that the neurocognitive impairment caused by chronic HCV infection is potentially reversible. This therefore suggests an added therapeutic benefit of antiviral treatment in HCV infection. Improvement of neurocognitive function may be an additional treatment indication in patients with HCV. (HEPATOLOGY 2013;58:497-504)

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An estimated 170 to 180 million people worldwide are chronically infected with the hepatitis C virus (HCV).[1,2] Chronic hepatitis C may lead to progressive hepatic injury and eventually to liver cirrhosis and endstage liver disease.[3,4] HCV infection is a leading cause of cirrhosis and hepatocellular carcinoma and a major indication for liver transplantation in the Western world.[4-7] The burden of chronic HCV infection remains substantial because of the high number of individuals infected before the identification of the virus.[8,9] Until recently, the standard treatment for chronic HCV infection was peginterferon alpha combined with ribavirin administered for 24 (HCV genotype 2 or 3) or 48 weeks (genotype 1, representing the most prevalent genotype in North America and Europe). This treatment leads to a sustained virologic response (SVR) in ~50% of HCV patients.[9]

Impairments of attention, concentration, and memory are frequent complaints among hepatitis C patients, and an aggravation of these symptoms is reported during antiviral therapy with peginterferon

Abbreviations: ANOVA, analysis of variance; EOT, end of treatment; HCV, hepatitis C virus; IVDU, intravenous drug use; t, evaluation timepoint; TAP, Test Battery of Attentional Performance.

From the [1]Medizinische Klinik und Poliklinik II, Department of Gastroenterology, University of Würzburg, Würzburg, Germany; [2]Kreiskliniken Altötting-Burghausen, Burghausen, Germany; [3]Medizinische Klinik I, Klinikum der Johann Wolfgang Goethe Universität, Frankfurt/Main, Germany; and [4]III. Medizinische Klinik, Krankenhaus Dresden-Friedrichstadt, Städtisches Klinikum, Dresden, Germany.

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**These authors contributed equally to this work.*

alpha and ribavirin. A decline in neurocognitive function in these patients resulting from antiviral therapy has been described in the recent literature.[10,11] However, little research has been performed to address the question of whether the chronic HCV infection and/or the concomitant hepatic inflammation per se lead to neurocognitive impairment, and whether such impairment may be reversible after successful interferon (IFN)/ribavirin therapy. The studies that have been published thus far are characterized by only small to moderate sample sizes and provide inconsistent results concerning the aspect of potential reversibility of morphological changes as documented by magnetic resonance spectroscopy.[12,13]

Therefore, we designed a longitudinal multicenter study to assess the long-term course of neurocognitive function in HCV patients treated with antiviral therapy, and to investigate the potential impact of SVR on neurocognitive performance.

Materials and Methods

Subjects. The participating patients were enrolled at three centers in Germany (Würzburg, Frankfurt, and Dresden) between 2005 and 2008.

Eligible outpatients had to be between 18 and 65 years of age and to be chronically infected with HCV (as confirmed by the presence of HCV RNA detected by PCR [polymerase chain reaction: Cobas Amplicor] testing) with an indication for antiviral treatment. Previous unsuccessful therapy attempts with less effective treatment protocols (e.g., IFN monotherapy) were not an exclusion criterion. All participants were seronegative for hepatitis B surface (HBs) antigen and for human immunodeficiency virus (HIV; types 1 and 2). The absolute neutrophil count had to be above 1,000/μL, the platelet count above 90,000/μL, and the hemoglobin level within the normal range. Patients were excluded if they had decompensated liver disease, nonviral causes of clinically relevant liver disease, or hepatocellular carcinoma. A recent liver histology was not available for all patients because a biopsy was not a precondition for study participation. We treated our patients according to the current German guidelines for hepatitis C.[14] These guidelines preclude active alcohol intake during antiviral therapy. To guarantee the necessary degree of abstinence, patients who had consumed more than 40 g (males) or 20 g (females) daily were not included in the study.

The study protocol was approved by the Ethics Committees of the participating study centers and conformed to the ethical guidelines of the Declaration of Helsinki. All patients provided written informed consent for participation in the trial before enrolment.

Study Design and Organization. This was a longitudinal trial with a repeated-measures design (dependent factor time) and one quasi-experimental independent factor (SVR versus no SVR). Due to the nature of the independent factor (SVR versus no SVR), randomization was not feasible in our study.

All participants received antiviral combination treatment after study enrolment and a baseline evaluation[15]; the treatment consisted of weekly subcutaneous injections of pegylated interferon (peginterferon alpha-2b: Pegintron 1.5 μg per/kg of body weight per week) and weight-adapted ribavirin (Rebetol 800-1,200 mg daily, given orally) for 24 weeks (genotypes 2 and 3) or for 48 weeks (genotypes 1 and 4). During the study period, we adopted a more flexible treatment regimen for a subgroup of our patients according to changing recommendations: HCV type-1 infected patients with a low viral load before treatment (<600,000 IU/mL) who became virus-negative at treatment week 4 (rapid virologic response [RVR]) were treated for only 24 instead of 48 weeks.[15,16] This shortened treatment duration was approved in the European Union (EU) in 2005.[15-18] The latter information was added to the original study protocol as an amendment. An SVR was defined as a negative PCR assay 24 weeks after completion of antiviral therapy for chronic HCV infection.

Neuropsychological Testing. Neurocognitive and attentional performance were assessed using a set of computer-assisted psychological tests (TAP: Test for Attentional Performance; v. 1.02c[19,20]).

Address reprint requests to: Arne Schäfer, Medizinische Klinik und Poliklinik II, University of Würzburg, Department of Gastroenterology, ZIM Zentrum Innere Medizin (A3.-1.879), Oberdürrbacher Str. 6, D-97080 Würzburg, Germany. E-mail: arne.schaefer@mail.uni-wuerzburg.de; fax: +49-931-201-640201.*

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Potential conflict of interest: Michael R. Kraus is a consultant for and advises the Merck Group (USA) and MSD (Munich, Germany) and Roche (Grenzach-Wyhlen, Germany). He has received grants from Merck. Arne Schäfer has no competing interests to declare. Gerlinde Teuber is a consultant for, advises, and has received grants from MSD/Essex Pharma (Munich, Germany), Roche (Grenzach-Wyhlen, Germany), and Gilead. Michael Scheurlen advises, is on the speakers' bureau of, and received grants from Merck. Heiner Porst, Kathrin Sprinzl, Sven Wollschläger, and Christian Keicher have no competing interests to declare.

The tasks consist of simple and easily distinguishable stimuli that the patients react to with a simple motor response. Based on a previously published study by our group,[10] the four most relevant (from a total of 12) computerized tasks were selected to monitor cognitive functions during treatment and follow-up periods (listed in the order of subtask presentation):

- *Alertness* (10 minutes): This examination includes a simple and a cued reaction time task (visual test stimulus with and without an additional acoustic cue). The simple reaction time has been shown to be a valid measure of general slowness, whereas the difference between a simple and a cued reaction time is a measure of phasic alertness. The visual stimulus consists of a white cross on a black background presented approximately every 3 seconds.
- *Divided Attention* (5 minutes): Divided attention (simultaneous attention to various aspects) can be investigated using so-called dual tasks, including independent visual and acoustic tasks. The visual task consists of crosses that appear in a random configuration in a 4 × 4 matrix. The subject is asked to detect whether the crosses form the corners of a square. The acoustic task consists of a regular sequence of high and low beeps. The subject is asked to detect any irregularity in the sequence.
- *Vigilance* (20 minutes): Sustained attention is assessed as follows: out of a series of monotonously presented acoustic and visual stimuli (alternating beeps and letters over a time period of 15 minutes), the patient must press a button if the sequence "high beep followed by E" or "low beep followed by N" occurs.
- *Working Memory* (15 minutes): This test measures the subject's ability to manage a continuous flow of information with short-term memory. Numbers are presented on the screen that must be compared with previously exposed numbers. The subject must identify the repetition of a number within a short interval by pressing a key. The subject is asked to press the key when the presented number equals the number before the previous one.

Statistical Analysis and Sample Size Considerations. All statistical analyses were performed at the study's data coordinating center, located in Würzburg University (Medizinische Klinik und Poliklinik II, Department of Gastroenterology, Würzburg, Germany). Data management and all statistical analyses were performed using SPSS software (German v. 15.0.1[21]).

The primary endpoint was the neurocognitive performance of the patients in each subgroup (SVR versus no SVR) 48 weeks after the end of the antiviral combination therapy. The primary analysis upon which the sample size consideration was based involved the comparison of the SVR subgroup and the subgroup of patients without SVR. The sample size calculation assumed a two-factorial design (time course × SVR) with the use of a two-way analysis of variance (ANOVA) analysis, a significance level of 5% and a statistical power of at least 80% to detect a medium effect size ($d = 0.5$) and thus to show a significant group difference. Based on this background, the optimal sample size was calculated to be a total of 102 subjects. To consider asymmetric subgroups and to allow for a moderate dropout rate and additional calculations (secondary study objectives), we aimed to include a total of at least 150 study participants.

Patients who dropped out of the study were considered as not having reached the primary endpoint. Therefore, their data were not included in the final analyses.

In accordance with the above-described study design we used ANOVA analyses to test for changes over time and between-group differences (SVR versus no SVR) in relevant measures of neurocognitive performance (e.g., TAP reaction time). All reported *P* values are two-sided.

Results

Patients. Beginning in 2002, pretherapeutic psychometric tests were offered to all patients scheduled for antiviral therapy with interferon plus ribavirin at the study center in Würzburg, Germany. Beginning in 2005, all patients, independent of their treatment outcome, were offered an additional session of psychometric testing to evaluate the possible influence of the treatment outcome on their long-term cognitive function. As defined by the study design, the minimum interval between the end of treatment and the follow-up testing was 12 months (19.1 ± 11.0). A total of 141 patients completed both tests. Fifty-six additional patients were enrolled at the other participating study sites: Med. Klinik I, University of Frankfurt ($n = 44$), and Klinikum Dresden-Friedrichstadt ($n = 12$). Therefore, the total size of the study sample was $N = 197$ patients.

Longitudinal Assessment: Dropout Rate. During the study period, a total of 29 of 197 (14.7%) patients were lost to follow-up. These participants did not show up for the final evaluation of cognitive function after the end of antiviral treatment. They were not included in the final evaluation. Consequently, we were able to include 168 study participants in the final longitudinal analysis. As shown in Table 1, the

Table 1. Relevant Sociodemographic and Medical Baseline Characteristics: Comparison Between Study Dropouts (n = 29) and the Remainder of the Study Population (n = 168)

Parameter	Study Dropouts (n = 29)	Patients With Follow-up (n = 168)	*P* Value
Age	39.8±13.0	43.2±10.8	$P = 0.137$
Gender	m: 72.4%	m: 50.6%	$P = 0.042$
	f: 27.6%	f: 49.4%	
Acquisition	unclear 31.6%	unclear 37.5%	$P = 0.855$
	IVDU 42.1%	IVDU 40.5%	
	transf. 26.3%	transf. 22.0%	
Genotype	GT1 61.1%	GT1 61.3%	$P = 0.819$
	GT2 5.6%	GT2 10.1%	
	GT3 33.3%	GT3 26.8%	
	GT4 0%	GT4 1.8%	
Liver histology	hep. 46.7%	hep. 38.4%	$P = 0.626$
	fib. 46.7%	fib. 46.3%	
	cirrh. 6.7%	cirrh. 15.2%	

Provided *P* values are based on ANOVA (age) or chi-square analyses. m, male; f, female; IVDU, intravenous drug use; transf., transfusion; GT, genotype; hep., hepatitis; fib., fibrosis; cirrh., cirrhosis.

dropout patients were not significantly different from the remainder of the study population with respect to the majority of the relevant demographic and medical variables assessed. However, male patients were overrepresented in the subsample of study dropouts (72.4 versus 50.6%; $P = 0.042$).

Approximately 15% of our study patients had liver cirrhosis at the beginning of the study (see Table 1), and all patients were in Child stage A. None of the patients had progressed to stage B or C at the time of the follow-up evaluation, which was at least 12 months after the end of antiviral therapy.

Longitudinal Assessment: TAP Retest Reliability. The short-term retest reliability of the applied TAP subtasks and the magnitude of any potential learning effect were evaluated in a subgroup of patients (n = 50) from the test center in Würzburg, in whom the pretherapeutic test was repeated after 1 week. The findings are presented in Table 2. The test results were stable and not subject to relevant fluctuation, variation, or a significant effect of training. We found that the neurocognitive measures test battery applied was suitable for the evaluation of neurocognitive changes over time in patients with chronic HCV infection.

Long-Term Evaluation: Possible Bias Related to the Interval Between EOT and Follow-up. The interval between the end of the antiviral treatment and the second psychometric testing varied in the study group from 12 to 48 months. To exclude the possibility that a deterioration of cognitive function due to the progression of the liver disease in the nonresponders might misleadingly appear to indicate a relative improvement in the responders, we examined whether the follow-up period was significantly different between both subgroups. This analysis demonstrated that there was no statistically significant difference ($P = 0.697$) between the responders (18.9 ± 10.8 months) and the nonresponders (19.5 ± 11.4 months). In addition, there were no changes in the final results when the exact length of follow-up period was taken as a covariate in the statistical analyses (data not shown).

Long-Term Evaluation: Cross-Sectional Comparison. Neurocognitive performance was compared between the subgroups with (n = 116; 69%) and without (n = 52; 31%) SVR. While there was no difference before treatment, the posttreatment neurocognitive performance was better in the group of patients with SVR compared to the patients who had not cleared the virus (Table 3). This difference was statistically significant for reaction times in the TAP subtasks related to vigilance ($P = 0.004$) and working memory ($P = 0.010$).

Longitudinal Assessment. According to our primary study objective, we compared changes over time within the subgroups of patients with and without SVR. Using repeated measures ANOVAs, we showed that within the subgroup of sustained responders (n = 116) the neurocognitive performance at the long-term follow-up evaluation was significantly improved in the TAP subtasks related to vigilance, divided attention [optical], and working memory compared to the

Table 2. Stability of TAP Subtests Over a Time Interval of 1 Week as Measured by Retest Reliability

Parameter Evaluated (Reaction Time [msec])	1. ETP (T1a)	2. ETP (T1b)	Reliability (rtt) (Significance *P*)	T-test for Dependent Samples (*P*)
Alertness (4^{th} trial)	285.7 (32.3)	277.1 (21.4)	0.548 (0.053)	0.758
Vigilance	542.1 (42.4)	528.3 (41.8)	0.700 (0.008)	0.679
Divided Attention (optical)	851.4 (39.4)	856.2 (39.1)	0.873 (<0.001)	0.809
Divided Attention (acoustic)	577.8 (28.1)	587.8 (28.9)	0.735 (0.004)	0.390
Working Memory	631.7 (43.3)	659.4 (36.2)	0.847 (0.004)	0.264

Subsample n = 50 patients. Reaction times are presented in milliseconds: mean (SEM). ETP, evaluation timepoint; T1a, first baseline evaluation; T1b, second baseline evaluation.

Table 3. Cross-Sectional Comparison of TAP Performance Between Patients With and Without SVR at the Time of Follow-up Evaluation, at Least 1 Year After the End of Antiviral Treatment

TAP Subtask	Patients With SVR (n = 116)	Patients Without SVR (n = 52)	*P* Value
Alertness	258.6 ± 5.8	275.7 ± 19.5	$P = 0.271$
Divided attention (acoustic)	558.4 ± 8.5	581.8 ± 14.3	$P = 0.149$
Divided attention (optical)	829.7 ± 11.1	874.6 ± 23.9	$P = 0.092$
Vigilance	466.2 ± 10.8	530.5 ± 22.1	$P = 0.004$
Working memory	611.6 ± 12.8	676.2 ± 22.5	$P = 0.010$

Reaction times at follow-up evaluation [msec]. Given values represent mean ± SEM.

baseline evaluation. These results are presented in Figs. 1-3.

In the group of patients who did not eliminate HCV (n = 52), the neurocognitive performance did not change significantly after termination of the antiviral treatment compared to measurements at baseline. This applied to all five TAP subtasks performed ($0.194 \leq P \leq 0.804$). However, we also did not detect any significant deterioration of test performance in the nonresponder group as a possible sign of worsening liver function during the study period.

Impact of Liver Histology on Outcome Variables. To control for the possible impact of advanced liver disease, we included the covariate "liver cirrhosis" in the general linear models performed for the detection of longitudinal (baseline versus follow-up) and between-group (SVR versus non-SVR) differences. The variable "cirrhosis" could not be identified as a significant covariate in any of these analyses ($P > 0.700$), indicating that our results were not biased by liver cirrhosis as a confounding factor.

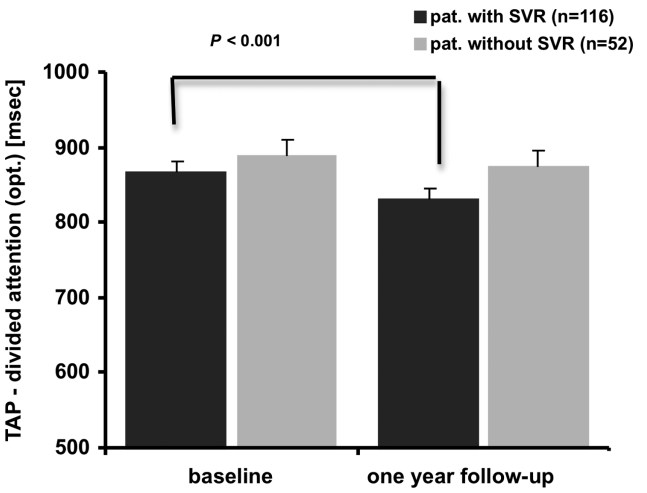

Fig. 2. Longitudinal changes in neurocognitive performance: TAP subtask divided attention (optical): comparison between baseline and long-term follow-up evaluation 1 year after the end of antiviral treatment.

Discussion

Among the well-documented neurological and psychiatric side effects of interferon, an impairment of cognitive function by this drug during antiviral treatment for chronic hepatitis C has been well documented by us and others.[10,11,22] However, evidence from smaller studies suggests that the brain may be affected in patients with chronic HCV infection and noncirrhotic liver disease even before an antiviral treatment has been initiated.[23-26] These studies have mainly focused on cerebral magnetic resonance

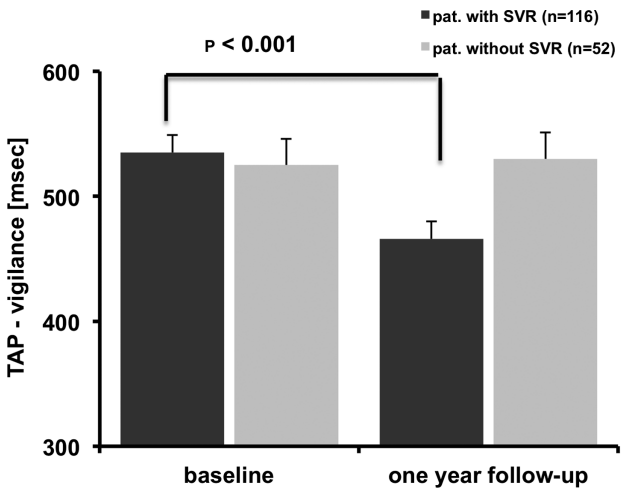

Fig. 1. Longitudinal changes in neurocognitive performance: TAP subtask vigilance: comparison between baseline and long-term follow-up evaluation 1 year after the end of antiviral treatment.

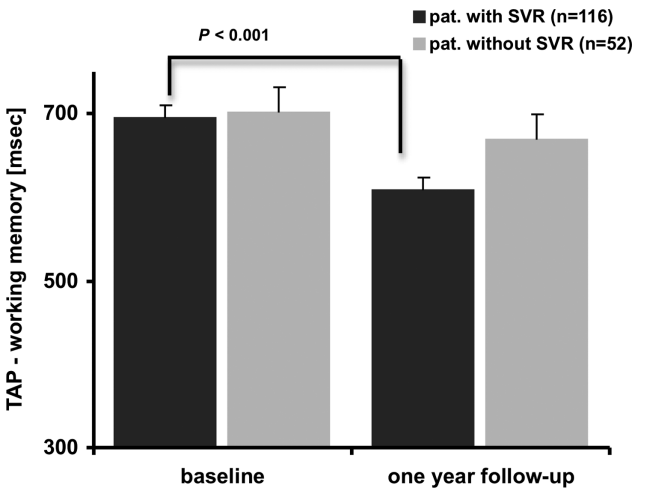

Fig. 3. Longitudinal changes in neurocognitive performance: TAP subtask working memory: comparison between baseline and long-term follow-up evaluation 1 year after the end of antiviral treatment.

imaging (MRI) and functional single photon emission tomography (SPECT) neuroimaging in infected patients in comparison with healthy controls. From their results it remains unclear whether the hepatitis C virus per se has a direct effect on cerebral function, or whether the impairment is caused by the chronic inflammation in the liver.

Quantitative data on functional impairment are less frequent,[27,28] and only few data are available describing the potential reversibility of cognitive disturbances associated with chronic HCV infection.[12]

Therefore, this study examined pretreatment and posttreatment cognitive functions in patients with chronic HCV infection. We used a computerized test battery to quantify even small effects of permanent virus elimination on neurocognitive performance. The TAP battery measures the patients' reaction with a simple motor response to simple and easily distinguishable stimuli. It has been shown that the test is not influenced by a significant learning effect[19,20] and is therefore applicable for longitudinal comparisons in a repeated-measures design. This was again confirmed in a subgroup of patients in this study, in whom we demonstrated the stability of performance without a relevant learning effect, even when the test was repeated after only 1 week (Table 2). In a previous study on antiviral therapy in HCV-infected patients, we used the TAP test battery to assess and quantify the negative but fully reversible effects of interferon-based therapy on neurocognitive performance.[10]

In our study, we identified a comparatively high rate of sustained responders (116 of 168 patients, SVR 69%). This might be explained to some extent by the fact that due to the study design no dropouts during the treatment phase were included (i.e., these represent per protocol rather than intention-to-treat data). In addition, our response rate corresponds well to published data for well-motivated and treatment-adherent patient groups. McHutchison et al.[29] published an SVR of 63% for a group (majority genotype 1) that received at least 80% of their medications over at least 80% of the time.

We observed a significant improvement of neurocognitive function measured at least 1 year after the completion of a successful antiviral therapy. However, in nonresponders or in patients that relapsed after treatment with interferon/ribavirin, there was no significant change of performance in any of the TAP subtasks. From this, it can be concluded that the cognitive impairment in patients with active HCV infection is potentially reversible. This result is further supported by the fact that we were able to exclude the exact duration of the follow-up period as a possible confounding factor. Remarkably, the posttreatment improvement consisted of only the more complex and demanding TAP subtests. The task "divided attention: optic" requires continuous visual scanning of the computer screen for predefined patterns, while in the task "divided attention: acoustic," where no posttreatment improvement was noted, the (acoustic) signals are more readily available to the sensorium. Equally, the subtask "vigilance" is characterized by the presentation of monotonous signals over 15 minutes, and the performance is therefore sensitive to a condition with an increased fatigability, as has been described for chronic hepatitis C.[30,31] Similarly, the subtask "working memory" requires the continuous concentration of the subjects on a sequence of numbers that is presented optically. While the pretreatment performance in all tests was identical in both patient groups, the patients after successful antiviral therapy had significantly better results in the above-mentioned subtasks "vigilance" and "working memory" in a cross-sectional comparison performed at least 1 year after treatment.

The study design chosen does not allow for an in-depth investigation of the possible underlying mechanisms. Plausible explanations for the SVR-associated neurocognitive improvement refer to either direct neurotoxicity of the HCV or indirect mechanisms mediated by HCV-triggered or inflammation-triggered induction of cytokine cascades. In an earlier study we demonstrated that a similar pattern of neurocognitive impairment, although considerably more pronounced than in the present investigation, occurs in HCV patients during high-dose IFN therapy.[10] However, it is controversial whether endogenous IFN production is induced during chronic hepatitis C infection. While it has been demonstrated *in vitro* that IFN production may be impaired by HCV,[32] another study found elevated IFN serum titers in approximately half of infected patients.[33] Therefore, it remains unclear whether IFN or other proinflammatory cytokines confer a cognitive impairment in chronic HCV infection.

Finally, it cannot be excluded that parenchymal recovery following HCV eradication might be responsible for the observed effects because comparative pretreatment and posttreatment liver biopsies were not taken.

Our findings are consistent with previously published results from smaller studies suggesting that HCV-associated neurocognitive decline may be reversible after viral clearance: For example, Forton et al.[28]

were able to demonstrate that the ability to concentrate and the speed of memory processes were significantly impaired in patients with chronic HCV infection compared to healthy controls. In contrast, the authors found no difference in neurocognitive performance between healthy controls and former HCV patients who had cleared the virus. However, the study had a small sample size (27 viremic HCV patients and 16 patients after virus clearance) and represented a cross-sectional study approach.

Interestingly, there are also reports suggesting that chronic fatigue and cognitive dysfunction may persist in several patients even after successful clearance of the HCV virus.[13,26] The question whether a cognitive deficit persisted even in our group of successfully treated patients compared to individuals who had never been infected cannot be answered. For this, a representative and well-matched control group would have been necessary.

In conclusion, our data confirm previous reports that in patients with chronic HCV infection, neuropsychological performance is affected not only by high-dose interferon alpha-2b therapy,[10,34] but also by the infection per se; furthermore, this latter impairment is potentially reversible after successful virus eradication. Thus far, the prevention of liver cirrhosis and its consequences have been the main goal of antiviral therapy in patients with chronic HCV infection. We suggest that the potential benefit of a successful therapy for chronic hepatitis C with respect to the patients' neurocognitive function should be considered as an additional treatment indication in this disease.

The aim of further studies would be to clarify the exact mechanisms that link HCV infection and neurocognitive function.

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