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Cognitive Function After Treatment for Alcohol Problems

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Abstract

Objective: The objective of this study was to assess cognitive function and the potential recovery in a group of patients with alcohol dependence (AD) in treatment for alcohol problems.

Methods: Patients with AD, fulfilling the ICD-10 diagnostic criteria, were recruited consecutively over a 9-months period from an outpatient clinic at Hvidovre University Hospital, Denmark. Patients' (n=74) cognitive function was repeatedly assessed within 100 days after start of treatment by means of two methods: The quick test of cognitive speed (AQT) and continuous reaction time (CRT). The association between days from start of alcohol treatment and cognitive function was assessed in linear generalized estimating equation models, taking account of correlation structure in data and incomplete follow-up. All analyses were adjusted for sex, years of alcohol dependence, days of high alcohol use 30 days before start of treatment, other drug use, relapse, use of psychoactive medicine, and psychiatric diagnosis.

Results: At treatment start, 46 % of the patients displayed a normal score on both tests, 12 % of the patients had abnormal scores on both tests, and 42 % of the patients had an abnormal score on one test. Our results indicate a slight improvement of AQT reaction time over time, whereas the CRT test score was almost stable throughout the follow-up.

Discussion: We found no clinically significant improvement of cognitive function among patients with AD treated for alcohol problems. Further research of alcohol related cognitive impairments and recovery is needed to guide clinical practice in treatment of AD and timing of cognitive behavioral therapy.

Keywords: Treatment; Recovery; Alcohol Dependence; Cognitive Function; The Quick Test of Cognitive Speed; Continuous Reaction Time

Introduction

Alcohol is the causal factor for more than 200 diseases and conditions (Rehm, *et al.*, 2017) [1] and is one of the leading global risk factors for the overall disease burden (World Health Organization, 2018) [2]. Studies among patients with alcohol dependence (AD) have demonstrated an approximately 3-fold higher mortality compared to the general population (Holst, Tolstrup, Sorensen, & Becker, 2017) [3]. Further, alcohol may damage multiple brain regions and a range of non-selective cognitive functions, especially if chronically consumed, causing cognitive impairments and behavioral changes (Oscar-Berman, Shagrin, Evert, & Epstein, 1997; Stavro, Pelletier, & Potvin, 2013) [4,5]. According to one study, 50 to 85 % of AD patients show signs of mild to moderate cognitive deficits (Parsons & Nixon, 1993) [6]. The degree of neuropsychological dysfunction does not correlate consistently with measures of previous alcohol consumption (George Fein, Torres, Price, & Di Sclafani, 2006) [7], but may arise from a complex interaction between the direct effects of ethanol, indirectly through damage of other organs that interferes with nerve cells in the brain, and coexisting health problems and behaviors. For example liver disease (Corrao, Bagnardi, Zambon, & La Vecchia, 2004; Udo, Vasquez, & Shaw, 2015) [8, 9], dietary deficiencies (Molina, 1994) [10], comorbid psychiatric disorders (Dawson, Grant, Stinson, & Chou, 2005) [11], use of psychoactive drugs (Berg & Dellasega, 1996) [12], family history of alcoholism (Drake, *et al.*, 1995; Peterson, Finn, & Pihl, 1992) [13,14], genetics (Edenberg & Foroud, 2013; Gierski, *et al.*, 2013) [15,16], other drug use (M. o. S. D. T. World Health Organization, 2004) [17], brain volume reduction (Ding, *et al.*, 2004; Zahr & Pfefferbaum, 2017) [18,19] and somatic comorbidity (Lauridsen, *et al.*, 2016) may impact cognitive function and recovery. In the most severe cases, AD patients may develop Korsakoff's syndrome, Wernicke's encephalopathy (Zahr & Pfefferbaum, 2017) [19] or dementia (Holst, *et al.*, 2017) [3].

The possibility of recovery of cognitive function after treatment for AD and cessation of drinking is an area that has not been extensively investigated and existing evidence is inconsistent. A study of cognitive function among long-term abstinent AD patients (abstained on average 6.7 years) showed that abstinent AD patients performed similarly to controls (George Fein, *et al.*, 2006) [20]. Another study showed impaired cognitive function among AD patients as compared to controls, regardless of abstinence duration (Nowakowska, Jablkowska, & Borkowska, 2007) [21]. While a meta-analysis of cognitive deficits in alcoholism, suggests that cognitive function among AD patients do not appear within the normal range, until over a year of sobriety (Stavro, *et al.*, 2013) [22].

Understanding how cognitive function among AD patients develops over time is important as it may add to evidence guiding clinical practice in treatment of AD, and timing of cognitive behavioral therapy.

The aim of the present study was to the assess the association between cognitive function (measured with AQT and CRT) and time since start of treatment for alcohol problems among AD patients.

Methods

Subjects

Patients with AD were recruited consecutively over a 9-months period from an outpatient clinic at Hvidovre University Hospital, Denmark (year 2007-2008). Treatment at hospitals and hospital outpatient clinics is free of charge in Denmark, and admission is open. Patients fulfilling the ICD-10 diagnostic criteria for AD, and seeking assistance at the clinic, were invited to participate in a study evaluating nutrient intake and nutritional status, as described elsewhere (Wilkens Knudsen, *et al.*, 2014) [23], in which cognitive function, along with other factors, were accessed.

Participation in the study was voluntary and participating patients provided informed consent that their data could be used for research. The study was approved by The Danish National Committee on Biomedical Research Ethics (ref.no. H-A-2007-0032) and the Danish Data Protection Agency (ref. no. 2007-41-0735).

Patients were excluded if they were under the age of 18[1], had received blood transfusion or major surgery within the last 3 months, had a malignant disease, were pregnant or breastfeeding, or if they did not understand Danish. A total of 80 patients with AD were included, comprising 29 % of all patients who entered the treatment program in the inclusion period. Included patients did not vary significantly from patients not entering the study, regarding age ($p = 0.48$), gender ($p = 0.84$), alcohol intake ($p = 0.94$) or duration of alcohol abuse ($p = 0.97$) (Wilkens Knudsen, *et al.*, 2014).

[1]There was no upper age limit, however the oldest patient included was 68 years old.

The initial test of cognitive function was conducted as quickly as possible after treatment initiation, and hereafter patients were invited for cognitive tests approximately every 2nd week the first 2 months, and a final test 6 months after start of treatment. Six patients never showed up for the initial test, and several of the following tests were delayed or missing for some patients, as they failed to show up for their scheduled appointment or to show up at all. The final test was only conducted among 26 patients, with the last test performed 454 days after start of treatment. Patients with complete data may not be representative of AD patients in treatment, and due to potential selection bias, these test results from the final test are excluded from the analysis. This left a study population of 74 patients, with three test estimates, and 191 participant observations.

Cognitive function

Cognitive function is a complex phenomenon and consists of several domains as attention, memory, processing speed, semantic fluency, motor control, executive function, and visual-perceptual function. In this study different domains were measured by means of two tests: The Quick Test of Cognitive Speed (AQT) and Continuous reaction time (CRT).

The Quick Test of Cognitive Speed (AQT)

AQT was designed to assess perceptual and cognitive speed from visual stimuli to verbal response (Nielsen, Wiig, Warkentin, & Minthon, 2004; Wiig, *et al.*, 2002) [24,25]. The test has been used in the evaluation of patients with Alzheimer disease (Nielsen, *et al.*, 2004) [24] and dementia evaluation in primary care (Kvitting, Wimo, Johansson, & Marcusson, 2013) [26]. In part 1 and 2 of the test one dimension is assessed at a time, thus the patient names forms (circles, squares, triangles, or rectangles) and colors (red, black, yellow, or blue) respectively. In part 3 overall cognitive speed is assessed using both dimensions, and the patient is asked to name colors and forms of the 40 visual stimuli. The main result is extracted from part 3 of the test and measured in seconds. A test result above 70 seconds is considered abnormal. AQT has shown to be independent of language, color blindness, education, age and gender (Kvitting, *et al.*, 2013; Takahashi, Awata, Sakuma, Inagaki, & Ijuin, 2012) [26, 27].

Continuous reaction time (CRT)

CRT is an approximately 10 minutes registration of motor reaction to audible stimuli, that measures and combines motor reactions speed, sustained attention, and inhibitory control. CRT is used for the assessment of mild forms of hepatic encephalopathy and is used as a screening tool for minimal hepatic encephalopathy in Scandinavia (Lauridsen, *et al.*, 2016 [20]). CRT is measured by means of a set of headphones, a trigger button, a laptop, and software (Lauridsen, Thiele, Kimer, & Vilstrup, 2013) [28] (in this study EKHO was applied). The patient must press a button as fast as possible in response to each audible stimulus in the headphones. During the test, the patient is exposed to 150 randomly occurring sound stimuli (90 dB and 500 mHz) with 2 to 6 seconds intervals. The CRT index (the ratio: 50 percentile/(90 minus 10 percentile)) is a measure of intra personal reaction time stability (Lauridsen, *et al.*, 2016) [20], and a value below 1.9 is considered abnormal (Lauridsen, *et al.*, 2013) [28]. The CRT index has shown to be independent of gender, age and intelligence (Lally & Nettelbeck, 1977; Lauridsen, Gronbaek, Naeser, Leth, & Vilstrup, 2012) [29,30].

Covariates

Information on age, sex, highest completed education, employment status, years of alcohol dependence, other drug use, use of psychoactive medicine, psychiatric diagnosis, days of a high alcohol use (≥5 drinks/day) 30 days before start of treatment, and weekly alcohol intake 30 days before start of treatment, was obtained through systematic interviews and registered in the Copenhagen Alcohol Cohort as described elsewhere (Holst, *et al.*, 2017) [3].

Years of alcohol dependency (<14 years/≥14 years), and days of high alcohol use (≥5 drinks per day) 30 days before start of treatment (not every day/every day) were dichotomized based on the median. Other drug use was dichotomized (yes/no), and due to the size of the study population no distinction was made between type of drug(s) used. Patients were defined as users of psychoactive medicine if they used at least one of the following products: antipsychotic medicine, antidepressants, anti-anxiety agents (benzodiazepine), anti-abstinence agents, unspecific sedatives (neuroleptic), or hypnotics (sleeping pills). Patients that were intoxicated by alcohol under the conduction of a test or in between tests were classified as having relapse (yes/no). Patients were identified as having a psychiatric diagnosis (yes/no) if they had at least one psychiatric diagnosis.

Statistical methods

The potential association between days from start of alcohol treatment and cognitive function was assessed in linear generalized estimating equation models, taking account of the cor-

relation structure in data, where most individuals participated in multiple tests (Hanley, Negassa, Edwardes, & Forrester, 2003) [31].

Days since starts of treatment, was applied as a continuous, quadratic, and categorical variable (0-21 days, 22-35 days, 36-70 days and 71-101 days) in the models, to assess how the association was best described. To compare model fit, we utilized the QIC_U statistic for GEE models, which is analogous to AIC (Pan, 2001) [32]. All analyses were adjusted for sex, years of alcohol dependence, days of high alcohol use 30 days before start of treatment, other drug use, relapse, use of psychoactive medicine, and psychiatric diagnosis. Incomplete follow-ups were assumed missing-at-random, under these adjustments (see appendix 1 for characteristic of patients with incomplete follow-up). As a descriptive measure, we estimated cubic smoothing splines to the data using the smooth.spline function in R (R Core Team, 2018) [33].

Sensitivity analyses were conducted, to assess whether cognitive recovery varied depending on years of alcohol dependence, days of high alcohol use 30 days before start of treatment, other drug use, relapse, use of psychoactive medicine, and psychiatric diagnosis. Thus, stratified analyses were performed, and potential interactions between these factors and time since start of treatment on cognitive function were assessed.

Results

Baseline characteristics

The study population consisted of 74 patients, 70 % were men, and the average age was 49 years (table 1). The majority had a short educational level (38 %), 20 % were employed, and consumed 100 drinks per week on average in the 30 days before start of treatment. At treatment start, 46 % of the patients displayed a normal

Table 1: Baseline characteristics of study population, normal/abnormal baseline tests of the Quick Test of Cognitive Speed (AQT) and Continuous reaction time (CRT) index

Variable	Total	Both AQT and CRT index normal	Only AQT abnormal	Only CRT index abnormal	Both AQT and CRT index ab normal
Total	74	34	6	25	9
Men, n (%)	52 (70)	24 (71)	3 (50)	19 (76)	6 (67)
Mean age (IQR)	49 (43-54)	46 (42-53)	47 (41-53)	51 (46-58)	49 (47-50)
Highest education completed					
Basic schooling, n (%)	23 (31)	11 (32)	0 (0)	9 (36)	3 (33)
Short education, n (%)	28 (38)	10 (29)	3 (50)	9 (36)	6 (67)
Tertiary education, n (%)	23 (31)	13 (38)	3 (50)	7 (28)	0 (0)
Employed, n (%)	15 (20)	11 (32)	0 (0)	2 (8)	2 (22)
Years of alcohol dependence, median (IQR)	14 (6-21)	13 (10-21)	5 (4-5)	14 (6-19)	19 (13-24)
Days of high alcohol consumption (≥5 drinks/day), median (IQR)a	30 (10-31)	20 (8-30)	30 (7-30)	30 (25-30)	30 (20-30)
Weekly alcohol intake (drinks/week), median (IQR)[a]	100 (50-168)	103 (42-140)	67 (35-102)	91 (66-175)	130 (90-210)
Other drug use (cannabis, cocaine or other substances), n (%)	11 (15)	7 (21)	1 (17)	1 (4)	2 (22)
Relapse, n (%)	13 (18)	5 (15)	0 (0)	4 (16)	4 (44)
Use of psychoactive medicine, n (%)	42 (57)	16 (47)	6 (100)	13 (52)	7 (78)
Psychiatric disorders, n (%)	32 (43)	15 (44)	1 (17)	13 (52)	3 (33)

IQR, interquartile range

[a]30 days before start of treatment

score on both tests, 12 % of the patients had abnormal scores on both tests, and 42 % of the patients had an abnormal score on one test.

The test results of AQT and CRT at baseline were weakly correlated with a correlation coefficient at -0.21 (p=0.07). Patients with abnormal values for both AQT and CRT were more likely to have a shorter education, to have been addicted to alcohol for a longer period of time, to have a higher weekly alcohol intake before start of treatment, and to experience relapse or use psychoactive medicine, than patients with normal test results for AQT and CRT at baseline.

Only few patients had biochemical signs of liver diseases (data not shown) (Wilkens Knudsen, *et al.*, 2014).

In figure 1, the distribution of test values for AQT and CRT during the study period is illustrated. During the study period, 52 % of the patients displayed normal scores on both tests, 8 % abnormal scores on both tests, and 39 % abnormal scores on one of the tests. The test results were weakly correlated, with a correlation coefficient at -0.23 (p=0.001).

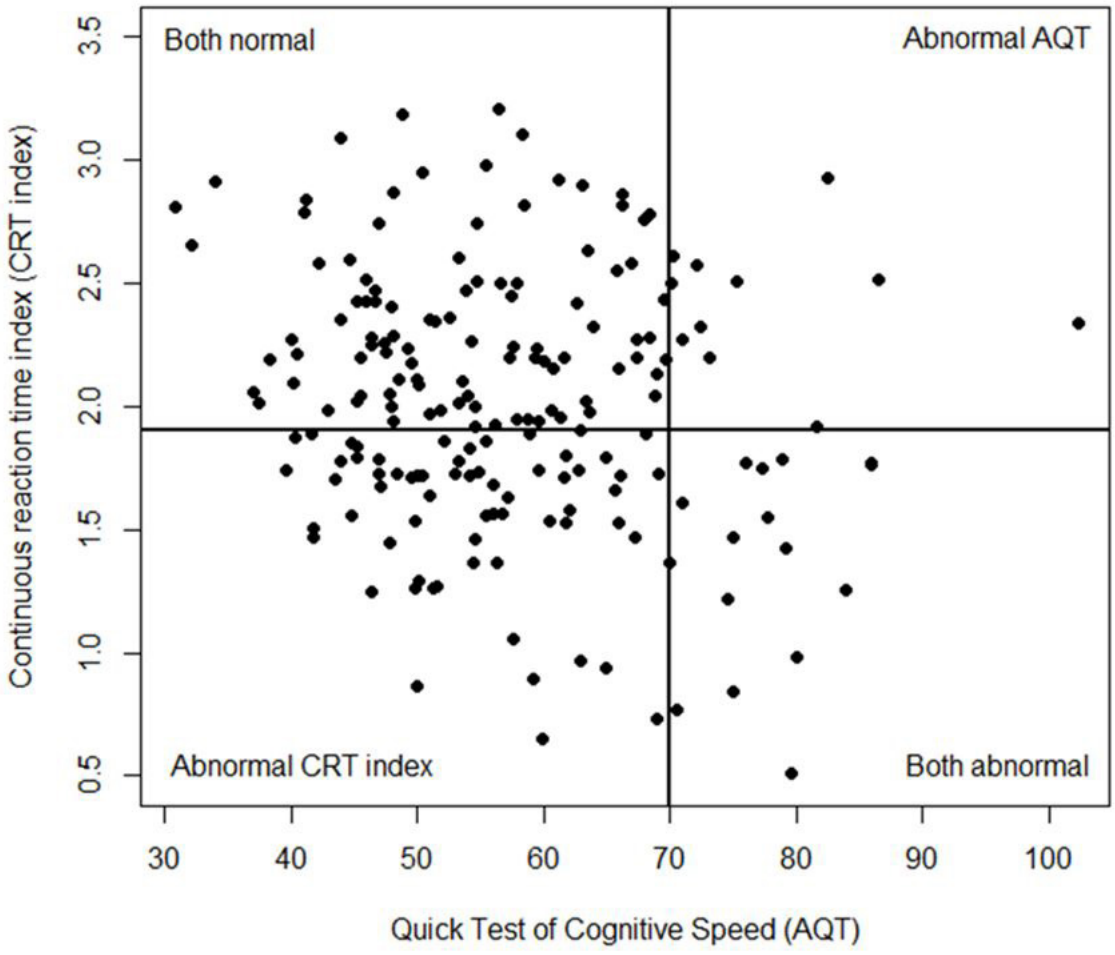

Figure 1: Test values for AQT and CRT index during the study period

The Quick Test of Cognitive Speed (AQT) after treatment for alcohol problems

The association between time since start of treatment and AQT, adjusted for sex, years of alcohol dependence, days of high alcohol use 30 days before start of treatment, other drug use, relapse, use of psychoactive medicine, and psychiatric diagnosis, is significant when time is applied as a continuous variable (p=0.002), and as a quadratic variable (p=0.03), and not when applied as categorical (p=0.09). Time as a continuous variable had the better fit (lowest QIC_U).

The AQT reaction time, adjusted for sex, years of alcohol dependence, days of high alcohol use 30 days before start of treatment, other drug use, relapse, use of psychoactive medicine, and psychiatric diagnosis decreased by 3.3 seconds per 30th day (β = -3.3 (95%CI: -5.4; -1.2), as presented in figure 2.

The Continuous reaction time (CRT) index after treat-

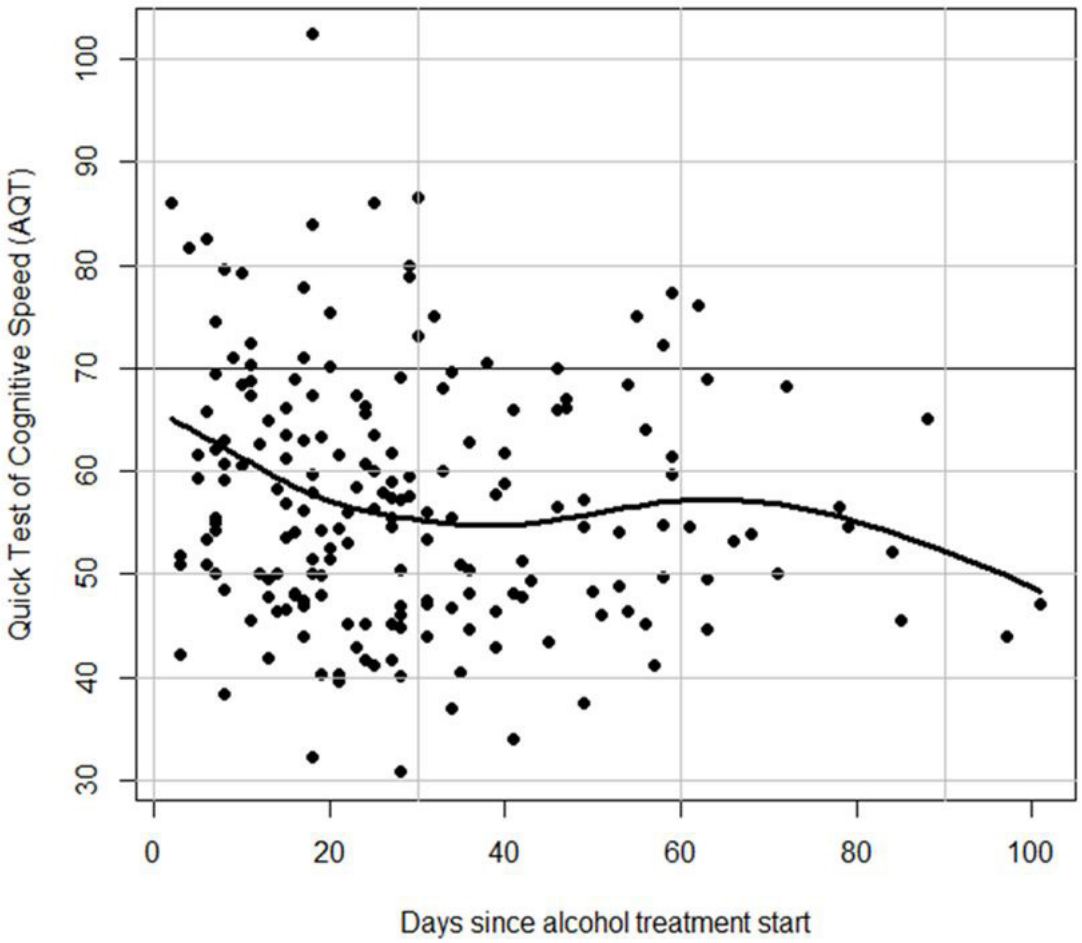

Figure 2: Test results of the Quick Test of Cognitive Speed (AQT) by days since alcohol treatment start. The black curve is a cubic smooth spline illustrating the association between days since alcohol treatment start and AQT

ment for alcohol problems

The association between time since treatment start and CRT index, adjusted for sex, years of alcohol dependence, days of high alcohol use 30 days before start of treatment, other drug use, relapse, use of psychoactive medicine, and psychiatric diagnosis, is not significant when time is applied as a continuous (p= 0.19), quadratic (p=0.28), nor categorical (p=0.43) variable. However, the model with the continuous variable had the best fit (lowest QIC_U).

As presented in figure 3, the CRT index, adjusted for sex, years of alcohol dependence, days of high alcohol use 30 days before start of treatment, other drug use, relapse, use of psychoactive medicine, and psychiatric diagnosis, increased by 0.08 per 30^{th} day (β = 0.08, 95%CI: -0.04; 0.20).

Sensitivity analysis

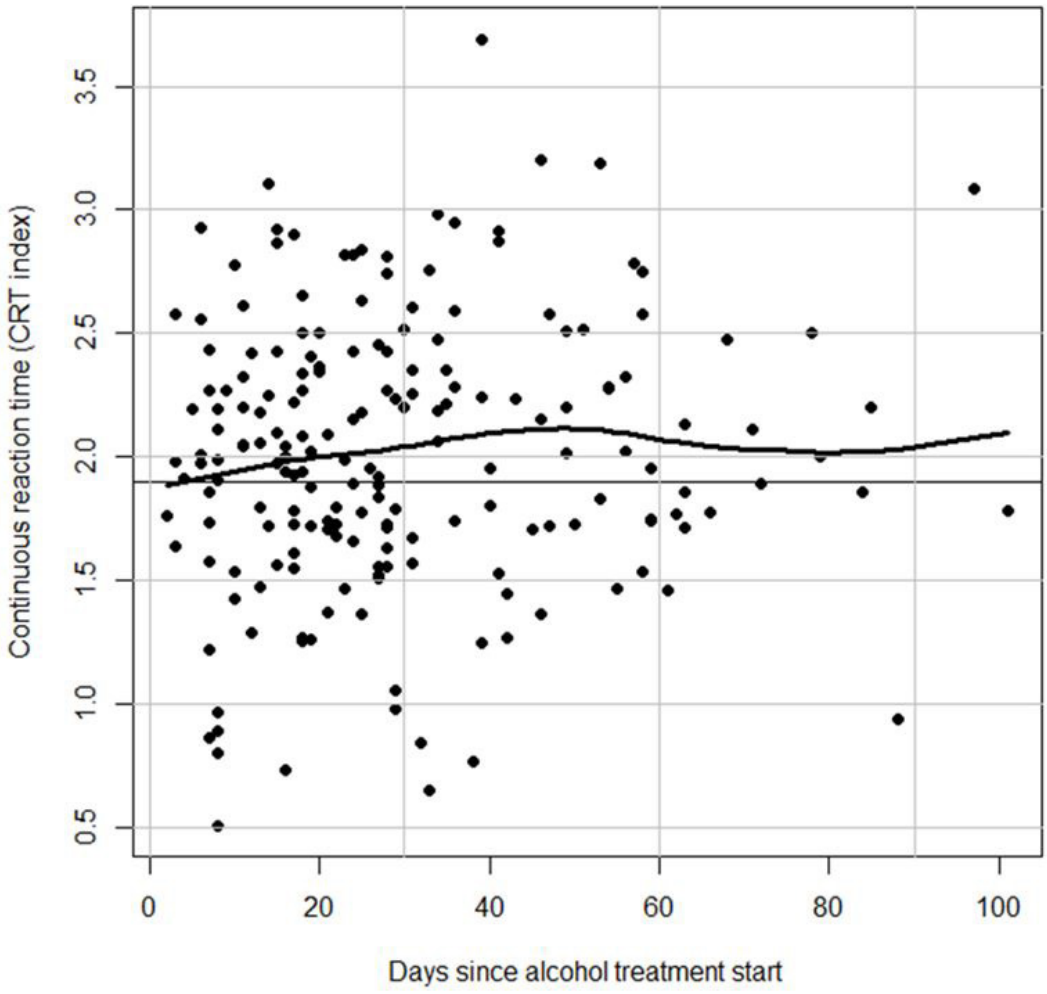

Figure 3: Test results of the continuous reaction time (CRT) index by days since alcohol treatment start. The black curve is a cubic smooth spline illustrating the association between days since alcohol treatment start and CRT

No variation was observed for the AQT test score or the CRT index by other drug use, use of psychoactive medicine, psychiatric diagnosis, days of a high alcohol use 30 days before start of treatment nor relapse (results shown in appendix 2 and 3). However, patients with less than 14 years of AD had a higher increase in CRT index per 30th day (β = 0.25, 95%CI: 0.09; 0.43), than patients with at least 14 years of AD (β = -0.05, 95%CI: -0.20; 0.09), being the only significant interaction (p=0.01).

Discussion

Our results show that 92 % of the AD patients in treatment for alcohol problems had a normal cognitive function, in at least one of the tests applied, while 54 % had an abnormal test score at either AQT or the CRT by start of treatment. The prevalence of cognitive abnormalities in our sample is relatively low compared to previous studies (Parsons & Nixon, 1993) [6]. The differences in prevalence may be related to the type of cognitive function(s) assessed and the test(s) applied. Similarly, our study demonstrated that the test scores of AQT, and CRT were weakly correlated. It is uncertain which cognitive functions that are mostly harmed by alcohol consumption, and the wide variation in the populations examined (with respect to e.g. genetic predisposition, length of AD, nutritional status and length of abstinence) has hampered researchers attempts to isolate specific brain regions and cognitive functions affected by alcohol (Zahr & Pfefferbaum, 2017) [19]. Some studies indicate that the greatest difference between AD patients and controls is found in visual modality (Glenn, Parsons, & Sinha, 1994) [34], which is essential for the AQT reaction time. While others conclude that the cerebellum part of the brain is severely affected by alcohol, resulting in loss of muscular coordination (Oscar-Berman, *et al.*, 1997) [4], and that alcohol negatively impacts hearing (Belle, *et al.* 2007) [35], which may affect the CRT test score. However, a meta-analysis assessing cognitive dysfunction among alcohol dependents, including 62 studies, concluded that multiple brain regions and a range of non-selective cognitive functions are af-

fected by alcohol, especially if chronically consumed (Stavro, *et al.*, 2013) [22].

Further, our results indicate a slight improvement of AQT reaction time among AD patients, whereas no improvement was observed for CRT test scores, within 100 days after start of treatment for alcohol problems. The slight improvement of scores over time, are of limited clinical significance, and indicate a relatively stable status of cognitive function. Results from meta-analysis of cognitive deficits in alcoholism, suggest that significant impairments across multiple cognitive functions remain stable during the first year of abstinence from alcohol. Whereas dysfunction generally decreases by 1 year of sobriety (Stavro, *et al.*, 2013) [22]. As thus, a longer follow-up period (than 100 days) may have revealed improvements of both AQT and CRT index.

Patients with less than 14 years of AD had a higher increase in CRT index per 30th day, than patients depended for at least 14 years. Cognitive impairments has been associated with longer duration of AD (Nowakowska, *et al.*, 2007), less treatment compliance and fewer days of abstinence (Bates, Pawlak, Tonigan, & Buckman, 2006) [36]. Thus, patients with shorter durations of AD may be better fit to respond to treatment, which could be explanatory for these results.

The repeated measurement approach secures temporality and is a strength, however it is a limitation that the follow-up was not complete. Further, as treatment for alcohol problems is free of charge in Denmark, and admission is open, inclusion in the study is not affected by ability to pay, which may improve generalizability of results. Additionally, due to data availability we were able to adjust for several factors, potentially impacting cognitive recovery after start of alcohol treatment. However, some limitations need to be considered. Due to the incomplete follow-up and inconsistency in conduction of the tests, the analyses are based on three repeated measures conducted at different timepoints, within approximately 100 days from treatment start. Compared to previous studies, this is a relatively short follow-up period to assess cognitive recovery among AD patients. Thus, it is unknown whether the cognitive impairments are irreversible or the limited improvement in cognitive functions is a due to the relatively short period of follow-up.

As mentioned previously, cognitive impairments may arise from a complex interaction between the direct effects of ethanol, indirectly through damage of other organs that interferes with nerve cells in the brain, and coexisting health problems and behaviors. These factors may as well impact cognitive recovery. However, no information was available for the patients' family history of alcoholism and genetics, or the prevalence of somatic comorbidity. Further, our results demonstrated that neither other drug use, use of psychoactive medicine, psychiatric diagnosis, days of a high alcohol use 30 days before start of treatment, or relapse affected either the AQT test score or the CRT index. A minority of individuals with AD seek treatment (Cohen, Feinn, Arias, & Kranzler, 2007), and AD patients that accept treatment tend to have more severe early alcohol use trajectories than untreated patients (G. Fein & Landman, 2005) [37-40], thus results may not be generalizable to untreated individuals. However, as we are interested in cognitive recovery after start of treatment, this selection bias is not of great concern.

In conclusion, we found no clinically significant improvement of cognitive function among patients with AD treated for alcohol problems. Further research of alcohol related cognitive impairments and recovery is needed to guide clinical practice in treatment of AD and timing of cognitive behavioral therapy.

Author Contributions: Sofie H. Hoffmann formulated and wrote the manuscript. Lau C. Thygesen conducted the statistical analyses and help editing and finalizing the manuscript. Anne W. Knudsen collected the majority of data. Anne W. Knudsen and Finn Zierau conceptualized the original idea of the manuscript and helped editing and finalizing the manuscript. Povl U. Becker provided significant guidance and helped edit and write the manuscript.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Ethical Approvals: The Danish National Committee on Biomedical Research Ethics (ref.no. H-A-2007-0032) and the Danish Data Protection Agency (ref. no. 2007-41-0735) approved the study.

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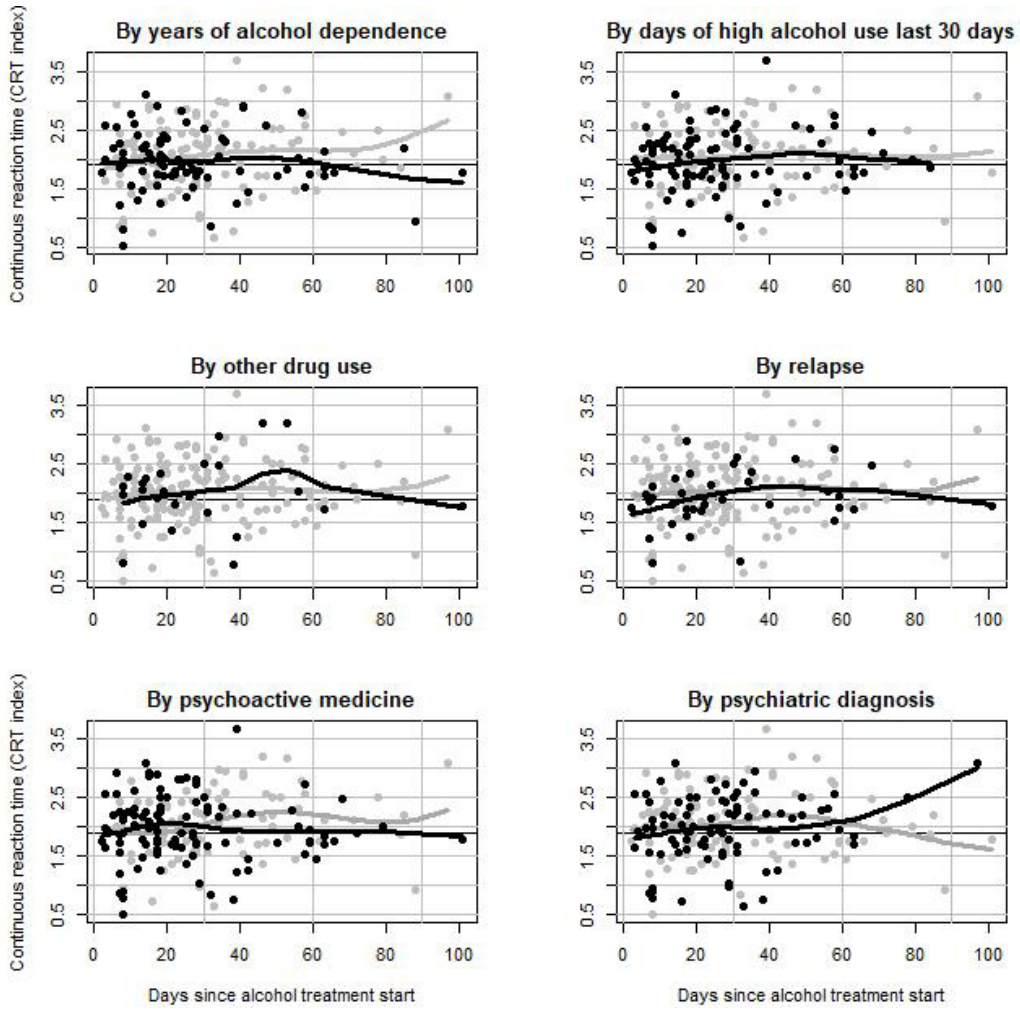
Appendix 1

Appendix 1, Table A: Characteristic of patients with incomplete follow-up and odds ratio for not participating in test 3 by sex, years of alcohol dependence and relapse

Variable	Total Frequency	Incomplete follow-up Frecuency (%)	Odds ratio for not participating in test 8 OR (95%CI)
Sex			
Female	22	0 (0)	1.00 (ref.)
Male	52	19 (37)	-
Years of alcohol dependence			
<14 years of alcohol dependence	43	9 (21)	1.00 (ref.)
≥14 years of alcohol dependence	31	10 (32)	2.31 (0.76-7.05)
Relapse			
No relapse	61	17 (28)	1.00 (ref.)
Relapse	13	2 (15)	0.33 (0.06-1.78)

Appendix 2



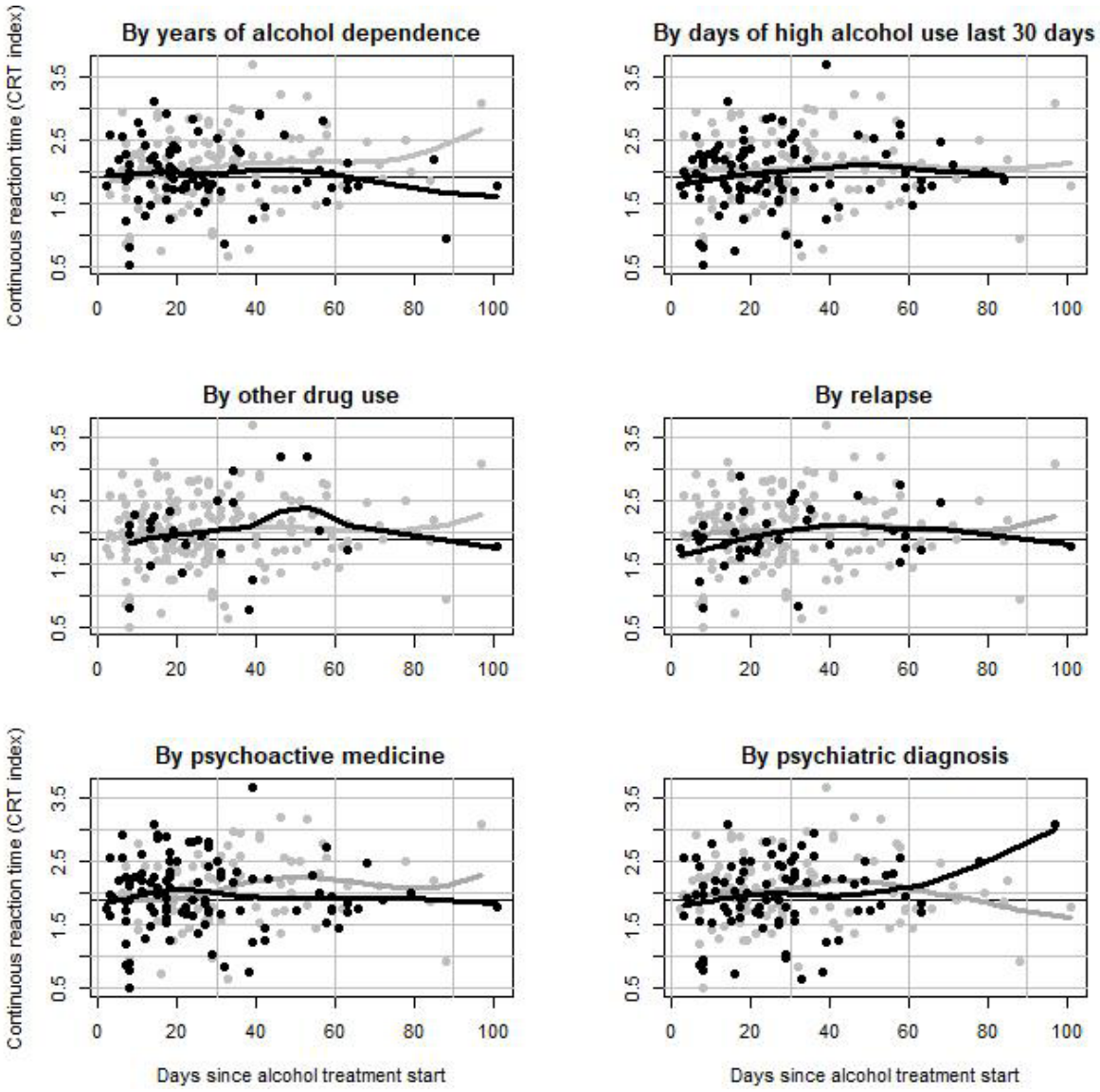
The black curves are cubic smooth splines illustrating the association between days since alcohol treatment start and CRT index for AD patients with respectively ≥14 years of alcohol dependence, ≥30 days of high alcohol use the month before start of treatment, user of other drugs, relapse, use of psychoactive medicine and psychiatric disorders. The grey curves are cubic smooth splines illustrating the association between days since alcohol treatment start and CRT index for AD patients with respectively <14 years of alcohol dependence, <30 days of high alcohol use the month before start of treatment, no use of other drugs, no relapse, no use of psychoactive medicine and no psychiatric disorders.

Appendix 2, **Figure A:** Test results of the Quick Test of Cognitive Speed (AQT) by days since alcohol treatment start, by years of alcohol dependence, by days of high alcohol use last 30 days, by other drug use, by relapse, by use of psychoactive medicine and by psychiatric diagnosis.

Appendix 2, Table A: Test results of the Quick Test of Cognitive Speed (AQT) by days since alcohol treatment start, by years of alcohol dependence, by days of high alcohol use last 30 days, by other drug use, by relapse, by use of psychoactive medicine and by psychiatric diagnosis, beta, 95%CI, p-value and test for interaction

	Linear regression (beta, 95%CI, p-value)	**Test for interaction**
All patients (N=191)	β = -3.3, 95%CI: -5.5; -1.2, p>0.05	
By years of alcohol dependence		
<14 years (N=113):	β = -3.0, 95%CI: -5.8; -0.3, p=0.03	p=0.80
≥14 years (N=78):	β = -3.5, 95%CI: -6.6; -0.4, p=0.03	
By days of high alcohol use (≥5 drinks/day) last 30 days		
<30 days (N=103)	β = -3.7, 95%CI: -5.8; -1.6, p>0.05	p=0.65
≥30 days (N=88)	β = -2.6, 95%CI: -6.8; 1.6, p=0.22	
By other drug use		
No other drug use (N=166)	β = -3.1, 95%CI: -5.2; -1.1, p>0.05	p=0.84
Other drug use (N=25)	β = -3.0, 95%CI: -9.4; 3.5, p=0.37	
By relapse		
No relapse (N=155)	β = -3.8, 95%CI: -5.9; -1.7, p>0.05	p=0.59
At least one relapse (N=36)	β = -2.4, 95%CI: -7.3; 2.5, p=0.33	
By use of psychoactive medicine		
No use of psychoactive medicine (N=88)	β = -3.3, 95%CI: -5.7; -0.9, p>0.05	p=0.81
Use of at least one psychoactive medicine (N=103)	β = -3.5, 95%CI: -6.7; -0.2, p>0.05	
By psychiatric diagnosis		
No psychiatric diagnosis (N=106)	β = -2.6, 95%CI: -5.0; -0.2, p>0.05	p=0.41
At least one psychiatric diagnosis (N=85)	β = -4.6, 95%CI: -8.5; -0.6, p>0.05	

Appendix 3



The black curves are cubic smooth splines illustrating the association between days since alcohol treatment start and CRT index for AD patients with respectively ≥14 years of alcohol dependence, ≥30 days of high alcohol use the month before start of treatment, user of other drugs, relapse, use of psychoactive medicine and psychiatric disorders. The grey curves are cubic smooth splines illustrating the association between days since alcohol treatment start and CRT index for AD patients with respectively <14 years of alcohol dependence, <30 days of high alcohol use the month before start of treatment, no use of other drugs, no relapse, no use of psychoactive medicine and no psychiatric disorders.

Appendix 3, figure B: Test results of the continuous reaction time (CRT) index by days since alcohol treatment start, by time, by years of alcohol dependence, by days of high alcohol use last 30 days, by other drug use, by relapse, by use of psychoactive medicine and by psychiatric diagnosis.

Appendix 3, Table B: Test results of the continuous reaction time (CRT) index by days since alcohol treatment start, by time, by years of alcohol dependence, by days of high alcohol use last 30 days, by other drug use, by relapse, by use of psychoactive medicine and by psychiatric diagnosis, beta, 95%CI, p-value and test for interaction

	(Linear regression (beta, 95%CI, p-value	Test for interaction
All patients (N=191)	β = 0.09, 95%CI: -0.04; 0.21, p=0.16	
By years of alcohol dependence		
<14 years (N=113):	β = 0.25, 95%CI: 0.09; 0.43, p=0.003	p=0.01
≥14 years (N=78):	β = -0.05, 95%CI: -0.20; 0.09, p=0.45	
By days of high alcohol use (≥5 drinks/day) last 30 days		
<30 days (N=103)	β = 0.03, 95%CI: -0.15; 0.20, p=0.76	p=0.26
≥30 days (N=88)	β = 0.17, 95%CI: -0.004; 0.34, p=0.06	
By other drug use		
No other drug use (N=166)	β = 0.10, 95%CI: -0.03; 0.24, p=0.13	p=0.59
Use of at least one drug (N=25)	β = 0.01, 95%CI: -.27; 0.29, p=0.92	
By relapse		
No relapse (N=155)	β = 0.11, 95%CI: -0.05; 0.26, p=0.19	P=0.83
At least one relapse (N=36)	β = 0.11, 95%CI: -0.09; 0.30, p=0.27	
By use of psychoactive medicine		
No use of psychoactive medicine (N=88)	β = 0.17, 95%CI: -0.05; 0.39, p=0.12	P=0.21
Use of at least one psychoactive medicine (N=103)	β = 0.01, 95%CI: -0.12; 0.14, p=0.85	
By psychiatric diagnosis		
No psychiatric diagnosis (N=106)	β = 0.01, 95%CI: -0.11; 0.13, p=0.85	P=0.08
At least one psychiatric diagnosis (N=85)	β = 0.22, 95%CI: 0.01; 0.44, p=0.04	