

ONSET AGE OF SUBSTANCE USE AND NEUROPSYCHOLOGICAL PERFORMANCE IN HOSPITAL PATIENTS

Irma Höijer, Tuula Ilonen, Eliisa Löyttyniemi, Raimo K.R. Salokangas

Abstract

OPEN ACCESS

Objective: Several studies have found neurocognitive deficits in adolescents following substance abuse. Predisposing risk factors may further impact vulnerability to neurocognitive deficits. Little is known about the cognitive performance of adult onset substance users compared to earlier onset users. This study aims to explore differences in neuropsychological functioning between early (EOAs) and late onset substance abusers (LOAs) when the effects of confounding factors are controlled.

Method: Data for this cross-sectional study was collected from hospital patients. A total of 164 patients with substance use disorder (SUD) aged 19 to 65, 76 with single-drug diagnosis and 88 with multidrug diagnosis, underwent neuropsychological tests for verbal capacity, attention, speed of processing, perceptual reasoning, memory and learning, executive functioning, and inhibitory capacity. Associations between regular onset age and neuropsychological measures were analysed using in multi-way ANCOVA, and the effect of age, multiple substance abuse, education level and learning difficulties were controlled.

Results: Compared with LOAs, EOAs had weaker performance in the Digit Symbol test for mono-substance users. Meanwhile, compared with EOAs, LOAs had weaker performance in the Delayed Visual Memory test and the Raven test for mono-substance users, and the Block Design test for poly-substance users. From the confounding factors, early onset age of substance use is heightened among individuals with learning disabilities.

Conclusions: Onset age of substance use is related to the deterioration of performance in neuropsychological tests. Premorbid poor learning and inhibitory capacity may be important predisposing risk factors of SUD. Conversely, high level of education may be a protective factor for cognitive performance in patients with SUD.

Citation: Höijer, I., Ilonen, T., Löyttyniemi, E., Salokangas, R.K.R. (2020). Onset age of substance use and neuropsychological performance in hospital patients. *Clinical Neuropsychiatry*, 17(5), 271-280.

doi.org/10.36131/cnforitieditore20200502

Copyright: © Clinical Neuropsychiatry
This is an open access article. Distribution and reproduction are permitted in any medium, provided the original author(s) and source are credited.

Funding: None.

Competing interests: None.

Corresponding author

Irma Höijer,
Doctoral Programme of Clinical Investigation,
University of Turku
E-mail: irhaho@utu.fi

Key words: substance abuse, onset age of substance abuse, inpatients, neuropsychological functions, predisposing and protective factors for SUD

Irma Höijer*, Tuula Ilonen**, Eliisa Löyttyniemi***, Raimo K.R. Salokangas**

*Doctoral Programme of Clinical Investigation, University of Turku, Finland

**Department of Psychiatry, University of Turku, Finland

***Department of Biostatistics, University of Turku, Finland

Introduction

Long-term alcohol and other psychoactive drug abuse impact brain functioning (Bava, Jacobus, Mahmood, Yang, & Tapert, 2010; Bava, 2013; Brumback, Castro, Jacobus, & Tapert, 2016; Jacobus, J. et al., 2009; Jacobus, Joanna, Squeglia, Sorg, Nguyen Louie, & Tapert, 2014; Squeglia, L. M., Jacobus, & Tapert, 2009) and neuropsychological functioning, leading to a range of cognitive deficits. Adolescence is regarded as a risk period for the initiation of alcohol and illegal drug use. Neurocognitive deficits following substance abuse have been found in adolescents across many domains of cognitive functioning such as verbal learning (Brown, Tapert, Granholm, & Delis, 2000), memory (Jacobus, Joanna et al., 2015; Madeline H. Meier et al., 2012), attention (Jacobus, Joanna et al., 2015), visuospatial functioning (Jacobus, Joanna et al.,

2015), psychomotor speed (Capella Mdel, Benaiges, & Adan, 2015; Jacobus, Joanna et al., 2015; Madeline H. Meier et al., 2012), perceptual and verbal reasoning and executive functioning (Hagen et al., 2016; Madeline H. Meier et al., 2012). Nguyen-Louie et al. (2017) found an inverse linear relationship between doses of alcohol and psychomotor speed, visual attention, cognitive inhibition and working memory. The authors concluded that any alcohol use is adverse at any age under 23 (Nguyen Louie et al., 2017).

Researchers suggest that early substance use affects neuropsychological functioning permanently (Hanson, Medina, Padula, Tapert, & Brown, 2011; Jacobus, Joanna et al., 2015; Madeline H. Meier et al., 2012) by disturbing the development of the brain in its critical maturation period. Compared to late onset substance abusers, early onset substance abusers have a lower premorbid IQ (Capella Mdel et al., 2015). Longitudinal

studies support the view that individual differences in cognitive ability, along with other individual, environmental, genetic and biological factors, increase the risk for addiction during youth (Conrod & Nikolaou, 2016). In a cross-sectional study of substance-dependent adults, poorer verbal intellectual ability was related to parental and one's own low basic education (Latvala et al., 2009). Early onset of substance use may predict long-term impairments and negative outcomes may lead to reduced educational and occupational attainment in adulthood.

Findings from prospective research provide evidence for earlier onset age and more impaired cognitive deficits. Meier et al. (2012) investigated persistent cannabis use over 20 years from 13 to 38 years old. Weekly use before age 18 was related to greater deterioration in cognitive performance. Cannabis use led to persistent deficits in executive function and processing speed and decline in full-scale IQ after controlling education. In addition, the study affirmed impairment of learning and memory. Adolescent-onset cannabis users did not recover neuropsychological functioning even after quitting. Volkow et al. (2016) asserted that the cohort study of Meier et al. (2012) involved only a small number of cannabis users and brain imaging did not perform. According to other brain imaging studies, it is possible that the observed changes already exist before the onset age of substance use. However, these results cannot be explained by, for example, socioeconomic status or psychiatric disorders. More follow-up studies are needed (Volkow et al., 2016).

Several studies have investigated associations between cognitive functioning and substance abuse. Most studies focused on adolescence. Little is known about the cognitive performance of adult onset substance users compared to earlier onset users. Some investigators did not find differences in the cognitive performance between early onset and late onset participants (Kist, Sandjojo, Kok, & van den Berg, Julia F, 2014). In contrast, Joos et al. (2013) found that early onset alcoholics perform generally as well as or even better than late onset alcoholics, especially on visual memory and interference tests (Joos et al., 2013). These inconclusive findings highlight the need for further research.

In previous studies, it has not been possible to dismiss the fact that poor neuropsychological performance related to early onset substance abuse is limited to premorbid cognitive differences (Latvala et al., 2009) and the short-term effects (Latvala et al., 2009; Rapeli, P. et al., 2005). In some studies, findings for young subjects have been limited to heavy, recreational use of alcohol and marijuana, not diagnosed problematic use (Jacobus, Joanna et al., 2015).

This study was developed based on the needs of clinical research. Patients were, on average, relatively young, majority of whom aim to return to work. Patients' poly-substance use revealed uncontrolled polydrug use. As such, this sample is more realistic in terms of background than studies where patients have been tested at regular intervals or where substance abuse and substance use rates have been monitored in more detail.

More research is needed to identify which neuropsychological functions can be improved by treatment and rehabilitation. It is equally important to determine which neuropsychological domains are recover faster, which are slower in rehabilitation, and which may not be recover at all. According to previous studies, several factors can influence the outcome of rehabilitation: onset age and duration of substance use,

duration of substance use, and length of abstinence and poly-substance use. Evidence suggest gender differences in cognitive vulnerability underlying substance abuse. Individual differences also explain some impairments in previous research. These considerations are important in evaluating factors that influence work ability.

The present study examines the impact of the onset age of regular substance use on neuropsychological performance in a sample of mid-life addiction hospital patients with a diagnosis of SUD. In addition, the study explores the impact of alternate conditions of substance abuse – single-drug and multidrug use and background factors such as education level learning difficulties, and gender – on neuropsychological performance. Patients were retrospectively selected inpatients diagnosed with SUD. All of them had been abstinent for at least one month. We hypothesise that earlier onset substance abuse is associated with worse cognitive deficits. It is equally important to determine which of the neuropsychological domains recover faster. Furthermore, some impairments may be related more to premorbid factors, such as learning difficulties.

Methods

Subjects

This is a retrospective cross-sectional study. Data was collected from patients who had undergone neuropsychological assessment at Järvenpää Addiction Hospital from 2004 to 2012. A minimum of one month of abstinence was required before testing. The study group consisted of 164 hospitalised patients with SUD, single-drug ($n = 74$) and multidrug ($n = 90$) diagnoses. Diagnoses were made according to the criteria of ICD-10 by experienced psychiatrists and based on all available information at the time of discharge. SUD diagnoses also included alcohol overuse or dependence.

Patients had numerous quit attempts, but their exact number was not available in hospital records. Substance abuse treatment is usually performed in outpatient settings. Services specifically aimed at treating substance abuse problems and rehabilitating substance abusers include outpatient clinics for substance abusers and detoxification treatment units, and rehabilitation units that provide longer-term rehabilitation. These institutions offer a range of low-threshold services. In cases when the patient is difficult, the need for institutional care is assessed. The addiction hospital is the only hospital in the country that specialises in treating addiction problems. The hospital is maintained by A-Clinic Oy, which is owned by the A-Clinic Foundation.

The inclusion criteria were as follows: 18 to 65 years old, native Finnish speaker, substance use diagnosis and minimum one-month abstinence. The exclusion criteria for all participants were as follows; younger than 18 years old, being HIV-positive, or having another chronic disease that can possibly affect the central nervous system, and having a history of neurological disorders, opioid substitution treatment or epileptic seizures.

Data on the onset age of the use of alcohol and other substances was obtained from medical records, medical examinations, and interviews with a nurse and a social worker. "Onset of regular substance use age" refers to the age when the patient reported at least regular weekly use. The study subjects were classified according to their onset age of regular abuse into early onset abusers (EOAs; ≤ 17 years) and late onset abusers (LOAs; $18 \geq$ years).

The sociodemographic and clinical characteristics of the study participants are presented in **table 1**. The EOAs had a regular onset age ≤ 17 , whereas LOAs had regular onset age ≥ 18 .

normative and clinical groups and sufficient test-retest reliability (Lezak, 1995). The neuropsychological measures are presented in **table 2**.

The Vocabulary subtest of the Wechsler Adult

Table 1. Sociodemographic and clinical information of the EOA and LOA populations, with means and standard deviations for continuous numerical variables and numbers and percentages are for categorical variables

	Total sample N = 164 Frequency (%) or Mean (SD)	EOA Regular onset age ≤ 17 N = 76 Frequency (%) or Mean (SD)	LOA Regular onset age ≥ 18 N = 88 Frequency (%) or Mean (SD)	EOA versus LOA p-value
Age	38.7 (10.0)	32.8 (9.6)	43.5 (9.8)	<0.001 (T-test)
Gender (male)	97 (59.1%)	45 (59.2%)	52 (59.1%)	0.99 (Pearson Chi-Square)
Level of Education				
Primary School	65 (39.6%)	45 (59.2%)	20 (22.7%)	<0.001 (Pearson Chi-Square)
Vocational Training	54 (32.9%)	21 (27.6%)	33 (37.5%)	
College-level Education	28 (17.1%)	8 (10.5%)	20 (22.7%)	
Higher Education	17 (10.4%)	2 (2.6%)	15 (17.0%)	
Learning difficulties	70 (42.7%)	44 (57.9%)	26 (29.5%)	<0.001 (Pearson Chi-Square)
Onset age of regular substance use	22.6 (10.4)	14.5 (2.0)	29.2 (9.8)	<0.001 (T-test)
Multidrug users	90 (54.9%)	57 (75.0%)	33 (37.5%)	<0.001 (Pearson Chi-Square)
Substance use duration, years	15.86 (9.1)	17.5 (9.2)	14.4 (8.7)	0.029 (T-test)

In the total sample, the distribution of the substances used for the single-drug group (55 %) was as follows: alcohol (41%), sedatives (7%), stimulants (4%) and opioids (3%). Meanwhile, the distribution of substances used for the multidrug group was as follows: alcohol and sedatives (27%), alcohol and cannabis (0.6%), alcohol and stimulants (0.6%), alcohol and other psychoactives (13%), opioids and other psychoactives (5%) and other psychoactive, substance-related disorders (9%). The diagnoses of polydrug users were generally variable in their combinations, making it difficult to investigate the effects of a single substance.

The study was approved by the ethical committee of the A-Clinic Foundation, and informed consent was obtained from all participants. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Neuropsychological Assessments

Neuropsychological testing was performed as part of a work clinical assessment and a treatment plan assessment by the first author who is experienced in using these methods. The tests were conducted after the acute symptoms of withdrawal had abated to allow testing. Patients underwent detoxification from benzodiatsepines and analgesics. There was no mention of any other medication. The psychological testing took about 2–3 hours. The tests were usually done in two phases. All the testing and scoring of the variables were done in accordance with the standard guidelines. The test battery shows good psychometric characteristics, revealing good differential validity in discriminating

Intelligence Scale-Revisited (WAIS-R; (Wechsler, Fieandt, & Kalimo, 1975) was used to assess premorbid IQ. Neuropsychological assessments of learning disabilities were co-worked with experienced neuropsychologists specialised in learning disabilities. Learning disabilities were classified as single variable consisting of attention, verbal and nonverbal reasoning, memory problems, dyslexia and mathematical difficulties. Assessment of attentional difficulties considered the patients' behaviour in test conditions (e.g., a short attention span). During an interview, the subjects were also asked about school success, school breaks, dropping out, and the need for special educational support.

Computerised CogniSpeed tasks (Portin et al., 2000) were used to measure simple reaction time and automatic and conscious information processing. A simple reaction time subtest of the computerised CogniSpeed test battery was performed first. Inhibitory capacity was assessed by the CogniSpeed version of the Stroop Color-Word Test (Revonsuo, 1995). The test consists of three subtests: (1) Neutral Condition (COL), (2) Congruous Word Condition (CON) and (3) Incongruous Word Condition (IN). COL and CON are related to more automatic information processing, while IN measure entail more conscious and effort-intensive processing. The CogniSpeed software has been found to be a sensitive instrument in measuring the performance of patients with various brain conditions (Lilja, Portin, Hämäläinen, & Salminen, 2001; Portin et al., 2000; Portin, 2001).

Statistical Analyses

The EOA (regular onset age ≤ 17) and LOA (regular

Table 2. Neuropsychological measures

Cognitive Domain	Test	Score units
Premorbid IQ	Vocabulary (WAIS-R; Wechsler, 1975)	Standard Score
Attention	Digit Span Forward Digit Span Backward	Total raw score, max 12 Total raw score, max 12
Speed of Processing	Digit Symbol (WAIS-R; Wechsler, 1975) Simple reaction time (CogniSpeed; Revonsuo et al., 1993)	Standard Score Time to complete (ms)
Perceptual Reasoning	Block Design (WAIS-R; Wechsler, 1975) Raven Standard Matrices (Raven, 2004)	Standard Score
Verbal Memory and Learning	Verbal subtests of the WMS-R (Wechsler, 1987) Immediate Logical Memory Delayed recall of Logical Memory Immediate Associate Learning Delayed recall of Associate Learning	Verbal Memory Index Total raw score, max 50 Total raw score, max 50 Total raw score, max 24 Total raw score, max 8
Visual Memory and Learning	Visual subtests of (WMS-R (Wechsler, 1987) Immediate Visual Learning Delayed recall of Visual Learning Immediate Visual Reproduction Delayed recall of Visual Reproduction	Visual Memory Index Total raw score, max 18 Total raw score, max 6 Total raw score, max 41 Total raw score, max 41
Delayed Memory	(WMS-R (Wechsler, 1987)	Delayed Memory Index
Inhibitory Capacity	CogniSpeed version of the Stroop Color-Word Test (Stroop, 1935) Neutral Condition, COL Congruous Word Condition, CON Incongruous Word Condition, IN2	Time to complete (ms), and number of errors
Executive Function Total Stroop (IN2-CON) Stroop Interference (IN2-COL)	CogniSpeed version of the Stroop Color-Word Test (Stroop, 1935)	Time to complete (ms)

onset age ≥ 18) populations were compared for sociodemographical information. The Student's *t*-test/Mann-Whitney *U*-test for continuous measurements and chi-square test (or Fisher's exact test) for categorical variables were used. For statistical comparisons, $p < 0.05$ (two-tailed) was considered statistically significant. Intravenous drug users (IV users) comprised a subgroup of multidrug users. Pearson and Spearman correlations were calculated between onset age (i.e., regular use, multidrug use and IV use) and psychological measures.

Associations between neuropsychological measurements (i.e., Digit Symbol, Block Design, Raven test, Visual Memory and Learning, Incongruous Word Condition (IN) and Executive function/Stroop Interference) and regular onset age and confounders (i.e., multiple substance abuse [yes/no], age, education level and learning difficulties [yes/no]) and their interactions were investigated using analysis of covariance. Every neuropsychological measurement was analysed separately (see **table 3**) but were removed in case of a non-significant result. If the interactions were not statistically significant at a level of 0.05, we removed the interaction from the model. In this model, age and regular onset age were used as numerical covariates, while multiple substance abuse, education level and learning difficulties were used as categorical explanatory variables.

Model-based means were also presented. Logarithmic transformation was used for simple reaction time, IN and COL to achieve normal distribution assumption for residuals. Data was analysed by using the Statistical Package for Social Sciences (SPSS) software (SPSS

Inc., Chicago, IL) and the SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

In the primary analyses, significant positive correlations were found between onset age of regular use and vocabulary (Pearson $r_{162} = 0.17$; $p = 0.032$) and time to complete tasks of inhibitory capacity i.e., neutral word (COL; Spearman's $\rho_{152} = 0.29$; $p < 0.001$), congruous word (CON; Spearman's $\rho_{152} = 0.33$; $p = 0.017$) and incongruous word (IN; Spearman's $\rho_{152} = 0.33$; $p = 0.002$). Significant positive correlations were also found between onset age of multidrug use and simple reaction time with the dominating hand in the CogniSpeed task (Spearman's $\rho_{92} = 0.21$, $p = 0.042$) and time to complete tasks of inhibitory capacity: neutral word (COL; Spearman's $\rho_{91} = 0.33$; $p = 0.001$), congruous word (CON; Spearman's $\rho_{91} = 0.35$; $p = 0.001$) and incongruous word (IN2; Spearman's $\rho_{92} = 0.30$; $p = 0.004$). Meanwhile, significant negative correlations were found between onset age of multidrug use and perceptual reasoning as measured by the Block Design test (Pearson $r_{39} = -0.34$; $p = 0.035$), and the Delayed Visual Learning test (Pearson $r_{34} = -0.46$; $p = 0.007$).

Intravenous drug users comprised a subgroup of multidrug users. Regular onset age of intravenous use correlated negatively with the speed of processing as measured by the Digit Symbol test (Pearson $r_{21} = -0.48$, $p = 0.026$), and with perceptual reasoning as measured by the Raven test (Pearson $r_{33} = -0.46$, $p = 0.007$).

Neuropsychological tests that reached significance in the primary correlation analyses were further analysed using multi-way analysis of covariance, adjusting for education level, learning difficulties, multiple-substance abuse and gender. Intravenous use was a subgroup of the multidrug use group; it was used as a variable instead of multidrug use if there was a primary significant correlation between the neuropsychological test administered and the onset age of intravenous use. Age was preferred as a confounding factor because, in addition to the effect of age, it includes the possible effect of abuse.

Those explanatory variables and interactions that did not significantly affect the outcome were removed from the analysis. Levene's test and normality checks were conducted, and the assumptions were met. Calendar age was controlled for neuropsychological tests without age correction norms, as were CogniSpeed tasks of simple reaction time, COL, CON, IN, the Block Design test, and the Delayed Visual Learning test.

Associations between neuropsychological tests, regular onset age, covariates, and their interactions utilising multi-way analysis of covariance are summarised in table 3. The table shows the correlations of the neuropsychological tests between the onset age of regular use and the covariates. Interactions between the

1 shows that the association between regular onset age is positively related to the Digit Symbol test, indicating that the earlier the onset age of regular use, the slower the performance.

There was a positive relation between the Digit Symbol test and the covariable of the education level ($F_{92} = 3.24, p = 0.026$), indicating that the lower the education level, the poorer the performance in the test.

Perceptual Reasoning. The interaction between onset age of substance use and multidrug use, predominantly alcohol, was significantly linearly correlated with the Block Design test ($F_{53} = 7.55, p = 0.008$). The study group with no multidrug use showed no significant connection ($\beta_{53} = 0.057, p = 0.269$) between onset age and performance in the Block Design test. The study group with multidrug use had a significant negative correlation ($\beta_{53} = -0.171, p = 0.033$) with onset age. Negative correlation between onset age of multidrug use and the Block Design test can be interpreted as indicating that the later the onset age, the poorer the performance.

Regular onset age of mono-substance use, predominantly alcohol, was related significantly inversely to perceptual reasoning ($F_{140} = 6.64, p = 0.011$) as measured by the Raven test, indicating that the later the onset age is, the poorer the participant's performance.

Table 3. Results of multi-way analysis of covariance of the association between neuropsychological tests, regular onset age and covariates

Cognitive Assessments	Regular Onset age and covariables											
	Onset age of Regular use		Education level		Learning difficulties		Multiple substance use		Age		Gender	
	F _{df}	p value	F _{df}	p value	F _{df}	p value	F _{df}	p value	F _{df}	p value	F _{df}	p value
Speed of processing The Digit Symbol test (N=99)	F ₉₂ = 5.00	0.028*	F ₉₂ = 3.24	0.026*	F ₉₂ = 0.88	0.351	F ₉₂ = 2.48 ³	0.119	-	-	F ₉₂ = 1.55	0.217
Perceptual Reasoning The Block Design test (N=63)	F ₅₃ = 1.24	0.270	F ₅₃ = 1.72	0.174	F ₅₃ = 3.85	0.055	F ₅₃ = 7.70	0.008**	F ₅₃ = 1.11	0.298	F ₅₃ = 0.35	0.559
Perceptual Reasoning Raven (N=149)	F ₁₄₀ = 6.64	0.011*	F ₁₄₀ = 1.77	0.156	F ₁₄₀ = 13.65	<0.0003***	F ₁₄₀ = 2.67	0.104	F ₁₄₀ = 2.73	0.100	F ₁₄₀ = 5.95	0.016*
Visual Memory and Learning Delayed Visual Learning (N=62)	F ₄₈ = 0.02	0.887	F ₄₈ = 0.97	0.415	F ₄₈ = 3.95	0.053	F ₄₈ = 0.22	0.641	F ₄₈ = 5.29	0.026*	F ₄₈ = 1.87	0.178
Inhibitory capacity IN (N=152)	F ₁₄₃ = 0.26	0.613	F ₁₄₃ = 1.53	0.210	F ₁₄₃ = 1.11	0.294	F ₁₄₃ = 0.16	0.689	F ₁₄₃ = 7.60	0.007**	F ₁₄₃ = 0.09	0.769

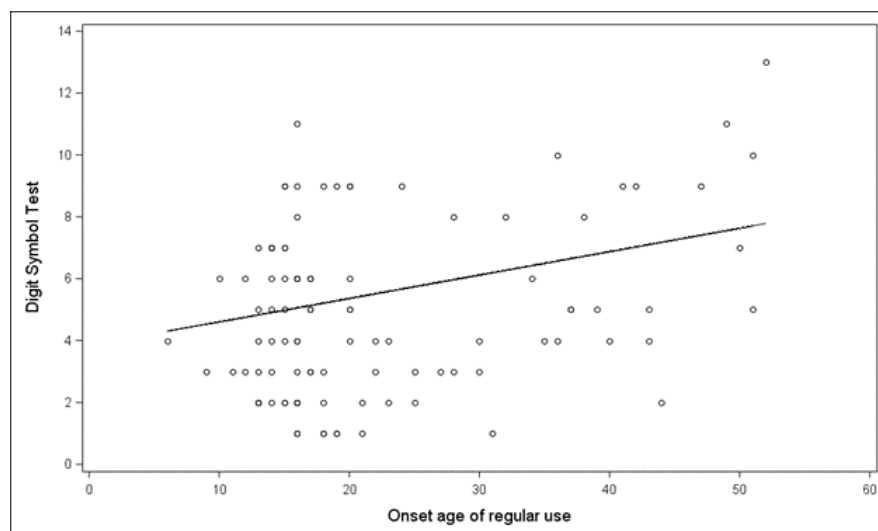
¹Calendar age was also controlled in the model due to the lack of age correction norms. ²Intravenous use was used as a subgroup of multidrug use (N=100) (*p <0.05, **p <0.01 and ***p <0.001).

neuropsychological tests, onset age and covariates are reported in the text, if they are statistically significant.

Processing Speed. Compared with LOAs, EOAs had weaker performance in the Digit Symbol test. Controlling covariates' onset age of regular use was significantly positively linearly associated with speed of processing as measured by the Digit Symbol test for mono-substance users, predominantly alcohol. **Figure**

The Raven test was significantly positively correlated with learning disabilities ($F_{140} = 13.65, p = 0.0003$) in the model, indicating that poorer performance in the Raven test is associated with learning difficulties. In the EOA group learning difficulties were more frequent (57.9%) compared to the LOA group (29.5%) (see table 1 and figure 2), indicating that early onset age of substance use is heightened among individuals with

Figure 1. A scatterplot matrix and regression line for the Digit Symbol test and onset age of regular substance use controlled for education level ($N = 93$)



learning disabilities. Notably, men performed better than women in the Raven test ($F_{140} = 5.95, p = 0.016$).

Visual Memory and Learning. There was a significant interaction between the onset age of regular use for mono-substance use, predominantly alcohol, and learning difficulties ($F_{48} = 5.00, p = 0.030$). This interaction can be interpreted as follows: If there is no learning disability, onset age of substance use is related to a negative slope ($\beta = -0.110, p = 0.017$); meanwhile, those with learning disabilities show no sign of this ($\beta = 0.097, p = 0.241$). This result indicated a worse performance in delayed visual memory in a group of LOAs. In addition, calendar age was inversely linearly related to delayed visual memory ($F_{48} = 5.29, p = 0.026$), indicating that older age is associated with worse neuropsychological test performance.

Inhibitory Capacity. There was no significant correlation between regular onset age of substance abuse and measures of inhibitory capacity. Conversely, there was a significant inverse linear correlation between calendar age and inhibitory capacity measure of IN ($F_{143} = 7.60, p = 0.007$), indicating that older age is associated with worse neuropsychological test performance.

Duration of illness and calendar age correlated strongly with each other ($r = .241, p = 0.002$). Replacing age by duration of illness did not change the result. We preferred to use calendar age as a confounding factor because, in addition to the effect of age, it also includes possible effect of duration of abuse.

Discussion

The present study aims to explore the association between the onset age of regular substance use and neuropsychological performance while controlling the effects of single-drug and multidrug abuse, years of education, learning difficulties and gender. We hypothesised that early onset abusers, EOAs, would have worse and different cognitive deficits compared to late onset abusers, LOAs. Any alcohol use is harmful at any age under 23 (Nguyen Louie et al., 2017). Hanson et al. (2011) affirmed that cognitive impairment related to substance use follows the course of brain development such that the development of the different parts of the brain peak at different ages. The prefrontal cortex and lateral temporal lobes, whose functions are essential for

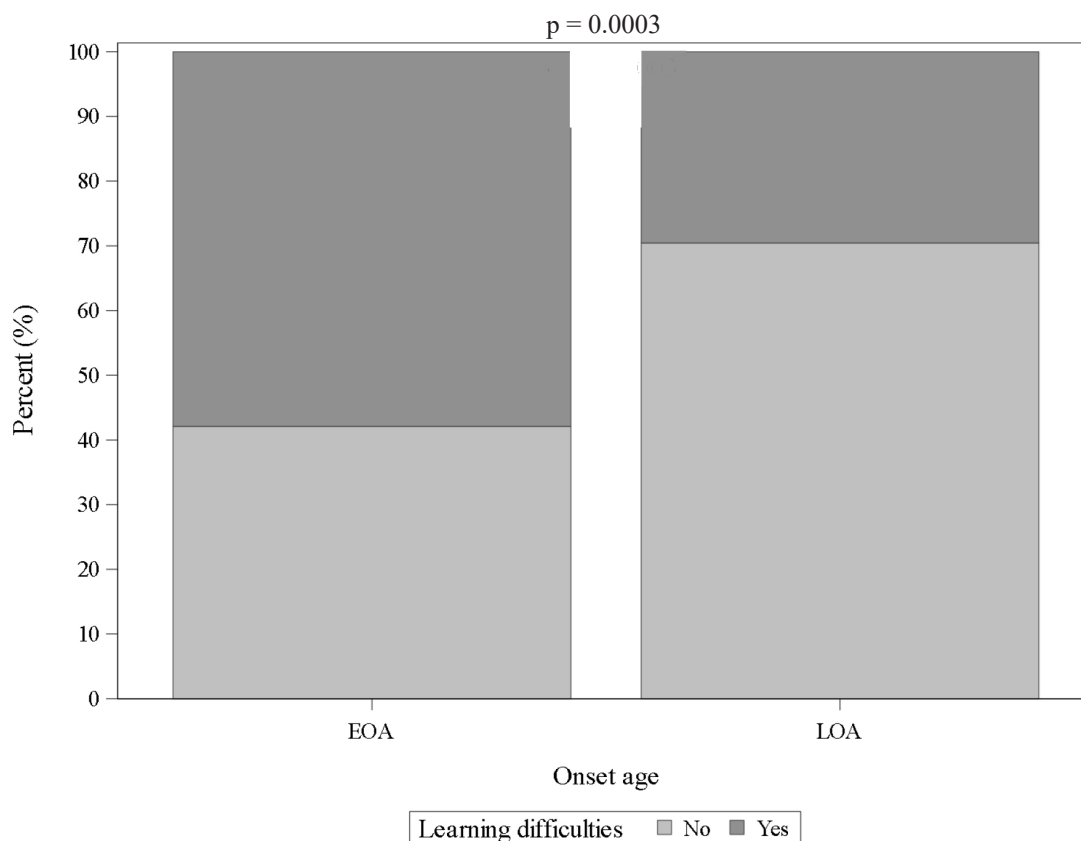
integrating memory, audiovisual information, and object recognition (Hanson, Cummins, Tapert, & Brown, 2011), mature last. Heavier use patterns are generally followed by poorer cognition (Hanson et al., 2011). Some impairments may be more related to premorbid factors, such as education level, learning difficulties and gender. Similarly, we found several differences in neuropsychological functioning associated with onset age of substance use.

Alcohol was the most commonly used substance among both mono-substance and poly-substance users. We therefore compared the results mainly with studies that have examined the cognitive impairment caused by alcohol use and the concomitant use of alcohol and other intoxicants.

Processing speed, measured through the Digit Symbol test was significantly associated with EOAs; the earlier the substance use began the slower the processing speed. This result is consistent with previous studies (Capella Mdel et al., 2015; Hagen et al., 2016; Jacobus, Joanna et al., 2015; Madeline H. Meier et al., 2012; Nguyen Louie et al., 2017). Alcohol use at earlier ages was more likely to be impaired in traditionally “lower level” neuropsychological performance, such as processing speed, but “higher order” performance can also be impaired (Nguyen Louie et al., 2017).

Processing speed was also related to the level of one’s education. Higher levels of education were associated with later onset age and were suggested to be a protective factor postponing the onset age. The protective effects of higher education and occupation-based social class on cognitive ability have been previously demonstrated in longitudinal studies (Alarcon, Nalpas, Pelletier, & Perney, 2015; Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012)

Perceptual Reasoning. The Block Design test and the Raven test were more impaired among LOAs than EOAs. Compared to EOAs, LOAs had worse visuospatial reasoning as measured by the Block Design test in multidrug users. This result aligns with the findings of Joos et al. (2013), where the early onset group with an alcohol use disorder performed generally as well as or even better than the late onset group with an alcohol use disorder, especially in visual tests. This result is also confirms Lezak’s (1995) suggestion that the visuospatial impairment of chronic alcoholics involved slowed visual organization and integration.

Figure 2. The onset age of regular substance use and learning difficulties

This may indicate that impairment results from the slowing of visual integration. Changes related to the use of benzodiazepines are most strongly reflected in visual perception and visuospatial perception, in addition to almost all other cognitive subareas (e.g. attention, memory psychomotor speed, reasoning, and problem solving) (Rapeli, 2015).

In addition, in the present study poorer performance in the Raven test was associated with learning difficulties. Learning difficulties were suggested to be present before the onset age of substance abuse although the effects of substance abuse can be exaggerated by extensive consumption (Harvey, Stokes, Lord, & Pogge, 1996). This result is consistent with earlier findings on premorbid factors of alcohol and substance use and cognitive ability. In a prospective study, Penick et al. (2010) found that alcohol-dependent subjects with cognitive difficulties were more likely to continue problem drinking. Variables that were significantly related to later alcohol dependence and failure to recover in men were neurological problems, the need for special education at school and poorer attention measures (e.g. WAIS Digit Span) (Penick et al., 2010). The results of this study also align with a Finnish population-based study of young adults (Latvala et al., 2009). The said study found that poorer verbal ability is associated with lifelong alcohol and other substance use disorders. Poorer verbal intellectual ability was correlated with low basic education, and slower psychomotor processing was associated with SUD, independently of risk factors.

There was no interaction between onset age of substance use and the covariable of gender. We examined gender and substance use in more detail in a later study.

Visual Memory and Learning. The delayed visual learning test was more impaired in LOAs than EOAs in

a group with no learning difficulties. This result supports the findings of Hanson et al. (2011), which suggest that for youth with a history of alcohol and substance use, subsequent use of either alcohol or other drugs during young adulthood (ages 18–26 years old) may negatively impact visuospatial memory. In contrast with Hanson et al. (2011), we did not find a decline in verbal memory. The mean onset age of substance use among LOAs was 29.2 (9.8) in this study. Hanson et al. (2011) concluded that mid-adolescence to the mid-twenties is a time of significant neurodevelopment, which may be influenced by increased substance use during late adolescence. Visuospatial memory may be differentially sensitive to continued substance use during this time period and damage resulting from sustained substance use persists beyond periods of heavy use. Although the most significant qualitative changes in brain maturation have been found to occur from childhood to adolescence, emerging evidence does suggest that the specialization of brain processes supporting both cognitive and motivational systems continues into the 30s (Bonnie, Stroud, & Breiner, 2014).

In addition to later onset age of substance use, ageing seems to aggravate the delayed visual learning. Heavy alcohol consumption has been shown to accelerate brain ageing (Sabia et al., 2014).

Inhibitory Capacity. The results of CogniSpeed tasks of inhibitory capacity measure was quite surprising, as we expected that early onset of substance abuse would impair cognitive processing speed and executive function of Stroop Interference and Total Stroop and impede the maintenance of information processing speed (Le Berre, Fama, & Sullivan, 2017). The results on the executive function suggests that impairment of prefrontal function is present before the onset of substance abuse (Squeglia, L., 2014; Tarter,

Kirisci, Reynolds, & Mezzich, 2004). Adolescence is an important phase in the development of executive functions of the brain, but inhibitory control may weaken prior to adolescence and the onset of substance use (Conrod & Nikolaou, 2016; Squeglia, Lindsay, Jacobus, Nguyen Louie, & Tapert, 2014). It is possible that early onset of substance abuse is not the sole cause but also a consequence of problems in executive and attentive functions and poor learning capacity. Our findings suggest that when the capability to self-regulate is initially poor, substance abuse can increase problems with self-regulation problems.

To summarise, the present cross-sectional study affirmed that early onset of substance use impairs psychomotor speed. As regards perceptual reasoning, visual learning, and memory, late onset of substance use can also be as adverse as early onset of substance use. On the other hand, premorbid cognitive impairment may be present before the onset of substance abuse. These results suggest that premorbid risk factors, such as impairment of inhibitory capacity and learning difficulties may be premorbid risk factors for early onset of addiction. These results are supported by the findings of previous studies that impairment of inhibitory capacity and cognitive efficiency is related to the risk of alcohol and substance abuse problems (Penick et al., 2010; Squeglia, Lindsay et al., 2014). According to brain imaging studies, it is possible that the observed changes already exist before the onset age of substance use (Volkow et al., 2016).

In our study patients' substance use had been, to an extent, uncontrolled so that they had to be recommended for hospitalization. The patients were relatively young; the mean age of EOA group was 32.8., while the mean age of the LOA group was 43.5. When patients had quit from substance abuse for a long time, many of them hoped to be able to return to work. It is therefore important to evaluate in clinical work how permanent the changes in neuropsychological functions impacted by substance use are. It is important to consider slowing psychomotor performance in substance use research because working life often requires the ability to work quickly and efficiently. In addition to speed, many demanding work tasks also require adequate capability for reasoning, learning and memory. Our research results show that changes in processing speed, perceptual reasoning and memory may be more permanent, which are essential skills when applying for a work, should be considered. For future clinical research should be conducted in a longitudinal setting to assess the degree of enduring effects of substance use on the performance of EOAs and LOAs. Adolescent onset age of substance use and initiation prior to age 16 are an important risk factors as they predict poorer neural health and neurocognitive outcome over time (Jacobus, Joanna et al., 2015); nonetheless, the later onset of drug use as a young adult is also detrimental. Hanson et al. (2011) identified long-term (10-year) patterns of NP functioning in relation to the dominant trajectories of alcohol and drug use for youth. Their findings suggest that substance use during adolescence and young adulthood may primarily influence performance that relies on later maturing brain structures, although further research is needed.

Prospective studies are useful, but it is hard to motivate hospital patients to engage in for long-term follow-up. Meanwhile, outpatient volunteers may have protective factors related to their cognitive functioning and their ability to remain in the community compared to research participants. Notably, elderly patients who receive psychosocial outpatient treatment for

alcoholism, have better 6-month outcomes within a range of drinking outcome measures compared to middle-aged patients (Wieben, Nielsen, Nielsen, & Andersen, 2018).

Limitations and Advantages

The main limitation of this study is that we were unable to investigate the effects of specific substances as nearly half of the study's subjects abuse multiple substances. The diagnoses of polydrug users were generally variable in their combinations, making it difficult to investigate the effects of a single substance. Each substance of abuse presents quite a diverse pattern of cognitive deficits; hence, this is a major limitation of the analysis. In multiple substance use, substances are commonly used together or in succession (Brown et al., 2000). It is thus difficult to attribute any deficit to a particular drug, especially in the context of polysubstance use (Hanson et al., 2011).

Moreover, dose-dependent relationships with lifetime use and early abstinence of use were not identified in this study. Abstinence was assessed with four weeks of monitored toxicology potentially excluding acute effects as reported in other studies (Rapeli, P. et al., 2006).

The common finding has been that all substances, except cannabis, are associated with sustained deficits in executive functioning, especially inhibition (van Holst & Schilt, 2011). It is impossible to recruit matched control groups, which is a fundamental shortcoming of observational research that cannot be solved by merely adding covariates to the analysis (Schulte et al., 2014). We expected that the sample in our study would be more realistic than in studies tracked the effects of various drugs with specified amounts. The different substance use groups were not analysed separately, mainly to avoid the type II error of multiple testing. The data collection method was naturalistic and observational. In the multi-way analysis of covariance, the significance of multidrug use in this study was generally negligible, and the results suggest that using only one substance is sufficient to impair performance level. The sample size was moderate. We excluded for Axis I psychiatric disorders at baseline to focus more specifically on the effects of substance use on cognition.

No reliable information about the number of overdoses and bouts of delirium could be obtained. Furthermore, there was no reliable information regarding the number of hospitalisations. These variables were therefore excluded from the analyses although they can influence on cognitive performance. Hanson et al. (2011) affirmed that substance withdrawal symptoms are related to poorer verbal learning and memory scores.

The number of patients allotted to the different neuropsychological tasks varied. The number of patients is fewer for memory and learning tasks. The aims of the neuropsychological assessments were different for different patients; some assessments were a part of a more exhaustive working ability evaluation, while some were a part of a more limited therapeutic evaluation. We used the old version of WAIS (WAIS-R) in the assessment of intellectual capacity since the study was initiated in 2004, when WAIS-III was not yet translated and standardised for use by psychologists in Finland. Likewise, WMS-R was used as the memory test because the new WMS-III came into use in Finland only in 2008. To ensure consistency, the tests were based on WAIS-R and WMS-R.

A major strength of the present study is the carefully diagnosed hospital participants. The patients were diagnosed by psychiatrists who specialised in substance abuse disorder. They use ICD-10 criteria for the diagnosis of each condition. The duration of abstinence was determined by laboratory tests.

References

- Alarcon, R., Nalpas, B., Pelletier, S., & Perney, P. (2015). MoCA as a screening tool of neuropsychological deficits in alcohol-dependent patients. *Alcoholism: Clinical and Experimental Research*, 39(6), 1042-1048. doi:10.1111/acer.12734
- Bava, S. (2013). Longitudinal changes in white matter integrity among adolescent substance users. *Alcohol Clin Exp Res*, 37 Suppl 1, E181.
- Bava, S., Jacobus, J., Mahmood, O., Yang, T. T., & Tapert, S. F. (2010). Neurocognitive correlates of white matter quality in adolescent substance users. *Brain and Cognition*, 72(3), 347-354. doi:2048/10.1016/j.bandc.2009.10.012
- Bonnie, R. J., Stroud, C., & Breiner, H. (2014). Investing in the health and well-being of young adults.
- Brown, S. A., Tapert, S. F., Granholm, E., & Delis, D. C. (2000). Neurocognitive functioning of adolescents: Effects of protracted alcohol use. *Alcoholism: Clinical and Experimental Research*, 24(2), 164-171.
- Brumbach, T., Castro, N., Jacobus, J., & Tapert, S. (2016). Effects of marijuana use on brain structure and function: Neuroimaging findings from a neurodevelopmental perspective. *Int Rev Neurobiol*, 129, 33-65. doi:10.1016/bs.irn.2016.06.004
- Capella Mdel, M., Benaiges, I., & Adan, A. (2015). Neuropsychological performance in polyconsumer men under treatment. influence of age of onset of substance use. *Scientific Reports*, 5, 12038. doi:10.1038/srep12038 [doi]
- Conrod, P., & Nikolaou, K. (2016). Annual research review: On the developmental neuropsychology of substance use disorders. *Journal of Child Psychology and Psychiatry*, 57(3), 371-394. doi:10.1111/jcpp.12516
- Hagen, E., Erga, A. H., Hagen, K. P., Nesvåg, S. M., McKay, J. R., Lundervold, A. J., & Walderhaug, E. (2016). Assessment of executive function in patients with substance use disorder: A comparison of inventory- and performance-based assessment. *Journal of Substance Abuse Treatment*, 66, 1-8. doi:2048/10.1016/j.jsat.2016.02.010
- Hanson, K., Cummins, K., Tapert, S., & Brown, S. (2011). Changes in neuropsychological functioning over 10 years following adolescent substance abuse treatment. *Psychology of Addictive Behaviors*, 25(1), 127-142. doi:10.1037/a0022350
- Hanson, K., Medina, K., Padula, C., Tapert, S., & Brown, S. (2011). Impact of adolescent alcohol and drug use on neuropsychological functioning in young adulthood: 10-year outcomes. *Journal of Child & Adolescent Substance Abuse*, 20(2), 135-154. doi:10.1080/1067828X.2011.555272
- Harvey, Stokes, Lord, & Pogge. (1996). Neurocognitive and personality assessment of adolescent substance abusers: A multidimensional approach. *Assessment*, 3, 241-253.
- Jacobus, J., McQueeney, T., Bava, S., Schweinsburg, B. C., Frank, L. R., Yang, T. T., & Tapert, S. F. (2009). White matter integrity in adolescents with histories of marijuana use and binge drinking. *Neurotoxicology and Teratology*, 31(6), 349-355. doi:2048/10.1016/j.ntt.2009.07.006
- Jacobus, J., Squeglia, L. M., Infante, M. A., Castro, N., Brumbach, T., Meruelo, A. D., & Tapert, S. F. (2015). Neuropsychological performance in adolescent marijuana users with co-occurring alcohol use: A three-year longitudinal study. *Neuropsychology*, 29(6), 829-843. doi:10.1037/neu0000203
- Jacobus, J., Squeglia, L., Sorg, S., Nguyen Louie, T., & Tapert, S. (2014). Cortical thickness and neurocognition in adolescent marijuana and alcohol users following 28 days of monitored abstinence. *Journal of Studies on Alcohol and Drugs*, 75(5), 729-743.
- Joos, L., Schmaal, L., Goudriaan, A., Fransen, E., Van den Brink, W., Sabbe, B. G. C., & Dom, G. (2013). Age of onset and neuropsychological functioning in alcohol dependent inpatients. *Alcoholism: Clinical and Experimental Research*, 37(3), 407-416. doi:10.1111/j.1530-0277.2012.01949.x
- Josefsson, M., de Luna, X., Pudas, S., Nilsson, L., & Nyberg, L. (2012). Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. *Journal of the American Geriatrics Society*, 60(12), 2308-2312. doi:10.1111/jgs.12000
- Kist, N., Sandjojo, J., Kok, R., & van den Berg, Julia F. (2014). Cognitive functioning in older adults with early, late, and very late onset alcohol dependence. *International Psychogeriatrics*, 26(11), 1863-1869. doi:10.1017/S1041610214000878
- Latvala, A., Castaneda, A. E., Perälä, J., Saarni, S. I., Aalto-Setälä, T., Lönnqvist, J., . . . Tuulio-Henriksson, A. (2009). Cognitive functioning in substance abuse and dependence: A population-based study of young adults. *Addiction*, 104(9), 1558-1568. doi:10.1111/j.1360-0443.2009.02656.x
- Le Berre, A., Fama, R., & Sullivan, E. (2017). Executive functions, memory, and social cognitive deficits and recovery in chronic alcoholism: A critical review to inform future research. *Alcoholism: Clinical and Experimental Research*, 41(8), 1432-1443. doi:10.1111/acer.13431
- Lezak, M. D. (1995). *Neuropsychological assessment* (3. ed. ed.). New York: Oxford University Press.
- Lilja, A. M., Portin, R. I., Hämäläinen, P. I., & Salminen, E. K. (2001). Short-term effects of radiotherapy on attention and memory performances in patients with brain tumors. *Cancer*, 91(12), 2361-2368. doi:AID-CNCR1269>3.0.CO;2-1
- Madeline H. Meier, Avshalom Caspi, Antony Ambler, HonaLee Harrington, Renate Houts, Richard S. E. Keefe, . . . Terrie E. Moffitt. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences of the United States of America*, 109(40), 15980. Retrieved from <http://www.jstor.org/stable/41763182>
- Nguyen Louie, T., Matt, G., Jacobus, J., Li, L., Cota, C., Castro, N., & Tapert, S. (2017). Earlier alcohol use onset predicts poorer neuropsychological functioning in young adults. *Alcoholism: Clinical and Experimental Research*, 41(12), 2082-2092. doi:10.1111/acer.13503
- Penick, E., Knop, J., Nickel, E., Jensen, P., Manzardo, A., Lykke Mortensen, E., & Gabrielli, W. (2010). Do premorbid predictors of alcohol dependence also predict the failure to recover from alcoholism? *Journal of Studies on Alcohol and Drugs*, 71(5), 685-694.
- Portin, R. (2001). Cognitive functioning in midlife. *Psykologia*, 36(4), 239.
- Portin, R., Kovala, T., Polo-Kantola, P., Revonsuo, A., Müller, K., & Matikainen, E. (2000). Does P3 reflect attentional or memory performances, or cognition more generally? *Scandinavian Journal of Psychology*, 41(1), 31-40. doi:2048/10.1111/1467-9450.00168
- Rapeli. (2015). Päihdehäiriöt ja keskushermostomyrkyt. In Jehkonen Mervi, Saunamäki Tiia, Paavola Liisa, Vilkki Juhani (Ed.), *Kliininen neuropsykologia* (pp. 313-332). Riika: Duodecim.
- Rapeli, P., Kivisaari, R., Autti, T., Kähkönen, S., Puuskari, V., Jokela, O., & Kalska, H. (2006). Cognitive function during early abstinence from opioid dependence: A comparison

- to age, gender, and verbal intelligence matched controls. *BMC Psychiatry*, 6, 9-10. doi:10.1186/1471-244X-6-9
- Rapeli, P., Kivisaari, R., Khknen, S., Puuskari, V., Autti, T., & Kalska, H. (2005). Do individuals with former amphetamine dependence have cognitive deficits? *Nordic Journal of Psychiatry*, 59(4), 293-297. doi:10.1080/08039480510023025
- Revonsuo, A. (1995). Words interact with colors in a globally aphasic patient: Evidence from a stroop-like task. *Cortex*, 31(2), 377-386. doi://doi-org.ezproxy.utu.fi/10.1016/S0010-9452(13)80370-X
- Sabia, S., Elbaz, A., Britton, A., Bell, S., Dugravot, A., Shipley, M., . . . Singh Manoux, A. (2014). Alcohol consumption and cognitive decline in early old age. *Neurology*, 82(4), 332-339. doi:10.1212/WNL.0000000000000063
- Schulte, M. H. J., Cousijn, J., den Uyl, T. E., Gouiaan, A. E., van den Brink, W., Veltman, D. J., . . . Wiers, R. W. (2014). Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment. *Clinical Psychology Review*, 34(7), 531-550. doi:10.1016/j.cpr.2014.08.002
- Squeglia, L. M., Jacobus, J., & Tapert, S. F. (2009). The influence of substance use on adolescent brain development. *Clinical EEG and Neuroscience*, 40(1), 31-38. doi:10.1177/155005940904000110
- Squeglia, L. (2014). The effect of alcohol use on human adolescent brain structures and systems. *Handbook of Clinical Neurology*, 125, 501.
- Squeglia, L., Jacobus, J., Nguyen Louie, T., & Tapert, S. (2014). Inhibition during early adolescence predicts alcohol and marijuana use by late adolescence. *Neuropsychology*, 28(5), 782-790. doi:10.1037/neu0000083
- Tarter, R. E., Kirisci, L., Reynolds, M., & Mezzich, A. (2004). Neurobehavior disinhibition in childhood predicts suicide potential and substance use disorder by young adulthood. *Drug and Alcohol Dependence*, 76 Suppl, S45-S52. doi:10.1016/j.drugalcdep.2004.08.006
- van Holst, R., & Schilt, T. (2011). Drug-related decrease in neuropsychological functions of abstinent drug users. *Current Drug Abuse Reviews*, 4(1), 42-56.
- Volkow, N. D., Swanson, J. M., Evins, A. E., DeLisi, L. E., Meier, M. H., Gonzalez, R., . . . Baler, R. (2016). Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: A review. *JAMA Psychiatry*, 73(3), 292-297. doi:10.1001/jamapsychiatry.2015.3278
- Wechsler, D., Fieandt, K. v., & Kalimo, E. (1975). *WAIS-käsikirja : Wechslerin aikuisten älykkysasteikko*. Helsinki: Psykologien kustannus.
- Wieben, E. S., Nielsen, B., Nielsen, A. S., & Andersen, K. (2018). Elderly alcoholics compared to middle-aged alcoholics in outpatient treatment - 6-month follow-up. *Nordic Journal of Psychiatry*, 72(7), 506-511. doi:10.1080/08039488.2018.1522373 [doi]