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NEUROPSYCHOLOGICAL CORRELATES IN SUBSTANCE USE DISORDER

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I wish to dedicate this dissertation to Antti Holopainen, retired chief physician of Järvenpää Addiction Hospital. Without his initiative and support, this dissertation would not have been possible.

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ABSTRACT

Previous studies show contradictory results concerning associations with age of onset of substance use, differences between genders, and comorbid substance use in patients with mood disorders on neuropsychological performance.

This dissertation aims to investigate the cognitive functions, mood, and personality of hospital patients after a month of sobriety and identify psychological test methods to monitor their rehabilitation progress. The study sample consisted of patients at Järvenpää Addiction Hospital between 2005 and 2012 (N = 164). The neuropsychological tests of attention, executive function, verbal and visual reasoning, and memory were studied. The neuropsychological tests used in this study were included to the neuropsychological test battery used in clinical assessments. Personality variables were measured using the subscales of the Minnesota Multiphasic Personality Inventory (MMPI).

The average age of onset of regular substance use was 14.5 (2.0) years in early-onset abusers (EOAs) and 29.2 (9.8) years in late-onset abusers (LOAs). EOAs had greater psychomotor slowness than LOAs. LOAs had more impaired visual performance compared with EOAs. The results align with previous studies on the development of the brain and cognitive functions. Higher level of education served as a protective factor that postpones the onset of substance use to a later age. Notably, learning difficulties were more common among EOAs.

After adjustment, all the differences between men and women disappeared in the neuropsychological tests. Although both men and women expressed strong negative emotions, the former were more depressed than the latter. Strong negative emotions can predispose individuals to substance use, but they can also be exacerbated by substance use.

The results revealed that co-occurring diagnoses of mood disorder and substance use are associated with greater psychomotor retardation and decreased visuospatial function compared with a lone diagnosis of substance abuse disorder.

KEYWORDS: Substance abuse, mood disorders, age of onset substance use, gender differences, inpatients, neuropsychological functions, personality

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TIIVISTELMÄ

Aiemmissa tutkimuksissa on ilmennyt ristiriitaisia tuloksia, jotka koskevat neuropsykologista suoriutumista ja päihteiden käytön alkamisiän vaikutusta, miesten ja naisten välisiä eroja, sekä samanaikaista mielialahäiriötä ja päihdehäiriötä.

Tämän väitöskirjan tavoitteena oli tutkia sairaalapotilaiden kognitiivisia toimintoja ja mielialaa kuukauden raittiuden ja päihdekuntoutuksen jälkeen. Tavoitteena oli löytää kuntoutumisen seurantaan psykologisia testimenetelmiä. Tutkimuksen kohteena oli otos Järvenpään sosiaalisairaalan potilaita, jotka tulivat sairaalaan kuntoutukseen ja työkyvyn arviointiin vuosina 2005–2012 (N = 164). Neuropsykologisista toiminnoista tutkittiin tarkkaavuutta, toiminnanohjausta, kielellistä ja visuaalista päättelyä sekä muistia. Kliiniseen työhön sisältyviä neuropsykologisia testejä käytettiin myös tutkimuksessa. Lisäksi käytettiin persoonallisuustutkimusta (Minnesota Multiphasic Personality Inventory, MMPI).

Varhain säännöllisen päihteiden käytön aloittaneiden aloitusikä oli 14.5 (2.0) vuotta. Varhain aloitettu päihteiden käyttö oli yhteydessä suurempaan psykomotoriseen hidastuneisuuteen verrattuna myöhemmin aloitettuun käyttöön. Myöhemmin aloitetun säännöllisen päihteiden käytön aloitusikä oli 29.2 (9.8) vuotta. Myöhemmin aloittaneilla päihteiden käyttö oli yhteydessä näönvaraisten toimintojen heikentymiseen. Korkeampi koulutustaso toimi suojaavana tekijänä ja siirsi päihteiden käytön aloitusta myöhempään ikään.

Sukupuolten välisiä eroja suorituksissa ei tullut esiin neuropsykologisissa testeissä. Miehet olivat masentuneempia kuin naiset, joskin molemmat toivat esiin kielteisiä tunteita.

Tutkimukset osoittivat, että jos potilaalla oli samanaikainen mielialahäiriödiagnoosi ja päihdediagnoosi, ne olivat yhteydessä erityisesti suurempaan psykomotoriseen hidastumiseen ja visuospatiaalisen toiminnan heikentymiseen verrattuna potilaisiin, joilla oli pelkkä päihdehäiriö.

AVAINSANAT: Päihteiden käyttö, mielialahäiriöt, päihteiden käytön aloitusikä, sukupuolten väliset erot, sairaalapotilaat, neuropsykologiset toiminnot, persoonallisuus

Table of Contents

Abbreviations

AUD	Alcohol use disorder
ACC	Anterior cingulate cortex
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
BD	Bipolar disorder
COL	Neutral Condition of the CogniSpeed version of the Stroop Colour-Word Interference Test
CON	Congruous Word Condition of the CogniSpeed version of the Stroop Colour-Word Interference Test
DEL	Delayed Recall
DLPFC	dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
DST	Digit Symbol Test
EOA	early onset abusers
GABA	gamma-aminobutyric acid
GM	grey matter
HIV	Human immunodeficiency virus
HRNB	the Halstead-Reitan Neuropsychological Battery
ICD	International Statistical Classification of Diseases and Related Health Problems
IN	Incongruous Word Condition of the CogniSpeed version of the Stroop Colour-Word Interference Test
iRISA	impaired response inhibition and salience attribution model
LNNB	Luria Nebraska Neuropsychological Battery
LOA	late onset abusers
MMPI	Minnesota Multiphasic Personality Inventory
MoCA	Montreal Cognitive Assessment
PFC	prefrontal cortex
pre-SMA	presupplementary motor area
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RPM	Raven´s Progressive Matrices

RT	Reaction time
SUD	Substance use disorder
VEM	Verbal Memory Index
VIM	Visual Memory Index
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WASI-PIQ	Wechsler Abbreviated Scale of Intelligence-Performance Intelligence Quotient
WCST	Wisconsin Card Sorting Test
WHO	World Health Organisation
WM	working memory
WMS	Wechsler Memory Scale

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Irma Höijer, Tuula Ilonen, Eliisa Löyttyniemi & Raimo K. R. Salokangas. Onset age of substance use and neuropsychological performance in hospital patients. *Clinical Neuropsychiatry*, 2020; 17(5): 271–280.

II Irma Höijer, Tuula Ilonen, Eliisa Löyttyniemi & Raimo K. R. Salokangas. Gender Differences in Cognitive and Personality Functioning in Patients With Substance Use Disorder. *Addictive Disorders & Their Treatment*, 2021; 20(4): 538–547.

III Irma Höijer, Tuula Ilonen, Eliisa Löyttyniemi & Raimo K. R. Salokangas. Neuropsychological performance in patients with substance use disorder with and without mood disorders. *Nordic Journal of Psychiatry,* 2020; 74(6): 444–452.

1 Introduction

Substance use disorder (SUD) is widely recognised as a complex episodic and chronic disease. SUD comprises use of psychoactive substances (e.g. alcohol, misuse of prescription drugs, and illicit substances). By definition, polysubstance use is the use of two or more different psychoactive substances simultaneously or sequentially (Rapeli, 2015).

The World Health Organisation (WHO) defines SUD as a group of conditions related to alcohol or other drug use. In ICD-10, section F10-F19, ”Mental and behavioral disorders due to psychoactive substance use”, contains a wide variety of disorders of different severity and clinical form, all having in common the use of one of more psychoactive substances which may or may not have been medically prescribed. The substances specified are alcohol, opioids, cannabinoids, sedatives or hypnotics, cocaine, and other stimulants. The clinical states that may occur, though not necessarily with all psychoactive substances include acute intoxication, harmful use, dependence syndrome, and withdrawal syndrome (state). The substances specified in this study are alcohol, opioids, cannabinoids, sedatives, stimulants and cannabis. The clinical states include harmful use and dependence syndrome.

Increasing evidence suggests that substance use during adolescence and early adulthood can result in transient or even permanent deficit to brain development and neuropsychological performance. According to Bates, Buckman, & Nguyen (2013), recovery of neuropsychological functions remains possible after discontinuing substance use. Based on review studies of Bates et al. (2013) the results of studies on whether abstinence can improve neuropsychological functions are contradictory.

The relationship between brain dysfunction and behaviour can be examined through neuropsychological assessment (Lezak, 1995). Neuropsychology does not entail the direct study of the brain but rather behaviours controlled by brain and information processing functions, which are easily impaired by substance use and thus relevant to the planning and success of treatment. It is worth mentioning that, although considerable research has been conducted in recent years on the association between substance use and cognitive functions, results remain contradictory due to different testing methods, diagnostic methods, population characteristics, sample size, and other factors. Further research is therefore needed in this field of research.

This dissertation aims to elucidate the neuropsychological functions and personality features of men and women with SUD after a month of abstinence, with a focus age of onset of substance use and mood disorders, and to compare the test values of the study groups to with the normal reference frame of neuropsychological tests and personality variables. The substances specified in this study are alcohol, opioids, cannabinoids, sedatives, stimulants and cannabis. The studies include participants who only used one substance and participants who used multiple substances. The clinical states include harmful use and dependence syndrome.

The dissertation consisted of three separate studies. The first study explored the impact the age of onset of regular substance use on neuropsychological test performance (Original article I). The second study focused on the differences in neuropsychological test performance and personality test variables between men and women diagnosed with SUD (Original article II). The third study examined the differences between the neuropsychological tests of the two groups - those with a SUD with mood disorders and those with SUD without mood disorder (Original article III).

2 Literature review

2.1 Substance use disorder; from experimentation and harmful use to addiction

Two main diagnostic systems have been used for diagnosing SUD: the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Statistical Classification of Diseases and Related Health Problems (ICD). The DSM is a U.S. system for diagnosing mental and behavioural disorders. The fifth version of the DSM (DSM-5) was completed and published in May 2013. The ICD is an international disease classification system developed by WHO. The latest version of the classification was published in 2018 and is known by the abbreviation ICD-11. In Finland, ICD-10, the previous version, is still in use. It seems that ICD-10 will continue to be used nationally in patient information systems for the time being, and the new version will not be widely used until the social welfare and health care reform is completed. The ICD-10 disease classification has been used officially in Finland since the beginning of 1996.

Schuckit et al. (1994) evaluated ICD-10 and recommended that individuals with SUDs be subdivided into groups: (a) those demonstrating a more severe and pervasive syndrome (i.e. dependence) and (b) those with less severe conditions (i.e. abuse or harmful use). In both diagnostic approaches, the disorders of persons using drugs were divided into different groups. More severe and pervasive syndromes were classified as addiction, whereas milder conditions were classified as abuse or harmful behaviour. ICD-10 focuses on problems in the previous year. ICD-10 is more require three of the six items. ICD-10 focuses on psychological and physical disadvantages and does not consider social, interpersonal, and legal issues. The sample of Schuckit (N = 1,922) consisted of individuals who have been in care, have used alcohol or five illicit substances, and met criteria for dependence, abuse or harmful use, or no diagnosis across DSM-III-R, DSM-IV, and ICD-10 and their counterpart in genetic research (Schuckit et al., 1994).

In ICD-10, substance use dependence is defined as the presence of three or more of the following at some time during the previous year: (a) a strong desire or sense of compulsion to take the substance; (b) difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use; (c) a physiological

withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance or the use of the same or a closely related substance with the intention of relieving or avoiding withdrawal symptoms; (d) evidence of tolerance such that increased doses of psychoactive substances are required to achieve effects originally produced by lower doses, as typified by alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users; (e) progressive neglect of alternative pleasures or interests because of psychoactive substance use and increased amount of time necessary to obtain or take the substance or to recover from its effects; (f) persistent substance use despite clear evidence of overtly harmful consequences, such as harm to the liver due to excessive drinking, depressive mood states as a consequence of periods of heavy substance use, or drug-related impairment in cognitive functioning. Accordingly, efforts should be made to determine if the user was actually or could be expected to be aware of the nature and extent of the harm.

Saunders (2021) distinguished the main differences between ICD-10 and ICD-11 as follows:

Substance dependence is defined in ICD-11 as a disorder of regulation of substance use arising from repeated or continuous use of a substance; it is characterised by a strong internal drive to use a substance. Substance dependence is usually evident over a period of at least 12 months, but diagnosis can be made if use is continuous (i.e. daily or almost daily) for at least three months.

ICD-11 includes a new grouping of conditions titled Disorders Due to Substance Use and Addictive Behaviours, which has four primary diagnoses: Substance Dependence, Harmful Pattern of Substance Use, Episode of Harmful Substance Use, and Hazardous Substance Use. These diagnoses are hierarchical and mutually exclusive; hence, only one can be diagnosed per substance group. However, different diagnoses may apply to different substances in one patient. These diagnoses contrast that in ICD-10 where only Substance Dependence and Harmful Substance Use have been included.

Episode of Harmful Use and Hazardous Substance Use, which are not stipulated in ICD-10, DSM-5, and DSM-IV, have been separately defined in ICD-11. ICD-11 emphasises the spectrum or range in use and disorder, with Substance Dependence as a clinical syndrome and with sub-dependence diagnoses representing patterns of use over time, leading to harm or conferring the risk of harm. In ICD-11, dependence requires one month of use. Harm reduction studies have supported and emphasised the importance and benefits of early initial screening for problematic alcohol use followed by brief and other interventions in first-contact medical healthcare facilities to reduce alcohol intake (Charlet and Heinz, 2017).

The National Institute on Alcohol Abuse and Alcoholism (2021) defines binge drinking as a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08% – or 0.08 grams of alcohol per decilitre – or higher. For a typical adult, this pattern of alcohol misuse corresponds to consuming 4 or more drinks for women or 5 or more drinks for men in about 2 hours. Research has shown that fewer drinks within the same time frame result in the same BAC in youth – only 3 drinks for girls and 3 to 5 drinks for boys, depending on their age and size. Meanwhile, high-intensity drinking is defined as alcohol intake at levels twice or more than the gender-specific threshold for binge drinking. This dangerous drinking pattern means 8 or more drinks for women and 10 or more drinks for men on one occasion. Research has suggested that high-intensity drinking peaks around age 21 and is most common among young adults attending college. This pattern of drinking is of particular concern because it is associated with an even greater risk of severe health and safety consequences (NIAAA, 2021).

In Finland, to determine the risks caused by alcohol and to facilitate treatment choices, problem alcohol use has been divided into three categories: risky use, harmful use, and alcohol dependence. In risky use, the limits for use are exceeded, but significant alcohol harm or dependence does not yet occur. In harmful use, alcohol use causes clearly identifiable physical or mental harm to the person but not addiction. The four criteria for harmful use are based on ICD-10 (Aalto et al., 2015).

Risky use usually refers to alcohol use that is likely to cause harm to the health of the user (Aalto et al., 2015). The average level of use is important, in addition to the drinking pattern. In Finland, it is customary to drink much alcohol at once ("humalajuominen"). These situational factors have been found to affect the risks of alcohol use. Results from the Drinking Habits Survey 2016 (Lintonen et al., 2019) showed that at least 5% of the Finnish population are high-risk alcohol users (i.e. 20 grams of alcohol per day for women, 40 grams for men, or about 12/23 servings per week). More than 550,000 Finns exceed the moderate risk limit (7/14 doses per week). More than 60% of those who exceed the risk limit are men. The study used the Alcohol Use Disorder Identification Test (AUDIT) questionnaire. Taking into account age and social background factors, risky use was found to be about twice as common in men than in women. The most serious health problems caused by alcohol use often affect this group.

Prevalence of 12-month alcohol use disorder (AUD) in Finland decreased from 4.6% (95% CI 4.0-5.1) in 2000 to 2.0% in 2011 (95% CI 1.6-2.4) (Peña et al., 2018). Lifetime AUD prevalence decreased from 10.8% (95% CI 9.9-11.6) to 7.5% (CI 95% 6.8-8.3) from 2000 to 2011. This reduction was observed among individuals aged 30 to 64. At both time points, AUD prevalence was higher among individuals aged 30 to 64, particularly men, and those who were unmarried, widowed, or divorced (Peña et al., 2018). According to the Health 2000 study, 17% of men and

5% of women aged 30 to 64 met the criteria for risk use, harmful use, or alcohol dependence. Aalto et al. (2009) claimed that it is likely that these figures have been underestimated (Aalto, Aalto, and Ripatti, 2015).

Polysubstance use patterns reveal an interlacing of alcohol and drug. Among heavy drinking individuals in Finland, nearly 30% have also tried illicit drugs (Hakkarainen and Metso, 2009).

In a population-based study conducted by Latvala et al. (2009a), the incidence of SUDs peaked during young adulthood, making epidemiological studies of SUDs in young adults noteworthy. Lifetime prevalence of abuse of or dependence in any substance, alcohol, and any illicit substance were 14.2%, 13.1%, and 4.4%, respectively (Latvala et al., 2009a). However, drug use in Finland is more prevalent than estimated in previous studies. Drug experimentation and drug use have increased in Finland this decade. According to the results of Rönkä et al.'s (2020) study, there were approximately 31,100 to 44,300 problem users of amphetamines and opioids in Finland in 2017. In relation to the entire population, this estimate constitutes 0.9 to 1.3% of Finns aged 15 to 64. The highest problem use rates were reported among 25- to 34-year-olds (1.1–2.8%), among men (1.3–1.7%), and in southern Finland (1.0–1.9%). Finland has a larger generation of young problem users of amphetamines and opioids aged 15 to 24 than ever before (Rönkä et al., 2020). Finland also has the seventh highest number of drug-related deaths in the EU (European Drug Report, 2020; Sedergren, 2021). Although the differences are partly explained by more detailed research methods, drug poisoning is the second most common cause of death among Finnish men under 40.

The report on drug-related population surveys in Finland 1992–2018 conducted by the Finnish Institute for Health and Welfare (Karjalainen et al., 2020) compiled the results of postal surveys and online surveys (2010–2018) on drug use and drug attitudes among Finns. Non-medical use of drugs included the use of sedatives, hypnotics, and analgesics for non-medical purposes. Drug abuse among men and women aged 25 to 34 has increased. In 2018, drug abuse was most common in this age group (i.e. 14% among men and 13% among women). Although men generally use drugs more than women, gender differences in the non-medical drug use are quite small. In the youngest age group (15–24 age group), non-medical use of drug abuse is almost as common in men as in women, whereas in the 35–44 age group, drug abuse was more common among women (9%) than men (7%).

In 2018, 16% of the respondents, specifically 18% of men and 13% of women, reported having used at least two different substances at the same time (i.e. alcohol/drugs/medicines). Compared to 2014, lifetime polysubstance use appeared to be slightly more common in women and older age groups (i.e. over 35 years). In women, the differences between the two youngest age groups levelled off from 2014, and the proportions in both groups were between 6 to 7% (Karjalainen et al., 2020).

2.1.1 Neurobiological studies of addiction

The term addiction is used to indicate the most severe, chronic stage of substance use disorder in which there is a substantial loss of self-control, as indicated by compulsive drug taking despite the desire to stop taking the drug. The term addiction is synonymous with the classification of severe substance use disorder (Volkow et al., 2016).

Goldstein and Volkow (2011) affirmed the significance of the prefrontal cortex (PFC) in addiction. The weakening of self-control mechanisms correlates with impaired performance in PFC circuits. Disorders emerge in all three areas of the PFC: the anterior cingulate, the orbitofrontal cortex, and the dorsolateral prefrontal cortex. The PFC is important for the performance of cognitive functions and the regulation of emotions and behaviours. Intracellular events and reward- and pleasure-related functions have been elucidated in animal studies. In humans, cognitions, goals, motivation for goals, and executive functions also determine behaviour. Brain imaging studies in adolescents have associated abnormalities in PFC function and structure with higher risk for SUD, underlining the role of PFC in self-regulation and its disruption as a factor contributing to vulnerability to use substances (Volkow et al., 2019).

Goldstein and Volkow (2011) proposed the impaired response inhibition and salience attribution (iRISA) model. The model asserts that impaired response inhibition and salience attribution underlie substance seeking and taking. Previous theories have emphasised the pleasure of substance use as an adherent, but subtle cognitive and emotional impairments and progressive changes in the brain contribute to uncontrollable substance use. Goldstein and Volkow (2011, p. 651) concluded that ‘As a result of these core deficits, drug seeking and taking become a main motivational drive, occurring at the expense of other activities, and culminating in extreme behaviours in order to obtain drugs’. Based on the disease model of addiction, neuropsychological functions of the forebrain are considered. The frontal brain is responsible for impulse control and executive functions. When this system is disrupted, behaviour becomes compulsive.

Badiani, Belin, Epstein, Calu, and Shaham (2011) challenged a unitary account of substance addiction. Although different abused substances have different mechanisms of action, they all increase dopamine in the brain (Goldstein and Volkow, 2011). Addiction over-sensitises dopamine neurons. Alcohol and other substances provide large amounts of dopamine to dopamine receptors at one time, producing more dopamine in the brain than any other activity. Dopamine enhances reward effects in the brain, and the brain prefers activities that produce the most dopamine (Konova et al., 2013; Goldstein and Volkow, 2011). Chronic substance use modifies activity in the dopamine areas of the midbrain (i.e. ventral tegmental area and substantia nigra) and the basal ganglia structures into which they project

(i.e. ventral striatum, nucleus accumbens, and dorsal striatum; Goldstein and Volkow , 2011). Basal ganglia structures are known to be involved in reward, conditioning, and habit formation (Goldstein and Volkow, 2011).

Volkow et al. (2019) reviewed major advances in recent years in addiction research. More finely grained understanding of the multiple circuits that become disrupted in addiction can help achieve new therapeutic effects and new solutions to addiction (Volkow et al., 2019; Volkow et al. 2016). Drug-induced neuroplasticity has been associated with chronic stress and with addictive and neurodegenerative disorders. Molecular processes are involved both in learning and in drug-induced neuroplasticity and have been a focus in neuroplasticity studies of addiction (e.g. silent synapses in dentate gyrus correlates with alcohol addiction; deleting gene Maged I abolishes reinforcing effects of cocaine).

Volkow et al. (2019) argued that the transition from drug experimentation to drug addiction is still under investigation. Volkow et al. (2019) pointed out that transition is associated with measurable disorders in several brain circuits, including those involved in conditioning, reward sensitivity, incentive motivation, self-monitoring or self-regulation, mood, and interoception. In parallel with the rewarding effects of drugs, sensitivity to negative reinforcements decreases, and this impairs the addicted person's capability to feel deterred by negative outcomes (e.g. incarceration, loss of child custody).

Volkow et al. (2019) recognised the "dark side of addiction," including drug withdrawal symptoms with intense distress and negative emotionality, which increases the risk of relapse. Distress is associated with reduced dopamine signalling in response to rewards (i.e. anhedonia) and enhanced sensitivity of the stress system, including the extended amygdala, habenula, and hypothalamus, which consequently contributes to relapse and high comorbidity with depression, anxiety, and suicidality.

Based on several studies, Volkow et al. (2019) suggested that in addiction, the motivation to take drugs is energised by drug-predictive cues and drug-induced transient dopamine stimulation, which facilitate compulsive intake. The development of powerful cue-conditioned cravings becomes even more deleterious when combined with growing deficits in the brain's ability to inhibit maladaptive behaviours, avoid risky or self-destructive behaviours, resist temptation, or delay gratification (e.g. future payoff of engaging in a long-term recovery programme).

Regarding the treatment of addiction, PFC has been a target of transcranial magnetic stimulation (TMS) and transcranial direct electrical stimulation (tDCS). TMS is a promising technique to treat patients with comorbid SUD and other mental illnesses. Strengthening of self-control capacity via the frontal cortical circuitry can help prevent relapse. There is experimental evidence suggesting that mindfulness-based techniques can positively impact cognitive processes and mitigate addictive behaviours. Important areas for research are factors that make some individuals

better able to recover than others or neurobiological mechanisms that support recovery.

More medications to treat other drug use disorders are needed. Naltrexone and acamprosate have been efficacious in the treatment of alcohol-use disorders, and other medications help patients recover from nicotine addiction. Existing medications, namely methadone, buprenorphine, and naltrexone, have been proven effective in reducing relapse risk and improving other outcomes in patients with opioid use disorder. There are several promising candidates for the treatment of stimulant and opioid use disorder that are currently undergoing clinical trials.

Results of both animal and human studies have provided compelling evidence that when exposure to drugs occurs during childhood or adolescence, it can interfere with developmental brain trajectories, thus exacerbating adverse outcomes. The Adolescent Brain Cognitive Development (ABCD) study will follow over 10,000 youth in the United States as they transition from childhood to adolescence to adulthood while monitoring their physical and mental health, neurocognition, social environment, substance use, genetic and other biomarkers, and structural and functional brain development.

2.2 Neuropsychological assessment of brain dysfunction

2.2.1 Processing speed

Mental processing speed or cognitive processing speed refers to the ability to rapidly process information; it is closely related to the ability to perform higher-order cognitive tasks (Ebaid, Crewther, MacCalman, Brown, & Crewther, 2017). Clinical test methods for assessing mental processing speed include computer-aided reaction time tasks or paper-and-pencil tests, which to some extent may also require psychomotor functioning. Completion time, not number of errors, is an essential factor in these tests. Simple tests, such as word reading and colour naming in the Stroop tasks, Part A of the Trail Making Test (Lezak, 1995), and the Digit Symbol Test enable distinctions between subcomponents. These measures are therefore regarded in this dissertation as general multidimensional speed tests that also include rates of reading, naming, and perceptual and visuomotor functions. The CogniSpeed tests of Stroop tasks (Portin, Revonsuo, Koivikko, & Rinne, 1993) distinguish task components of implicit and conscious processing speed and reaction times from simple tasks to more complex tasks of inhibitory capacity. The CogniSpeed tests of Stroop tasks are discussed in greater depth in Section 4.3.

The Digit Symbol Test (DST) of the WAIS is a sensitive and valid test that screens for brain dysfunctions and includes measures of cognitive dysfunction

impacted by many domains. The DST is a pencil-and-paper test that consists of two areas: a key area that contains nine pairs of digits and nonsense symbols and an answer area that contains randomly ordered digits and blank spaces. Subjects must fill in the blanks with symbols according to the key as rapidly as possible in the allotted time of 120 s (WAIS-III). The DST is a test of complex visuomotor tracking and learning (Lezak, 1995). In addition to the Block Design Test and 'digit backward' assessments, the DST evaluates an individual's capacity for abstract and speed-dependent attention to and learning of new and unfamiliar items. As such, patients in general are more likely to perform poorly in this test than others. Both DST and processing speed are considered to be highly specific for differentiating bipolar disorder (BD), both euthymic BD probands, and unaffected first-degree relatives in healthy controls (Daban, 2012).

Scores in the DST reflect impairment due to general brain damage, ageing, and various pathological conditions (Bonnelle, Manohar, & Husain, 2014) regardless of the lesion's locus (Lezak, 1995). The test is extremely sensitive to dementia and correlates with coma duration (Lezak, 1995). Impaired processing speed is often an underlying factor in attentional deficits (Bonnelle et al., 2014; Lezak, 1995).

Reaction time (RT) frequently slows with brain disease or injury; this disproportionately increases with increasing task complexity (Lezak, 1995). Focal brain lesions, traumatic brain injury, and Parkinson´s disease slow RT and cause deficits in attention (Bonnelle et al., 2014). In ageing populations, cognitive processing speed is often assumed to be the core issue responsible for deficits in performance related to complex cognitive measures (Ebaid et al., 2017). A slowdown in mental processing speed is frequently reported as a result of dementia and depression (Lezak, 1995). Slower psychomotor speed with ageing can serve as a biomarker of risk for clinical disorders of cognition, mobility, and mood (Rosano & Rosano, 2016).

2.2.2 Executive functions and attention

Executive function consists of adaptive and flexible behaviours, such as monitoring for situations in which automatic actions must be suppressed or changed, inhibiting or changing these actions, monitoring performance outcome, and adjusting behaviour as needed (Bonnelle et al., 2014). Executive control of attention has often been studied using paradigms that involve conflict, such as the Stroop task, in which conflict or interference occurs when the colour word name differs from the colour of the ink (Bonnelle et al., 2014).

In clinical practice, a variety of tests can be applied to assess executive skills, such as planning, initiating, progressing, and monitoring complex goal-directed behaviour (Diamond, 2013). The most frequently used tasks in assessment tests are

the Stroop tasks (i.e. interference), Part B of the Trail Making Test, verbal fluency, the Wisconsin Card Sorting Test, and the Tower of Hanoi tests, which measure response inhibition, set shifting, mental flexibility and problem solving (Lezak, 1995). The frontal regions of the brain have both activating and inhibitory connections to other regions, with inhibitory regulation especially occurring through the orbital region. Go/no-go, stop signal reaction time tasks, and Stroop tasks are classic measures of inhibitory control (Alvarez & Emory, 2006).

Inhibitory control, which is defined as the ability suppress inappropriate or no longer required responses, is an important aspect of executive attention that is frequently impaired in many neurological disorders (Bonnelle et al., 2014). Impulsivity or the lack of inhibition is generally considered to be action without conscious judgment or control (Stephan et al., 2017).

Lesion and imaging research have implicated the dorsolateral prefrontal cortex (DLPFC) in executive control and in maintaining and switching attention (Alvarez & Emory, 2006; Bonnelle et al., 2014). Medial frontal regions, such as the anterior cingulate cortex (ACC) and the presupplementary motor area (pre-SMA), have been implicated in conflict detection, error monitoring, and inhibition or change of motor plans. These regions are both functionally and structurally connected but distinct from other brain networks involved in attention, such as the dorsal and ventral attention network or the default mode network and have been referred to as the 'core' or 'salience' network (Bonnelle et al., 2014).

One of the main problems with substance use and addiction is generally viewed as impaired inhibitory control, which may be due to developmental causes, substance use, or both (Zhao, Qian, Fu, & Maes, 2017). Many studies have shown that inhibitory problems may precede substance use and that the onset of addictive substances results in brain dysfunctions (Wetherill, Squeglia, Yang, & Tapert, 2013). Alcohol-induced PFC damage predisposes individuals to continue or increase alcohol use (Crews, He, & Hodge, 2007). A recent meta-analysis showed that lifetime cannabis use was associated with impaired response inhibition (Liu et al., 2019).

A meta-analysis (Stephan et al., 2017) showed that inhibition and self-regulation, in addition to planning and problem solving, are severely affected in participants with AUD compared to controls without the disorder, although effect sizes were generally low to moderate. In this meta-analysis, alcohol group abstinence time was a minimum of 24 hours prior to any neuropsychological testing. The relatively short abstinence period may have affected the results, and it was specified that recovery could take at least a year (Stephan et al., 2017).

2.2.3 Memory functions

Human memory is composed of separate but interactive neurobiological systems (Jehkonen, Saunamki, Paavola, Vilkki, & Akila, 2015). Memory functions can be classified into several subcategories based on their temporal scale (short-term vs. long-term) and type (e.g. declarative vs. nondeclarative or episodic vs. semantic). Memory can be studied as a process (e.g. storage or restoration) and modality (e.g. verbal or visual).

Memory problems vary. Some are temporary (e.g. depression, stress, deficiency, or metabolic disorders), and such changes in memory may be reversible. More permanent deterioration can occur with age (Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012) or neurological diseases (Jehkonen et al., 2015). Dementia disorders can cause progressive memory interference. Memory impairment at the behavioural level may be due to memory interference and, at times, the underlying problem may not lie in memory (e.g. verbal processing, observation functions, regulation of attention, and general cognitive retardation). Patients with mild diffuse brain damage frequently report problems with short-term memory and simply do not register as much information as people normally do (Lezak, 1995). An examination can usually detect slowed mental processing and consequent reduced attentional capacity (Lezak, 1995).

Memory performance is related to executive functions of controlled, conscious, and effortful processing. The term ‘working memory’ is currently regarded as a part of executive function (Schulte et al., 2014). Working memory can be assessed through combined scores on the Digit Span Backward and Digit Span Forward tests. Age-related weakening in memory is reflected in tasks that require more voluntary effort. PFC regions are involved in the performance of more demanding and effortful memory tests. It has been suggested that activity in PFC regions decrease with age, which can affect memory processing (Hess, 2005).

The medial temporal lobe in the brain is important for memory and learning. It includes the hippocampus, thalamus, and connections from the anterior cortex to the basal ganglia (Bear, Connors, & Paradiso, 2007). Memory functions appear to be particularly susceptible to the effects of alcohol and substance use than other functions (van Holst & Schilt, 2011).

A review of prospective studies on neurocognitive recovery after sustained abstinence from alcohol dependence (Stavro, 2013) indicated recovery, full recovery, or even normal average performance in visual-short term memory, visual long-term memory, and episodic memory but not verbal short-term memory. Findings from magnetic resonance imaging (MRI) studies showed that an increase in hippocampal volume was positively related with visual short-term memory and visual long-term memory, indicating that the hippocampus is a biomarker for improved memory functions.

2.2.4 Visuospatial functions

Vision is generally considered to be one of the five major senses. It is estimated that more than half of the cortex's surface area is involved in the processing of visual information. The processing of visual information in the brain represents a hierarchical system in which the complexity of information increases as visual information progresses to the next stage. Two systems are responsible for processing information: (1) the ventral pathway, which corresponds to the object or to object identification and the visually controlled movement, and (2) the dorsal plane, which handles spatial information (i.e. where and how). Difficulties in handling spatial information include problems with mental rotation and detection of three-dimensional objects and environments. To identify suspected defects in the processing of visual information or spatial information, neuropsychological test methods combine, identify, name, and copy visual objects and line drawings, in addition to interviews (Jehkonen et al., 2015).

Constructional abilities include the ability to copy, draw, and construct two- and three-dimensional objects. Visuoconstructive abilities are needed when working on part-whole relationships at the imaginary level. Visuomotor ability is also required when the object is produced concretely via hand-eye cooperation (Lezak, 1995).

Visuospatial functions are supported by the occipital, parietal, and medial temporal lobe regions. Alcohol use can cause profound damage to the functioning of these regions (Hunt, Baker, Michie, & Kavanagh, 2009; Konova et al., 2013). Fernandez Serrano et al. (2010) found specific effects of duration of cannabis use on visual–spatial working memory.

A component of the WAIS Test is the Block Design Test, one of the most commonly used visuoconstructional tests (Lezak, 1995). It requires patients to look at a constructed model or picture in the Stimulus Book and use two-colour blocks to recreate the design within a specified time limit. The Block Design Test is generally considered to be the best measure of visuospatial organisation in the Wechsler scales (Lezak, 1995). Scores on the Block Design Test tend to be lower when any kind of brain damage is present (Lezak, 1995). Scores can also be lower in patients with frontal impairment, because their performance often demonstrates impulsivity and carelessness (Lezak, 1995).

Raven´s Progressive Matrices (RPM;(Raven, 2000) is a multiple-choice, paper-and-pencil test of non-verbal intelligence. RPM consists of a series of visual pattern matching and analogy problems presented as nonrepresentational designs. The matrices assess intellectual ability by presenting image patterns and visuospatial problems rather than focusing on verbal conceptual comprehension. RPM requires the subject to conceptualise spatial design and numeric relationships. The questions are ordered according to difficulty, proceeding from the obvious and concrete to the complex and abstract (Lezak, 1995). The presence of unilateral neglect may be

identified through this test. RPM was intended as a test of general ability that is fair to all cultural groups. Neither language nor academic skills are necessary for test performance, although RPM has demonstrated a small degree of education bias (Lezak, 1995).

RPM reflects general or global intellectual ability and has been used as an index of fluid intelligence (Bayliss, Jarrold, Baddeley, & Leigh, 2005). The test's deficits seem to be related to wider and more general cognitive problems. Performance on RPM has been used in some studies on learning disabilities and autism (Morsanyi & Holyoak, 2010).

Early studies have associated long-term alcohol use with poor performance in the RPM (Lezak, 1995). Alcohol-dependence disorder, defined according to DSM-IV-TR, caused significant lower scores in the RPM in a sample of 53 alcohol-dependent patients (i.e. alcohol abstinence for at least 1 month; Pombo et al., 2008). Similarly, cannabis use disorder (CUD) was associated with lower RPM in a large normative sample (N = 1,121 of adults; 54% female). There was no abstinence; on the same day as the neurocognitive task assessments, participants were assessed in terms of SUD (Petker et al., 2019).

2.2.5 Verbal Functions

In neuropsychological research, verbal functions are studied using the verbal reasoning subtests of the WAIS test. The previous verbal intelligence quotient (VIQ) is replaced by the verbal comprehension index (VCI) that contains verbal reasoning problems, vocabulary, general knowledge, and general comprehension. The similarities task examines the ability to find linguistic super concepts. The general comprehension task assesses the ability to explain everyday cause-and-effect relationships.

In diffuse or bilateral injuries and early dementia, the vocabulary test tends to be among the least affected sections of the WAIS (Lezak, 1995). In SUD, Latvala et al (2009b) assessed the vocabulary subtest of the WAIS–Revised (WAIS-R) as a measure of verbal ability. They found a decline of verbal intellectual ability in young adults with a life-time SUD diagnosis. Hanson et al. (2011) noticed a marginally significant group × time effect for the language composite score (Vocabulary and Similarities) in a 10-year follow-up study of SUD in young adults. Manning's et al. (2008) study of alcohol-dependent inpatients (N = 30) were tested at intake (day 4 of admission) and post detoxification (day 26), using a test-retest design. The patients mean age was 44.0 years (7.6). In a preliminary set of analyses, no statistically significant differences were found between males and females in neuropsychological performance at intake and, therefore, the results are presented

for the combined (male and female) sample. There was significant increase in the vocabulary scores after detoxification.

Although the results on the persistence of the vocabulary function in different disorders have been contradictory, it was hypothesised that in this study the vocabulary function would be the least susceptible to impairment from various neuropsychological tests and it was taken as a measure of baseline capacity.

2.3 Personality assessment with The Minnesota Multiphasic Inventory

The Minnesota Multiphasic Inventory (MMPI), developed by Hathaway and McKinley (1940, 1942), is one of the most widely used tests to assess personality traits and psychopathology. The main advantage of the MMPI is that a single test provides much information. The MMPI-2 (Butcher et al., 1989) presents a new standardization of the MMPI and provides current norms for the inventory. Continuity between the MMPI and the MMPI-2 has been maintained; thus, the items in the validity and clinical scales of the MMPI are essentially unchanged in the MMPI-2 (Graham, 1993). Graham (1993) suggested that much of the research literature accumulated for the two versions can be applied to both. At present, there is no Finnish translation or standardization of the MMPI-2, hence, the original version was used.

The MMPI consists of 566 self-reference statements that must be answered with ‘true’, ‘false’, or ‘cannot say’. The scoring procedures yield scores for four validity scales and 10 basic clinical or personality scales. Raw scores from the standard validity and clinical scales are transformed into T-scores (mean = 50, SD = 10) using the data provided manual. Scores of 65 or above are considered clinically significant. The responses of the Minnesota normal group provide the basis for the T-score conversions. Separate norms are available for males and females. The T-scores are utilized to construct a profile in the standard profile sheet that helps generate inferences about the examined individual (Graham, 1977).

For the first 399 statements, a standardized score is calculated for 14 clinically defined scales. The clinical interpretation of the scales (Graham, 1993) is briefly described below. In the literature, clinical variables are written as follows; : 1 – Hs, 2 – D, 3 – Hy, 4 – Pd, 5 – MF, 6 – Pa, 7 – Pt, 8 – Sc, 9 – Ma, and 0 – Si (Taurino, 2021).

1 – Hs Hypochondriasis (34 items) is designed to measure excessive preoccupation with the body and physical symptoms. 2 – D Depression (60 items) measures sadness, discomfort, and dissatisfaction with life. 3 – Hy Hysteria (60 items) evaluates response to physical and emotional stress and awareness of

problems and vulnerabilities. 4 – Pd Psychopathic Deviate (50 items) measures antisocial behaviours and attitudes, absence of satisfaction in life, family problems, delinquency, sexual problems, and difficulties with authorities. 5 – MF Masculinity-Femininity (60 items) evaluates stereotypical masculine or feminine interests and behaviours. 6 – Pa Paranoia (40 items) evaluates level of trust, suspiciousness, and sensitivity; very high scores indicate psychosis disorder or a paranoid personality disorder. 7 – Pt Psychasthenia (48 items) evaluates anxiety, tension, and worry. 8 – Sc Schizophrenia (78 items) measures disorganization, unusual thought processes, and social alienation. 9 – Ma Hypomania (46 items) evaluates high energy and agitation, overactivity, and unrealistic self-appraisal. 0 – Si Social Introversion (70 items) evaluates people's orientation, the degree to which they seek out or withdraw from social interactions.

In addition, the MMPI includes four validity scales, one of which is defined simply in terms of the number of 'cannot say' responses. The Lie (L) scale detects unsophisticated and naïve attempts to present oneself in an overly favourable light. It covers situations such as a person's unwillingness to admit even extremely minor weaknesses in character. The Validity scale (F) scale measures the intrusive effects of the subject's carelessness and confusion in taking the MMPI. The Weighting scale (K) scale assesses clinical defensiveness. According to Graham (1977), items in the K scale were selected by comparing the responses of a group of patients known to be clinically deviant but produced normal MMPI profiles and for whom there was no indication of psychopathology. The K scale was utilised to develop a correction factor for some of the clinical scales.

The MMPI can have adequate psychometric properties if it is used for the purposes for which it has been designed and validated. Moderately high levels of reliability (.71 to .84) and stability (.63 to .86) have been found for all scales in studies published between 1970 and 1981 (Hunsley et al., 1988).

In the subsample from the National Finnish Adoptive Family Study of Schizophrenia (Siira et al., 2006), test results of the MMPI were collected before the onset of any psychiatric disorder at a mean age of 24 years. High scores on the PD scale of 68.5 (11.5) predicted psychiatric disorder at the 11-year follow-up. The study results suggested that the 4 – Pd scale can be a useful indicator of predisposition to the later onset of psychiatric disorder since it measures traits associated with asocial behaviour, egocentricity, impatience, and shallow affect.

When screening for substance abuse problems, the scales of the original MMPI did not reveal a single pattern (Graham, 1993), except 4 – Pd scale. There is convincing evidence that scale 4 is likely to be elevated in groups of persons who use substances. Scale 4 – Pd is not significantly elevated in groups of medical patients. High scorers are seen as impulsive individuals, who do not plan their behaviour very well and thus act without considering the consequences of their

action. They are very impatient and have a limited frustration tolerance. Their behaviour may also involve considerable risk- taking. They tend not to learn from experience and often find themselves in the same difficulties (Graham, 1977). Notably, the 24/42 two-point code type is common among alcohol- using men in treatment, while this same code type and the 46/64 code type are common among alcohol-using women in treatment. Gripshover (1994) and Davis (1987) investigated comparisons of the Mac Andrew Alcoholism Scale between men and women, but comprehensive research into personality differences between men and women with SUD has been scarce.

Walvoort et al. (2012) reviewed studies evaluating personality using the MMPI-2. They did not find unique alcohol personality in AUD patients but reiterated the importance of meeting the treatment needs of these patients to improve their treatment outcomes. A consistent finding was the high score on the scale 4 - Pd, which was stable over time but not unique to AUD patients. Three personality types were observed in alcohol- dependent patients: (a) the antisocial, immature, risk-taking type; (b) the negativistic, alienated, schizoid type; and (c) the anxious, passive, introverted type. This distinction is not independent of cognitive deficits, such as inhibitory dysfunctions. In future investigations, it is important to study the neuropsychological and cognitive correlations of personality features. Walvoort (2012) noted that the scores of code type 24/42, which indicate psychopathic deviation, acting- out behaviour, and negative treatment attitude, were particularly high when patients were evaluated after two weeks of abstinence. When patients were evaluated after 30 days, scores were clearly reduced on all MMPI scales, except in the scale 4 - Pd. Walvoort et al. (2012) concluded that the MMPI typology does not remain stable and that during early abstinence, the MMPI-2 scales tend to reflect symptoms of withdrawal and cognitive recovery, consequently leading to overestimating psychopathology.

2.4 Age of onset of regular substance use and neuropsychological performance

2.4.1 Individual vulnerability underlying substance use

Addiction vulnerability are characteristics known to be correlated with greater risk for the development of addictive disorders. Risk factors can increase chances for substance abuse, while protective factors can reduce the risk. Risk and protective factors can affect at different stages of life (NIDA, 2020).

Several studies of neuropsychological, structural, and functional brain imaging have suggested that neural differences predate substance use (Squeglia, & Gray, 2016). Findings have indicated deviations in brain activation during tasks of

inhibition, working memory, and reward processing (Squeglia, & Gray, 2016). Some individuals are more sensitive than others to substance use, and the accumulation of problems during development appear to lead to unfavourable development. Volkow (2017) highlighted a number of factors that adversely affect development and affirmed that 75% of mental illnesses, including addiction, occur before the age of 25; thus, they emerge as the brain is still developing. Environmental factors are also important contributors to both the emergence of mental illness and the emergence of SUDs and addiction. Factors associated with social stressors, including social deprivation, physical abuse, neglect, and lack of supportive systems, increase the risk of these disorders. Social stressors also increase the risk of depression, schizophrenia, addiction, and other mental illnesses (Volkow, Hampson, & Baler, 2017).

In addition to genetic and environmental risk factors, many individual differences related to neuropsychological, cognitive, and personality variables have been considered as predictors of the subsequent start and/or acceleration of alcohol use (Spear, 2018) and substance use (Conrod & Nikolaou, 2016). Several psychiatric disorders have been associated with an increased risk of SUD, including externalising disorders and impulsivity, mood disorders, anxiety, and psychotic disorders (Conrod and Nikolaou, 2016; Niemelä, 2008). Table 1 outlines the neural correlates and risk factors discussed in this section and their association with the developmental process of SUD (Conrod & Nikolaou, 2016).

Table 1. Overview of neurodevelopmental factors for substance initiation and progression to addiction.

Predisposing factors	**Adolescent developmental processes**	**Maintenance**	**Addiction**
Genetic factors Environmental context Example: Early childhood adversity Cognitive factors Learning Self-management	Neuromaturation Autonomous decision making Example: Self-management Experimentation	Substance-induced neurotoxicity Further prefrontal and striatal dysregulation Poor impulse control Attentional biases to substance cues Stress dysregulation	Hypofunction of prefrontal cortex Dysregulated dopamine response Hypersensitivity of HPA circuits to stress

(Conrod & Nikolaou, 2016)

One of the most important risk factors for SUD is its extensively documented heredity. Behavioural genetic research has affirmed that as much as 40–60% of an individual's vulnerability to developing a substance dependence is heritable (Conner, Hellemann, Ritchie, & Noble, 2010).

Genes and heritability are important in the transition from experimentation to addiction (Conrod & Nikolaou, 2016; Goldstein and Volkow, 2011). An individual's environment and adolescent developmental processes are equally important. Social stressors can also increase a child or an adolescent's vulnerability to a SUD trajectory. The greater the number of social stressors, the greater the risk of transitioning into addiction (Conrod & Nikolaou, 2016; Gerra, 2017).

Gerra (2017) hypothesised psychiatric disorders as the endpoint of risk development alongside SUD. He emphasised that risk factors such as prenatal stress, insecure attachment, early childhood adversity, and epigenetic factors underlie an individual vulnerability to substance initiation and alcohol abuse. Gerra's hypothesis is supported by evidence from a 25-year longitudinal study of developmental antecedents of illicit substance use. The findings suggested that abuse and dependence were associated with a range of early life circumstances, parental adjustment and substance use, and exposure to adversity (Fergusson, Boden, & Horwood, 2008).

Adolescence itself is regarded as a risk period for the initiation of alcohol and gradually illegal substance use. According to Volkow and Boyle (2018), the greatest risk associated with the transition from experimentation to loss of control, which

characterises addiction, occurs during adolescence and young adulthood (i.e. between the ages of 11 and 25).

Neuropsychological studies by Squeglia et al. (2014) found that poorer baseline performance on tests of inhibition prior to substance use in early adolescence (i.e. ages 12–14) was related to more frequent and intense alcohol and marijuana use by late adolescence (i.e. ages 17–19). Meanwhile, performance in short-term memory, sustained attention, verbal learning and memory, visuospatial functioning, and spatial planning did not predict subsequent substance involvement (Squeglia, Lindsay, Jacobus, Nguyen Louie, & Tapert, 2014).

Khurana et al. (2017) confirmed Squeglia et al.´s (2014) findings by showing that adolescents with poorer baseline working memory (WM) had less control over impulsive urges and were at greater risk for later SUD. They found that a weakness in WM at an early age (i.e. ages 11–13) were associated with imbalance and that imbalance indicators predicted SUD (e.g. alcohol, marijuana, and tobacco dependence) in late adolescence (i.e. ages 18–20). They suggested that a weakness in WM reflected an inability to control impulses related to substance use reward and to access information that discouraged substance use from memory (Khurana, Romer, Betancourt, & Hurt, 2017).

Longitudinal studies on the relationship between cognitive function and substance abuse confirmed that weak cognitive capability was related to the risk of substance abuse problems later in life (Crane, Schuster, Mermelstein, & Gonzalez, 2015; Fergusson, Horwood, & Ridder, 2005; Penick et al., 2010; Sjölund, Allebeck, & Hemmingsson, 2012). A population-based study on the health and psychological well-being of young adults in Finland found a relationship between poor performance in language assessments and the speed of general information processing and substance abuse problems amongst 21- to 35-year-olds (Latvala et al., 2009b).

2.4.2 Substance use and negative consequences associated with neuropsychological performance

During adolescence, the brain undergoes major reorganisation and remodelling, which contribute to age-specific behavioural characteristics and vulnerabilities (Cherry, Cherry, Baltag, & Dillon, 2016). Morphology, volume, composition, and function during brain development and maturation change; hence, brain function becomes more efficient (Gogtay et al., 2004). During the reorganisation process means that the brain is in a phase of particular plasticity and vulnerability in which development is also susceptible to disruption (Conrod & Nikolaou, 2016; Squeglia & Gray, 2016; Spear, 2018). The risk of developing mental disorders during adolescence therefore increases (Kessler et al., 2005).

During adolescence, white matter begins to increase whilst grey matter (GM) decreases (Cohen, 2006). An increase in axon myelinisation accelerates neuronal signalling. Functionally related neurons become increasingly wired together, whilst functionally unnecessary synapses are pruned. As a result, the structure and neural activity of the brain becomes more efficient, improving cognitive and mental processing (Conrod & Nikolaou, 2016).

Prominent developmental transformations in the PFC and limbic brain regions affect cognitive control systems that influence self-regulation (Spear, 2018). The prefrontal region continues to develop even after age 20 (Cohen, 2006). Bidirectional connections that regulate emotions between the limbic and the prefrontal regions develop late. Incomplete prefrontal function predisposes young people to risk-taking actions (e.g. experimentation). It has been established that the ability to regulate impulses and behaviour continues to develop up to age 25 (Cohen, 2006). The mesocorticolimbic dopamine system plays a key role in the brain's reward system. In the adolescent brain, the dopamine-sensitive nuclei of the brain stem and limbic system mature before the frontal lobes. Increased dopamine production drives the continued search for new sources of high reward in the environment. Risky and novelty-oriented behaviour increases during adolescence, especially amongst boys (Spear, 2018; Wahlstrom, White, & Luciana, 2010).

Along with the PFC, the lateral temporal lobes mature last. They are involved in organizing memory, audio-visual information, and object recognition (Gogtay et al., 2004).

Early substance use may permanently impact neuropsychological functioning, inhibiting the brain from fully developing. Early substance use can also alter long-term normative neurodevelopmental trajectories and compromise neural health, whilst alcohol may interfere with temporal sequences of neurodevelopment (e.g. thinning), myelinisation, and/or the generation and survival of cortical cells (Jacobus, Squeglia, Sorg, Nguyen Louie, & Tapert, 2014). Underlying causes of behavioural impairments with substance use include neural death and damage, changes in neural plasticity, and the impairment of brain maturation (Guerri & Pascual, 2010). With regard to youth alcohol use, Spear (2018) summarised evidence concerning the emergence of neural alterations across species, including disrupted myelinisation, reduced white matter integrity, alterations in connectivity between the frontal and limbic regions of the brain, and electroencephalographic changes.

Substance use hijacks the brain's reward system and produces adaptations that ultimately lead to a loss of control in addicted individuals. Repeated substance use changes the brain by weakening its dopamine system (Volkow & Boyle, 2018).

The PFC is important for self-control, which is needed to regulate or stop behaviour when it is unacceptable or incorrect (Goldstein and Volkow, 2011). Addiction is characterised by impaired self-control. Behaviour inhibition is a key

operation in exercising self-control and regulating negative emotions (Goldstein and Volkow, 2011)

Impairments in the PFC and self-control are believed to predispose individuals to later alcohol and substance use. Alcohol-induced PFC damage also predisposes individuals to increasing alcohol use (Crews et al., 2007). Impairments in self-control, such as labile affect, externalizing behaviour (e.g. oppositional defiant disorder, conduct disorder, and ADHD symptoms), depression, and impaired executive cognitive function are common risk factors for SUD (Groenman, Janssen, & Oosterlaan, 2017; Tarter, Kirisci, Reynolds, & Mezzich, 2004).)

Studies have examined the associations between neuropsychological performance and early or later age of onset in alcohol and substance use (see Table 2). Cross-sectional and prospective studies have demonstrated that early onset of alcohol and substance use can affect performance in several cognitive domains, including learning and memory and visuospatial and executive performance.

Cross-sectional studies cannot distinguish between pre-existing alterations and post-substance effects on brain development. Thus, longitudinal studies are needed to assess neuropsychological performance before the onset of alcohol or substance use and over time during the natural transition to substance use. Table 2 summarises longitudinal designs that differentiate between neuropsychological findings before and after substance use. Some cross-sectional studies are also included (Parada et al., 2012; Sneider, Cohen Gilbert, Crowley, Paul, & Silveri, 2013) because they highlight binge drinking. A study by Brown et al. (2000) focused on withdrawal symptoms, which are associated with decreases in learning and memory and tests of visual motor integration and visuoperception (Brown, Tapert, Granholm, & Delis, 2000) The results of these studies are discussed in more detail in sub-sections 2.4.2.1 (´Age of onset of alcohol use and neuropsychological performance´) and 2.4.2.2 (`Age of onset of polysubstance use´).

There is notable heterogeneity in patterns of substance use and co-use during adolescence (Hanson, Cummins, Tapert, & Brown, 2011; Squeglia, Jacobus, & Tapert, 2009). Squeglia and Gray (2016) also noted that the majority of studies predominately include youth from upper middle-class families and exclude youth with co-occurring psychological disorders. It is also important to understand the interactive effects of substance use on other disorders (e.g. ADHD, depression, and anxiety).

Most studies have focused on adolescence. Less is known about differences in cognitive performance amongst adult-onset substance users. Some investigators have not found any differences in cognitive performance between early and late onset participants (Kist, Sandjojo, Kok, & van den Berg, 2014). In fact, Joos et al. (2013) found that early onset alcoholics generally performed as well as or even better than late onset alcoholics, especially on visual memory and interference tests (Joos

et al., 2013). Amongst middle-aged participants, a positive relationship may exist between the quantity of alcohol consumed and the severity of brain damage (Sabia et al., 2014). These inconclusive findings highlight the need for further research.

Table 2. Summary of studies on the correlation between early onset age of regular use and neuropsychological impairment.

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures and Tools	Results
Castellanos-Ryan et al. 2017 Canada	Prospective sub-sample of the Montreal Longitudinal-Experimental Study Low socioeconomic status boys n = 294	13 to around 20 years	Assessment at age 10 to around age 20	Cannabis	Social Behaviour Questionnaire: Teacher-rated externalizing problems (i.e. attention deficit hyperactivity disorder and conduct disorder symptoms, including physical aggression) were assessed with the symptoms on a 3-point scale (i.e. from 'never' to 'often') at yearly intervals from ages 13 to 15.	Parental age at birth of first child, occupational status, education, and family status (i.e. intact or nonintact) were noted. Academic achievement from ages 13 to 15 was assessed using teacher-reported global academic performance. The same was evaluated in adulthood, using a dichotomous measure (i.e. whether participant had been awarded a high school diploma).	NCF[1]: Number randomization (NR), working memory function (SOP), and inductive reasoning or learning by trial and error (CAT). Working memory, strategic planning functions, and ability to learn associations between two arbitrary visual stimuli through trial and error Trial-and-error learning (CAPT) Abilities related to executive function, such as short-term and working memory, planning, trial-and-error learning, and IQ Paired associates learning and digit span subtests of the WMS-R[2]	Earlier onset of cannabis use, and frequency of use were related to impaired verbal IQ, executive function, trial-and-error learning, and reward processing. School engagement was also impaired.

[11] NCF Changes in neurocognitive functioning score; The neurocognitive battery included a number of tapping cognitive functioning related to different regions of the brain: working memory, planning, and trial and error learning are functions associated with frontal brain areas (Petrides, Reference Petrides1990; Petrides, Alivisatos, Evans, & Meyer, 2013)

[2] WMS-R The Wechsler Memory Scale Revised

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures and Tools	Results
Nguyen-Louie et al. 2017 USA	Prospective study of healthy adolescent drinkers n = 215	12 to 15 years at baseline	Assessed without prior drug baseline Second test done 6 years later	Alcohol binge drinking (i.e. 10 drinks per occasion)	No history of any neurological or DSM-IV Axis I disorder, head trauma or loss of consciousness, chronic medical illness, learning or intellectual disability, psychoactive medication use, and noncorrectable sensory problems. Also excluded if: ≥10 total lifetime drinking days, ≥3 lifetime experiences with marijuana, ≥5 lifetime cigarette use, and history of other intoxicant use	No externalizing symptomology Parent reports Child Behaviour Checklist at baseline and the parallel Adult Self-Report at follow-up Controlling for baseline neuropsychological performance	At baseline: D-KEFS[3] Colour Word Interference (CWI) TMT[4] CVLT[5] WASI[6] Block Design Wechsler Intelligence Scale for Children Digit Symbol-Coding and Digit Span Rey-Osterrieth Complex Figure Task At follow-up with participants 18 years and older: CVLT[5]-Second Edition WAIS-III[7] (Coding and Digit Span subtests) At follow-up: Taylor Complex Figure Test (i.e. alternate form of complex figure) Cognitive Inhibition D-KEFS	Positive linear relationship between first drinking onset of alcohol dose and psychomotor speed, visual attention, Cognitive inhibition, and working memory was noted. No relationship between early onset of alcohol was found with verbal learning and memory and visuospatial ability.

[3] D-KEFS Color Word Interference
[4] TMT Trail Making Test, TMT-A, TMT-B
[5] CVLT California Verbal Learning Test
[6] WASI Wechsler Abbreviated Scale of Intelligence
[7] WAIS-III The Wechsler Adult Intelligence Scale, Third Edition

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures and Tools	Results
Nguyen-Louie et al., 2016	Prospective study n = 112 The 3 binge drinking groups: Moderate (≤4 drinks per occasion), Binge (5+ drinks per occasion), or Extreme-binge (10+ drinks per occasion) drinkers	12 to 16 years at baseline	Follow-up approximately 6 years later	Alcohol binge drinking	The Family History Assessment Module A Hollingshead Index of Social Position score The Pubertal Development Scale Child Behavior Checklist Youth Self Report Adult Self Report Beck Depression Inventory-II Mini International Neuropsychiatric Interview	The Customary Drinking and Drug Use Record (Brown et al., 1998) and Timeline Follow-back (Sobell and Sobell, 1992) were administered at baseline and follow-up to assess quantity and frequency of substance use. The alcohol use variables of interest were number of drinks consumed during the peak-drinking episode in the past 3 months.	CVLT[5]: auditory attention; immediate recall; global verbal learning ability; proactive interference; short delay free recall; immediate recall; short delay cued recall; long delay free; cued recall; measures of delayed memory 20 minutes after learning trials; learning slope; average number of new words learned per trial; and retention	No distinct thresholds in alcohol quantity to differentiate the 3 groups were detected. Estimated peak blood alcohol concentrations were linearly associated with verbal learning and immediate, short delay free and long delay free recall. The acquisition of new verbal information may be particularly affected, notably for those who initiated drinking 10+ drinks in an occasion.

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures and Tools	Results
Jacobus et al. 2015 USA	Prospective study N = 108 3 years Alcohol and marijuana groups versus control group MJ+ALC: n = 49 Con: n = 59 Participants' ages from 18 to 21 years	Early onset of regular marijuana use <16 years (n = 27) Late onset of marijuana use ≥16 (n = 22)	Baseline and follow-up at 1.5 and 3 years	Alcohol and marijuana	Cannabis or alcohol abuse/ dependence DSM-IV No mental disorders No history of learning disabilities, neurological disorder, traumatic brain injury, serious physical health problem, or complicated birth	Beck Depression Inventory Spielberger State Anxiety	CVLT[5]- WAIS-III[7] (Arithmetic, Digit Span Forward and Backward, Digit Symbol, and Block Design) D-KEFS TMT[4] WMS-III[8] (Logical Memory Immediate and Delayed) Complex Figure Copy and Delay	MJ+ALC users performed worse in complex attention, memory, processing speed, and visuospatial functioning. Earlier onset age of MJ was associated with impaired processing speed and executive functioning.

[8] WMS-III Wechsler Memory Scale - 3rd ed.

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures and Tools	Results
Jacobus et al. 2014 USA	28 days of monitored abstinence Adolescent marijuana users with regular alcohol use n = 54 Non-using controls n = 30 Participants recruited from local schools	Assessed at 17.7 years Average onset age for marijuana: 15.4 Average onset age for alcohol: 15.8	Compared before and after 4 weeks	Marijuana and alcohol	Diagnostic Interview Schedule for Children Predictive Scales No history of any Axis I disorders other than alcohol or cannabis disorder	Beck Depression Inventory, Spielberger State Trait Anxiety Inventory Family History Assessment Module Family history of psychiatric and substance use disorders Parental income and grade point average	Magnetic resonance imaging Complex attention: CVLT-II[5] WAIS-III[7] /Arithmetic, Digit Span, Digit Symbol D-KEFS[9] Verbal memory: WMS-III[8] /Logical Memory I, II and Recognition Visuospatial functioning: ROCF[10] Taylor Complex Figure WASI/Block Design Executive functioning: D-KEFS	More reported marijuana use and regular use at an earlier age was related to thinner cortices in the temporal and frontal regions. More lifetime alcohol use was related to thicker cortices in all four lobes. Increased thickness was associated with poorer cognitive performance. No associations between age of onset of regular substance use and global cognitive functioning.

[9] D-KEFS The Delis–Kaplan Executive Function System
[10] ROCF The Rey–Osterrieth complex figure

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures and Tools	Results
Sneider et al. 2013 USA	Adult binge drinkers (BD, n = 22) and age- and sex-matched light drinkers (LD, n = 29)	BD (n = 22), age 22.1 (1.3) LD (n = 29), age 21.5 (1.7)	Cross-sectional study	Alcohol BD group: at least 3 heavy-drinking episodes every month for the past 6 months. LD group: less than 3 drinks per occasion in no more than 5 days within a span of 30 days	Exclusion criteria: history of head injury; loss of consciousness; history of organic mental disorder, seizure disorder, or central nervous system disease; or Axis I clinical pathologies (e.g., mood or anxiety disorders)	Structured Clinical Interview for Diagnostic and Statistical Manual (DSM–IV) Beck Depression Inventory Spielberger Trait Anxiety Inventory Barratt Impulsivity Scale (BIS [47])	A measure of general intellectual ability (IQ) was derived from the vocabulary and matrix reasoning subtests of the WASI[6] Visuospatial ability and spatial perception were assessed using the WASI Block Design subtest and Mental Rotation Task. Virtual Morris Water Maze Task CVLT-II[5]	Decrements in learning and memory were noted. Emerging adult BD had worse performance in verbal memory than LD, but they had unimpaired spatial memory. No sex differences or interactions with drinking status were observed on either memory domain.
Meier et al. 2012 Dunedin Birth Cohort Study New Zealand	Prospective persistent cannabis use over 20 years Subsample of the Dunedin Study Birth cohort of 1,037 individuals	From birth to age 38	Follow-up from birth to age 38	Cannabis		Association between persistent CU and neurocognitive decline remained even after controlling for education, personality, other persistent substance use (SU), and socioeconomic status.		Persistent deficits in executive function, and processing speed were observed. There was also a decline in full-scale IQ and impairment of learning and memory.

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures and Tools	Results
Parada et al. 2012	Sample of 122 university students consisting of 62 BD (30 females) and 60 non-BD (29 females)	18 to 22 years	Cross-sectional	Alcohol	NA		Executive functions were assessed using WMS-III[8] (Backward Digit Span and Backward Spatial Span), SOPT[11] (i.e. abstract designs), Letter Fluency , BADS[12] (i.e. Zoo Map and Key Search) and WCST[13] .	Decrements in executive functioning were noted. BD subjects had poorer performance in the Backward Digit Span test and had more perseveration errors in the SOPT.
Hanson et al. 2011 Hanson, Cummins, Tapert, and Brown 2011	Prospective youths with and without AUD/SUD history N = 213	13 to 18 years M = 15.7 SD = 1.5 46% female	Over 10 years follow-up Baseline assessment and other assessments during 10 years	Alcohol and other drugs (e.g. marijuana, amphetamines, barbiturates, hallucinogens, cocaine, inhalants, opiates, prescription medications, or other drugs not previously specified			WISC-R[14] /Vocabulary, Similarities, Block Design, Arithmetic, and Digit Span WMS[8] Visual Reproduction subtest CVLT[5] At Year 2: TMT[4] At Year 10: WISC-R[14] subtests were changed to the WAIS–R[15], while the CVLT[5] was replaced with the newer CVLT-II[5]. At Years 8 and 10: WMS III[8] / Visual Reproduction was replaced with ROCF[10] copy and 30-minute delayed recall.	Cumulative alcohol and drug withdrawal predicted year 10 visuospatial decline. Decline in executive function and verbal and visual learning and memory was also observed.

[11] SOPT the abstract design version of the self-ordered pointing task Petrides, M., & Milner, B. (1982)
[12] BADS The Behavioural Assessment of Dysexecutive Syndrome
[13] WCST Wisconsin Card Sorting Test
[14] WISC-R The Wechsler Intelligence Scale for Children-Revised
[15] WAIS-R Wechsler Adult Intelligence Scale Revised

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures and Tools	Results
Fried et al. 2005 Fried, Watkinson, and Gray, 2005	N = 113 Current heavy smokers (n = 19) Current light smokers (n = 19) Former regular users (n = 16) Comparison group of nonusers (n = 59)	Yearly tests up to age 7 and once during the age ranges 9–12, 13–16, and 17–21 Sample of 50 females and 63 males	Assessments at baseline and follow-up	Marijuana, excluding alcohol dependence and abuse	Exclusion criteria: generalized anxiety, major depression, dysthymic disorder, attention deficit hyperactivity disorder, conduct disorder, and oppositional defiant disorder.	Potential confounds: SES variables; maternal use of alcohol, cigarettes, and marijuana during pregnancy; age and sex of subject; and young adult's cigarette and alcohol use.	Overall IQ, memory, processing speed, vocabulary, attention, and abstract reasoning were assessed.	Former marijuana smokers did not show any cognitive impairments. Residual marijuana effects were evident, but similar deficits were no longer apparent 3 months after cessation of regular use, even among former heavy using young adults.

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures and Tools	Results
Tapert et al. 2002	Prospective study of youths with and without SUD	From ages 13 to 17 to age 30	Assessments at baseline and during 8-year follow-up	Alcohol and withdrawal symptoms	Clinical participants met DSM-III-R criteria for alcohol abuse or dependence and abuse of or dependence to at least one other drug at project intake.	Excluded youths who had an Axis I psychiatric disorder other than conduct disorder, a history of head trauma with loss of consciousness greater than 2 minutes (6), or any medical condition that could compromise NP performance.	WAIS-R[14] subtests on Vocabulary, Similarities, Information, Block Design, Arithmetic, Digit Span, and Coding COWAT[16] Embedded Figures WMS/ Visual Reproduction CVLT–C[5] TMT[4] Category Test	Decrements in verbal learning and memory, attention, and information processing were noted. Alcohol and drug withdrawal symptoms predicted attention and visuospatial functioning impairment.
Brown et al. 2000	Alcohol dependent adolescents n = 33 Matched comparison group N = 24	15 to 16 years	Cross-sectional study	Alcohol	DSM-III-R criteria for lifetime diagnosis of alcohol dependence	Excluded youths who had an Axis I psychiatric disorder other than conduct disorder, a history of head trauma with loss of consciousness greater than 2 minutes, any medical condition that could compromise NP performance, or prenatal exposure to alcohol	WISC-R[14] /Vocabulary, Information, Similarities, Arithmetic, Digit Span, Block Design, and Coding CVLT-C[5] WMS-III[8] /Visual Reproduction, Immediate Recall, Delayed Recall, and Retention TMT[4] Embedded Figures Boston Naming Test Letter Fluency/ Category Test	Withdrawal symptoms were associated with decrements in learning and memory and in tests of visual motor integration and visuoperception. WISC-R/Digit Span weakened.

[16] COWAT Oral Word Association Test

2.4.2.1 Age of onset of alcohol use and neuropsychological performance

A cross-sectional study that compared adolescents who were light drinkers, non-drinkers, and heavy drinkers showed neuropsychological decrements in learning and memory (Brown et al., 2000; Sneider et al., 2013), visuospatial functioning and psychomotor speed (Brown et al. 2000), executive functioning (Parada et al., 2012), and language skills (Moss, Kirisci, Gordon, & Tarter, 1994).

Repeated and long-term alcohol use and associated withdrawal symptoms may accelerate and aggravate the progressive injurious effects of alcohol on brain structure and functioning (Spear, 2018). The frequency of alcohol use and the intensity of withdrawal are important considerations in neuropsychological task performance (Hanson et al., 2011; Nguyen Louie et al., 2016; Tapert, Susan, Granholm, Leedy, & Brown, 2002).

Nguyen-Louie et al. (2017) found a positive linear relationship between the earlier age of first drinking onset of alcohol and psychomotor speed, visual attention, cognitive inhibition, and WM in a longitudinal study of 6.8 years (on average). The study indicated that there was no 'safe' age of onset for alcohol use between the ages of 10 and 23. Another clinical application was the notion that, since neurocognitive performance changes with age of onset in a linear manner, treatment can thus be individualised based on the age that the individual began to drink in order to increase its efficacy.

In the study of Nguyen-Louie et al. (2016), participants were between 12 and 15 years old at baseline. Youth who later transitioned into weekly drinking had their first standard drink at 15.6 years old on average. Youth who began drinking at an earlier age were more likely to perform worse on tasks that are traditionally associated with 'lower level' cognitive abilities (i.e. psychomotor speed and visual attention). The study also found that earlier and regular alcohol consumption (i.e. one or more standard drinks at least once per week for six or more continuous months) led to worse executive function (i.e. inhibition ability and Digit Span Backward) at follow-up. Executive function is considered a 'higher order' ability.

2.4.2.2 Age of onset of polysubstance use

Spear (2018) noted that a statistical study of alcohol and polysubstance use is difficult to conduct because, even if one substance is used as a covariate, its effect cannot be completely eliminated. It is also difficult to conclusively relate the observed effects to alcohol use. Spear recommended animal models for this purpose

in order to enable a more reliable study of the interactions between alcohol and other substances.

Adolescent cannabis use supposedly interferes with synaptic pruning, impedes the development of the PFC (Castellanos Ryan et al., 2017), leads to reduced white matter integrity (Jacobus, J. et al., 2009), and causes changes in grey matter and deviations in neural functioning (Jacobus, Squeglia, Sorg, Nguyen Louie, & Tapert, 2014). However, neuroimaging findings on adolescent and adult cannabis use remain inconclusive (Volkow et al., 2016).

Earlier onset and frequency of cannabis use are negatively related to verbal intelligence, executive function, trial-and- error learning, and reward processing (Castellanos Ryan et al., 2017). Findings from prospective research have provided evidence that earlier age of onset of persistent cannabis use (i.e. over 20 years) causes more impaired cognitive deficits at age 38 (Meier et al., 2012).

Studies have suggested that cannabis use leads to persistent deficits in executive function, processing speed, and full-scale IQ after controlling for education as well as learning and memory impairment. Moreover, weekly use before age 18 has been found to cause greater deterioration in cognitive performance. The neuropsychological functioning of adolescent onset cannabis users did not recover even after they quit using the substance. However, another longitudinal study (Fried, Watkinson, & Gray, 2005) found that cognitive deficits were no longer apparent three months after cessation of regular use, even amongst young adults who were formerly heavy users. A total of 113 children were assessed through neuropsychological testing annually up to age 7 and once during each of the following age ranges 9–12, 13–16, and 17–21. For those tested between the ages of 17 and 21, the duration of regular marijuana use amongst heavy users was 2.6 years on average. By comparison, the average duration of heavy use was over 20 years in Meier et al.'s (2012) study.

Volkow et al. (2016) have critized the cohort studies conducted by Meier et al. (2012) and Fried et al. (2005) involved a small number of cannabis users and did not entail any brain imaging. According to brain imaging studies, it is possible that the observed changes already existed before the age of onset of substance use; however, the results cannot be explained by factors such as socioeconomic status or psychiatric disorders. The acute effects of cannabis use on learning and memory, attention, and WM are well-known, but the outcomes of longer-term use are less clear (Volkow et al., 2016). Thus, follow-up studies are needed.

For over 10 years, Hanson et al. (2011) followed youth with and without a history of alcohol use and other substance use (AOD). Mean ages in each group at baseline ranged from 15 to 16.4 years. The researchers found a decline in visuospatial performance, verbal and visual learning, and memory and executive function. Hanson et al. (2011) confirmed that six distinct patterns of alcohol and other

substances use in adolescence (Anderson, Ramo, Cummins, & Brown, 2010) clearly correlated with neuropsychological results of verbal learning and memory, visuospatial memory, verbal attention, and memory. Heavier use patterns generally preceded reduced cognition. Heavy use of alcohol was independently associated with reduced verbal memory and learning over time. Furthermore, substance withdrawal symptoms at each follow-up were related to decreased verbal learning and memory scores. Cumulative alcohol use and substance withdrawal predicted at 10 -Year follow up decline in visuospatial function (Hanson et al., 2011).

Hanson et al. (2011) revealed six distinct patterns of alcohol and other substance use were as follows: abstainers/infrequent users, late adolescent resurgence, emerging adulthood resurgence, frequent drinkers, frequent drinkers/substances dependent, and chronic use. In addition, the study included a group of normal controls. Users who demonstrated a pattern of late adolescent resurgence experienced an increase in substance use, particularly in late adolescence (rising from the follow-up at Year 2), and a subsequent decrease in early adulthood. Users who demonstrated a pattern of emerging adulthood resurgence experienced a sharp increase in substance use beginning in Year 4 and peaking in Years 6 and 8. Whilst this group drank alcohol less frequently than the late adolescent resurgence group, they used other substances more heavily, particularly amphetamines. Substance use then decreased through Year 10. Increased substance use in late adolescence and decreased AOD use at the ages of approximately 24 and 26 did not improve learning and memory.

The executive function of verbal attention, which was measured via WM (i.e. Arithmetic/WAIS-R), declined over time and more regularly in the group that experienced an increase in substance use, particularly in late adolescence (i.e. late adolescent resurgence) and amongst chronic users. Conversely, statistically significant differences between other groups in measures of attention, or executive function over time were not found.

The study also examined the timing of brain maturation, with certain parts of the brain maturation. Between ages 4 and 21, regions that were more associated with primary functions (e.g. primary motor cortex) developed earlier compared to regions involved in more complex and integrative cognition (e.g. temporal and prefrontal lobe; (Gogtay et al., 2004). The medial temporal lobe in the brain is important for memory and learning; it includes the hippocampus, thalamus, and connections from the anterior cortex to the basal ganglia (Bear et al., 2007). Cerebral white matter myelination effects continue to increase beyond age 60, and the volume of the hippocampus region increases until mid-life (Jernigan & Gamst, 2005). Several studies of humans and animals have indicated that heavy alcohol use is associated with hippocampal abnormalities in adults (Spear, 2018). A study by Hanson et al. (2011) confirmed that this also applies to youth.

The results of Hanson et al.´s (2011) study suggested that the development of learning and memory continue beyond age 20. Increased substance use after a period of relatively lower use in late adolescence or early adulthood appears to have a negative impact on verbal learning and memory and WM of verbal attention. A peak in heavy substance use in late adolescence was also associated with a decline in visuospatial memory. Meanwhile, participants who engaged in chronic AOD use at follow-up demonstrated the greatest impairment in performance on verbal learning, recall, and recognition relative to other groups. Increased AOD use in late adolescence and decreased AOD use at the ages of approximately 24 and 26 did not improve learning and memory. It is possible that impaired learning and memory in late adolescence (ages 17–19) is more permanent. Hanson et al. (2011) suggested that group differences in free recall were not primarily a function of differential learning amongst groups but rather reflected a difficulty in recalling or recognising information. The authors noted that the relationship between cumulative alcohol withdrawal episodes and cognitive impairment also applied to youth. Their research established that neuropsychological functions improved after the cessation of substance use in adolescence, which implies that the frontal and temporal areas – and perhaps the parietal regions – continue to develop beyond adolescence. In contrast to, for example, Nguyen-Louie (2017), Hanson et al. (2011) mentioned that abstinence from alcohol use impacted performance and recovery.

In another study (Jacobus et al., 2015) marijuana and alcohol users were compared before and after four weeks of abstinence at 17.7 average years of age; the age of onset for marijuana users was 15.4 years and 15.8 years for alcohol users. Researchers did not find any associations between the age of onset for regular marijuana or alcohol use and global cognitive functioning; however, they established that regular alcohol use was related to a thicker cortex and poorer neuropsychological functioning. Earlier age of onset for marijuana use was associated with slower processing speed and decreased executive functioning (Jacobus et al., 2015).

Previous studies have investigated the association between early substance use and neuropsychological impairment in adolescents and the alterations of these functions in adults, suggesting that more permanent impairments in cognition were related to an earlier age of onset of substance use. The observed impairments were related to all cognitive domains (see Table 2). Studies on substance use that started in adulthood (i.e. over 18 years of age) and later (i.e. over 40–60 years of age) have found no differences between age groups. This finding confirms the significance of early onset substance abuse. Spear (2018) noted that most of the participants in previous studies were from well-to-do families. Adolescents who engaged in early substance use and also experienced early childhood adversity, a low economic background, and learning difficulties may be at greater risk of cognitive impairments

resulting from substance abuse. Later in life, chronic stressors, traumatic brain injury, or ageing-related cognitive decline may intensify the impairments (Spear, 2018)

Most studies have focused on adolescence. Less is known about differences in cognitive performance amongst adult onset substance users. Some investigators have not found any differences in cognitive performance between early and late onset participants (Kist, Sandjojo, Kok, & van den Berg, 2014). In fact, Joos et al. (2013) found that early onset alcoholics generally performed as well as or even better than late onset alcoholics, especially on visual memory and interference tests (Joos et al., 2013). Amongst middle-aged participants, a positive relationship may exist between the quantity of alcohol consumed and the severity of brain damage (Sabia et al., 2014). These inconclusive findings highlight the need for further research.

2.5 Gender differences in substance abuse

Studies have suggested significant differences between men and women in their vulnerability to substance abuse and their pathways to drug use. In the studies of Erol and Karpyak (2015) and Hammerslag and Gulley (2016), female alcoholism was associated with mood disorders, especially depression. Comorbidities in women with alcohol use disorders show a significantly higher prevalence of psychiatric disease than that in men. Women with major depression have a 2.6 to 4.1% higher risk of developing alcohol abuse or dependence than women who are not depressed.

Men consume more alcohol and psychoactive drug than women, while women transition faster than men from initiation to problematic use and addiction (Hammerslag & Gulley, 2016; Kuhn, 2015). The development of addiction is not unambiguous in men and women. Regarding onset age of substance use, girls and boys are equally likely to start drinking at different ages. Gender differences in vulnerability to developing addiction are drug dependent. Boys are more likely to switch from occasional to addictive cannabis and alcohol use, while girls are more likely to develop nicotine and cocaine addiction (Hammerslag & Gulley, 2016). Women have more cultural factors that prevent them from using drugs compared with men (Kuhn, 2015).

Erol and Karpayak (2015) affirmed that it is difficult to separate cultural (i.e. gender-related) and biological (i.e. sex-related) components of male-female differences in the impact of mood changes on alcohol use and misuse. Women are more likely than men to drink heavily when experiencing unpleasant emotions, psychological distress, and internal tension, while men more often report drinking in response to pleasant emotions and social pressure. Men expect more positive effects from drinking and report more positive mood states during relapse than women.

2.5.1 Gender differences in vulnerability to substance use

The prevalence, age of onset, and symptomatology of many neuropsychiatric conditions differ between men and women. Male-biased conditions include autism, attention deficit/hyperactivity disorder, conduct disorder, specific language impairment, Tourette syndrome, and dyslexia, whilst female-biased conditions include depression, anxiety disorder, and anorexia nervosa (Gobinath, Choleris, & Galea, 2017; Kaczkurkin, 2019; Ruigrok et al., 2014).

Although the frequency of substance use, abuse and dependence is higher amongst men than women, recent studies have shown that this difference has narrowed in recent decades. In alcohol-related disorders, for example, the male-to-female ratio was 5:1.8 at the beginning of 1980; currently, it is 3:1 (Hammerslag & Gulley, 2016). Inadequate 'self-care' strategies may lead to increased substance use and addiction. Alcohol use in many countries has risen. Both genders demonstrate an earlier onset of drinking and earlier development of AUD symptoms in younger cohorts compared to cohorts born in earlier decades (Erol & Karpyak, 2015).

Research has affirmed significant differences in vulnerability to substance abuse and pathways to substance use between men and women. In many studies (Erol & Karpyak, 2015; Hammerslag & Gulley, 2016), female alcoholism has been associated with mood disorders, especially depression. Co-morbidities in women with AUD include a significantly higher prevalence of psychiatric disease than men. Women with major depression have a 2.6 to 4.1-fold risk of developing alcohol abuse or dependence than women who are not depressed. A history of sexual abuse and posttraumatic stress disorder increases the risk of alcohol dependence in women. Other disorders associated with alcoholism in women include bulimia, posttraumatic stress disorder, other substance use, and social phobia. Lifetime psychiatric disorders are frequent amongst substance-dependent women, mainly phobic and depressive disorders, suicidal behaviour, and Human immunodeficiency virus (HIV) risk behaviour (e.g. sexual practices and the use of intravenous drugs). A history of physical and/or sexual abuse is also associated with substance dependence.

In adolescent boys, sensation-seeking and impulsivity may drive substance and alcohol use, whilst stressful experiences and comorbid internalising disorders may stimulate substance use in adolescent girls (Hammerslag & Gulley, 2016; Niemelä, 2008). Conner's (2010) findings support significant differences in pathways to substance use between men and women. In a pilot study, Conner examined the gender of young adolescents to model the complicated associations between dopaminergic genes and SUDs. Predictors of substance use varied based on the gender of the participant. Significant differences were found in brain dopaminergic activity between men and women. For men, the best predictor of substance use was the hypodopaminergic genetic risk variable; for women, it was negative life events (Conner et al., 2010).

2.5.2 Gender differences in the negative consequences of substance use

Generally, gender differences in neuropsychological performance have provided contradictory evidence. Women tend to consume less alcohol than men but exhibit a similar overall cognitive profile, implying that women are differentially sensitive to the effects of alcohol on the central nervous system (CNS). In some studies, controlling for this variable in analysis of alcohol related gender differences were supported but in some studies they are not.

Different intoxicants affect brain development in men and women in different ways. Brain development disorders in women appear to be more due to alcohol use, but they are less susceptible to amphetamine-induced brain development disorders (Hammerslag & Gulley, 2016).

2.5.2.1 Studies on brain deficit

Erol and Karpyak (2015) reviewed sex and gender-related differences in alcohol use and its consequences. Women displayed fewer and less severe signs of alcohol withdrawal and had a lower risk of withdrawal-induced seizures and delirium tremens than men. These differences may be mediated by allopregnanolone, an endogenous neurotransmitter gamma-aminobutyric acid (GABA) receptor ligand with anxiolytic and anticonvulsant properties, or by estradiol, which reportedly reduces the neuronal damage caused by alcohol withdrawal. The authors also mentioned the strong influence of gender-related socio-cultural factors, as social norms restrict female drinking in many countries. Attitudes towards traditional gender role are also associated with higher abstinence rates and lower alcohol consumption amongst women and lower abstinence rates and heavy drinking amongst men (Erol & Karpyak, 2015).

In cocaine-dependent individuals, neuroimaging studies have shown qualitatively different patterns of frontal and limbic structures and functions (Fattore & Melis, 2016; Potenza et al., 2012). Corticostriatal-limbic hyperactivity appears to be associated with stress cues in women, substance cues in men, and neutral-relaxing conditions in both (Potenza et al., 2012). Tanabe et al. (2013) found that women with AUD had smaller insulae, whereas men with AUD had larger and thinner insulae. Thinner insulae in women with AUD may be related to more negative affective processing than in men. Furthermore, the orbitofrontal cortex was larger and thicker in men than in women; this feature is correlated with better negative reinforcement in controls (Tanabe et al., 2013).

2.5.2.2 Neuropsychological studies

Neuropsychological studies have examined the association between gender differences related to substance use and neuropsychological performance. Although there is active exploration of emerging sex differences in the literature on alcohol and substance use (Spear, 2018), only a few studies are available at present. Table 3 presents a summary of studies on gender differences in chronic substance abuse and cognitive performance were published between 1994 and 2017 in the PubMed/Medline database. Three studies focused on adolescents, and the other studies focused on adult participants.

Studies on gender differences in neuropsychological performance have provided contradictory evidence (Green, 2010). Women tend to consume less alcohol than men, but they exhibit a similar overall cognitive profile, which implies that women are differentially sensitive to the effects of alcohol on the central nervous system (CNS). Some studies controlled for this variable in the analysis of alcohol-related gender differences, whilst others did not. As Green (2010) noted, these findings should be considered in light of several methodological constraints that relate to small sample sizes and the unequal distribution of men and women in each group.

The results of studies on adolescents have been controversial (see Table 3). In adolescent girls, alcohol is associated with a greater decline in visuospatial performance, poorer sustained attention and WM performance, and poorer inhibition than in adolescent boys (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009; Squeglia, Schweinsburg, Pulido, & Tapert, 2011; Squeglia et al., 2012). Although a decline in attention has been reported amongst boys, they appeared to be more resilient to the deleterious effects of binge drinking than girls (Squeglia et al., 2011). By contrast, Simonelli (2017) found that, overall, women scored better on neuropsychological tests than men. Young men (average age of 21.05 years) had lower scores in tests of perception and executive function than young women (average age of 20.9 years). However, women scored lower in tests of memory abilities than men. The participants in Simonelli´s research was very different from those in other studies in terms of personality disorders; the samples in several of the longitudinal studies did not have serious personality problems (Simonelli, 2017).

Neuropsychological studies on adults affirmed women´s vulnerability to alcohol compared to men. Earlier findings by Parsons (1994) found that differences between participants with AUD and controls were greater amongst women than men although the former has significantly shorter periods of alcoholism (Parsons, 1994). Sullivan et al. (2002) found that women with alcohol-related disorders performed worse on tests of visuospatial ability and verbal and nonverbal WM than controls. Gait and balance were also adversely affected. These deficits implied dysregulation of the prefrontal, superior parietal, and cerebellar brain regions (Sullivan, Fama, Rosenbloom, & Pfefferbaum, 2002). Similarly, Tapert et al. (2000) found that

functional brain damage was evident in young alcohol-dependent women as early as late adolescence and young adulthood (Tapert, & Brown, 2000). In a study of alcohol-related disorders, Flannery et al. (2007) found that women exhibited more impaired performance in a wide range of neuropsychological tests than men (Flannery et al., 2007). Recent evidence also suggested revealed gender differences in neuropsychological impairments associated with cannabis use (Crane et al., 2015).

Table 3. Summary of studies determining gender differences in chronic substance abuse and cognitive performance

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adolescents								
Simonelli, 2017 Italy	Young adults with substance use disorders Participants (i.e. 20 men and 20 women) were recruited in a therapeutic community in Venice, Italy.	Mean age: 21 (2.2) Onset of drug-related problems occurred, on average, between ages 13 to 14. First contact with SUD treatment services occurred between ages 17 and 18. Participants were all inpatients in a therapeutic community	Cross-sectional and correlational study	Mainly poly-drug users Participants used different synthetic drugs other than cocaine and alcohol. 60% of males and 70% of females had methadone replacement therapy. Participants had been abstinent from drugs for an average of 3.2 months.	Men presented higher rates of antisocial subclinical and clinical features, while girls presented more histrionic subclinical and clinical traits. All participants were diagnosed with at least one personality disorder. Using the DSM classification, Cluster B disorders were diagnosed.	DSM-IV-TR (APA, 2000) criteria for substance use disorder Shedler Westen Assessment Procedure (SWAP200; Westen & Shedler 1999a, 1999b) 10 prototypical descriptions of DSM-IV personality disorders Symptom Checklist-90-Revised (SCL-90-R; Derogatis 1994)	Brief Neuropsychological Examination-2 (Esame Neuropsicologico Breve-2 [ENB-2]; Mondini et al. 2011). ENB-2 allows the investigation of several cognitive domains, such as attention, executive functioning, perception, praxis abilities, and comprehension. The battery assesses single cognitive tasks and provides a total score (i.e. global cognitive index), indicating the overall cognitive profile.	Women showed less cognitive impairment, but higher psychological distress compared with men. No differences between the two groups were noted in terms of personality profiles. The womens' life histories contained more experiences of abuse and maltreatment. Women also moved more quickly from substance use to dependence, whereas boys were more involved in criminal activity.

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adolescents								
Crane, Schuster, Mermelstein, and Gonzalez, 2015 USA	Sample of 44 men and 25 women young adult cannabis users from the Chicago-metropolitan area recruited through word-of-mouth and informational fliers.	18 to 24 years Age of regular cannabis use Men: 17.36 ± 1.98 (13–22) Women: 17.96 ± 2.32 (13–23)	Cross-sectional	Cannabis Marijuana No significant recent alcohol use No illicit drug use other than cannabis in the past 30 days or >10 times in life for each drug class other than cannabis	BDI-II Total Score BAI Total Score WURS percentage of scores BIS-11 Total Score	No diagnosis of a learning disability, developmental delay, mental illness (e.g. ADHD), or neurological condition; no significant birth complications; no loss of consciousness >10 minutes; no current use of psychotropic medication; and identified cannabis as drug of choice	Episodic memory and decision-making Verbal Episodic Memory HVLT Immediate Recall (z score) HVLT Delayed Recall (z score) HVLT Recognition Discrimination (z score) Decision-Making IGT Net Total (T score)	After controlling for cannabis use, earlier age of regular initiated use was found related to poorer episodic memory, especially immediate recall, in females but not in males. Earlier age of regular use was associated with better decision-making in females. There were gender differences in the associations between age of initiated cannabis use and neuropsychological functioning.

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adolescents								
Squeglia et al. 2012	Young men and women recruited from local schools *N* = 59 Recent binge drinkers (*n* = 29, 48% female) were compared with non-drinkers (*n* = 30, 50% female) in terms of age, gender, pubertal development, and familial alcoholism	16 to 19 years Complete neuropsychological data were available for 11 female bingers and 13 male bingers. Adolescent female and male participants with and without histories of binge drinking	Cross-sectional	Alcohol	No participant scored in the clinical range on any psychopathological or mood measure.	Child Behaviour Checklist Adult Self-Report (i.e. measures of internalizing and externalizing psychopathological syndromes) Beck Depression Inventory (BDI)-II Spielberger State Anxiety Inventory Magnetic resonance imaging (MRI) to examine cortical thickness	Measures of executive functioning, attention, and planning, and spatial skills D-KEFS[1] / Colour Word Interference WAIS-III[2] /Digit Span, Complex Figure Copy and 30-minute accuracy and delay Measure of premorbid functioning and intellectual capacity: WRAT-3[3] Reading Score	Female adolescents who participated in binge drinking presented thicker cortices than female controls. Thicker cortices were associated with poorer visuospatial performance, inhibition, and attention. Male bingers had thinner cortices than male controls, suggesting poorer attention.

[1] D-KEFS The Delis–Kaplan Executive Function System
[2] WAIS-III The Wechsler Adult Intelligence Scale, Third Edition
[3] WRAT-3 The Wide Range Achievement Test 3 is a brief, individually administered achievement test containing three subtests: Reading, Spelling, and Arithmetic.

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adolescents								
Squeglia, Schweinsburg, Pulido, and Tapert, 2011	40 binge drinkers (BD) Females = 13 Males = 27 55 controls Females = 24 Males = 31 Young women and men ages 16 to 19 recruited from public schools	16 to 19 years	Cross-sectional	Alcohol lifetime, other drug use occasions, and lifetime marijuana use	Child Behaviour Checklist Adult Self-Report (i.e. measure of internalizing and externalizing psychopathology) BDI Spielberger State Anxiety Inventory Karolinska Sleepiness Scale	1-hour brain imaging session while performing the task on a laptop Spatial Working Memory task (e.g., Tapert et al., 2001, 2004) “DOTS” was the simple attention vigilance condition that served as the active baseline. “WHERE” is the spatial working memory condition.	Spatial functioning and working memory (SWM task) ROCF[4] and 30-minute delay accuracy WASI[5] / Block Design WAIS-III[2] /Digit Span Vigilance Test (DVT) WAIS-III[2] /Digit-Symbol Coding WRAT-3[3] (i.e. measure of premorbid functioning and intellectual capacity)	Binge drinking during adolescence was associated with gender-specific differences in frontal, temporal, and cerebellar brain activation during an SWM task, which in turn related to cognitive performance. For female binge drinkers, less activation was associated with poorer sustained attention and working memory. For male binge drinkers, greater activation was linked to better spatial performance. Alcohol, marijuana, other substance use, and recency did not correlate with BOLD response for female or male binge drinkers.

[4] ROCF The Rey–Osterrieth complex figure
[5] WASI Wechsler Abbreviated Scale of Intelligence

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adolescents								
Squeglia, Spadoni, Infante, Myers, and Tapert, 2009	Adolescents (*N* = 76) who transitioned to heavy (*n* = 25; 11 females, 14 males) or moderate (*n* = 11; 2 females, 9 males) drinking were compared to demographically matched controls (*n* = 40; 16 females, 24 males) who remained non-users throughout the approximately 3-year follow-up period.	12 to 14 years (i.e. when they had little or no drinking experience)	3-year follow-up period *N* = 40 females *n* =16 males *n* = 24 participants	Alcohol	Family History Assessment Module (FHAM; Rice et al., 1995) Conduct Disorder Questionnaire (CDQ; Brown, Gleghorn, Schuckit, Myers, & Mott, 1996) Using as a covariate	Family socioeconomic status (SES) Premorbid functioning and intellectual capacity WASI/ Vocabulary and Similarities WRAT-3 rate Using as a covariate	ROCF[4] and 30-minute delay accuracy WASI[5] /Block Design Sustained attention, speeded information processing, and working memory DVT[6] D-KEFS[1] TMT[7] WAIS III[2] /Digit Span and Coding CVLT-C[8] SCWT[9] The Tower of London[10] At the 4-year follow-up, subtests were replaced.	Among girls, more drinking days in the past year predicted a greater reduction in performance on visuospatial tasks from baseline to follow-up, above and beyond their performance on equivalent measures at baseline (R 2Δ = 10%, $p < .05$). Boys exhibited more hangover symptoms in the year before follow-up testing, indicating a relative worsening of sustained attention (R 2Δ = 7%, $p < .05$).

[6] DVT Digit Vigilance Test; Assesses attention during rapid visual tracking
[7] TMT Trail Making Test, TMT-A, TMT-B
[8] CVLT California Verbal Learning Test
[9] SCWT The Stroop Color and Word Test
[10] The Tower of London task; measure of planning ability

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adults								
Alarcon, Nalpas, Pelletier, and Perney, 2015	166 patients men, *n* = 104 women, *n* = 62 Tests were administered at least 1 week after participants stopped drinking.	49.9 ± 9.2 years	Cross-sectional	Alcohol	Dependence on alcohol was assessed using the DSM-IV criteria.	NA	Montreal Cognitive Assessment (MoCA) 8 cognitive domains: visuospatial/executive, naming, memory (i.e. not scored), attention (i.e. 3 different items with separate scoring), language (i.e. 2 different items with separate scoring), abstraction, delayed recall, and orientation.	Neither age nor sex was significantly related to the MoCA score. A high education level (>12 years) significantly increased the likelihood of a high MoCA score.

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adults								
Sabia et al. 2014 United Kingdom	Whitehall II cohort study men n = 5,054 women n = 2,099	Mean age: 56 years Age range: 44–69 years	3 assessments in the 10 years preceding the first cognitive assessment (1997–1999)	Alcohol	History of depressive symptoms	Covariates: sociodemographic variables (i.e. age, sex, ethnicity, marital status, occupation), and education. Health behaviors were assessed using a questionnaire	Short-term verbal memory Executive function: inductive reasoning verbal fluency phonemic semantic fluency A global cognitive score was generated using all 4 tests.	Men who consumed ≥36 gram/day of alcohol experienced faster 10-year decline in all cognitive domains, with an effect size comparable to 1.5 to 5.7 extra years of cognitive decline. Among women, there was only weak evidence that heavy drinking is associated with faster decline in executive function.
Sneider, Cohen, Crowley, and Silveri, 2013 USA	Binge drinkers (BD, *n* = 22) and age- and sex-matched light drinkers (LD, *n* = 29)	BD (*n* = 22) age: 22.1 (1.3) LD (*n* = 29) age: 21.5 (1.7)	Cross-sectional	Alcohol	Emerging adults who are at a heightened risk for alcohol abuse disorders but who do not yet meet diagnostic criteria	Barratt Simplified Measure of Social Status (BSMSS) Beck Depression Inventory Spielberger Trait Anxiety Inventory Barratt Impulsivity Scale	Visuospatial memory: Human analogue of the Morris Water Maze Task (WMT) CVLT[8]	Emerging adult BDs demonstrated worse performance on verbal learning and memory than LDs. No significant group differences were observed on spatial learning and memory. No sex differences or interactions with drinking status were observed on either memory domain.

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adults								
Green, 2010 UoB brain tissue donor programme between April 2002 and September 2005 Australia	Participants with moderate to heavy alcohol use (*n* = 28) and matched controls (*n* = 28; age, education, and premorbid IQ) were compared n = 28. The alcohol group comprised 21 men and 7 women, while the control group comprised 10 men and 18 women.	Drinkers: 58 (17) years Controls: 57 (17) years	Cross-sectional	Alcohol	None of the participants in the alcohol group met the DSM-IV criteria for a diagnosis of alcohol abuse or dependence. Participants in the alcohol group consumed an average of 26 (i.e. range from 21 to 49) standard drinks per week as opposed to 6 (i.e. range from 3 to 6) among controls.	A detailed medical and social history: diet; past hospitalisations; current medica-tions; smoking history; past and present medical illnesses.	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) 12 subtests (i.e. most of which are analogous to traditional neuropsychological measures) Immediate Memory Attention Visuospatial Ability Language Delayed Memory	The alcohol group performed statistically below the control group on tests of visuospatial ability, learning, and memory. Participants in the alcohol group also had poorer RBANS total scores than controls. There was a trend towards significance in the Delayed Memory index, with participants in the alcohol group performing well below controls. Results did not support gender differences.

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adults								
Flannery et al. 2007 USA	Russian alcohol-dependent inpatients	18 to 40 years mean age: 32.2	Cross-sectional	Alcohol	No dual Axis I diagnoses according to the International Classification of Diseases (ICD-X) Negative HIV/AIDS status Age No head injury (i.e. not more than 3 minutes of unconsciousness)	Abstinence length of 3 weeks Women were significantly younger than men. Average age for men was 33 and 30 for women. Onset age of alcohol use was, on average, 18 for men and 17 for women.	CANTAB[11] tests: immediate and delayed perceptual matching and visual working memory, PAL[12], SOC[13] Cambridge Decision-Making Task (CDMT) SCWT[9]	Female alcoholic subjects exhibited poorer performances on tests of visual working memory, spatial planning and problem solving, and cognitive flexibility than male subjects. Sensitivity to interference (i.e. Stroop test) more strongly impacted female performance than male performance.

[11] the Cambridge Neuropsychological Test Automated Battery (CANTAB)
[12] PAL CANTAB/Paired Associates Learning
[13] 19SOC CANTAB/Stockings of Cambridge/ a test of spatial planning

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adults								
Sinha et al. 1989 USA	Men and women with (FH+) and without family history (FH-) of alcoholism Men FH- (*n* = 35) Men FH+ (*n* = 42) Women FH- (*n* = 23) Women FH+ (*n* =44) Controls	Age range: Males FH- = 36.4 Males FH+ = 35.7 Females FH- = 23 Females FH+ = 44	Neuropsychological test and retest during 14 months	Alcohol	Years of alcoholism: Men FH- = 11.3(8.5) Men FH+ = 12.4 (7.0) Women FH- = 6.5 (5.2) Women FH+ = 9.2 (6.4)	Event-related potentials (ERPs) recorded to visual stimulation	Verbal: WAIS-R[14] /Information WAIS-R[14] /Comprehension Face-Name Learning Visual-Spatial: WMS-III[15] Figural Immediate and Delayed WAIS-R[14] / Block Design Perceptual-Motor: Peg Board WAIS-R[14] /Digit Symbol TMT-A[7], TMT-B[7] Semantic Memory; Wechsler Semantic Immediate and Delayed	Differences between alcoholics and controls were greater among females than males even though the former had a significantly shorter duration of alcoholism. Alcoholics performed poorer than controls on each factor. No significant FH main or interaction effects were noted. Resumers had lower NTP scores and differed in ERP variables. A residual brain dysfunctional state may be associated with recidivism.

[14] WAIS-R Wechsler Adult Intelligence Scale Revised
[15] WMS-III Wechsler Memory Scale - 3rd ed.

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adults								
Parsons 1994 USA	Residents in a hospital alcoholic treatment programme, versus matched control group Alcoholic men, *n* = 72 Alcoholic women, *n*= 33 Control men, *n* = 46 Control women, *n* = 40	Men average age: 42 years Women average age: 43 years	Cross-sectional	Alcohol	Excluded those with a history of head injury, boxing, drug abuse, or major physical or mental illness that could affect cerebral function	Onset age of alcohol use was not considered.	'Pencil and Paper' battery: Logical Memory, Benton Visual Retention, TMT[7], Digit Span, New Adult Reading Test (NART). Automated test battery: Spatial Orientation, Psychomotor Speed, Verbal and Spatial Memory, Visuo perceptual Ability, and Abstract Reasoning	Men and women with alcohol use performed significantly worse on the cognitive tests than matched controls.Women performed worse in tests of immediate recall and psychomotor speed. This performance difference persisted even when male and female groups were statistically equated for drinking history differences. The findings indicated greater vulnerability among women.

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Substance Used	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adults								
Van den Berg, Julia F, Dogge, Kist, Kok, & Van der Hiele, 2017 Netherlands	*N* = 164, 62.2% men Older alcohol-dependent inpatients tested within 3 weeks after detoxification	50 and older Mean age: 62.6 ± 6.4 years	Cross-sectional	Alcohol	Men had been drinking excessively (i.e. 5 or more alcoholic drinks per day) for an average of 6.4 years.	Addiction Severity Index Premorbid verbal intelligence test Dutch Adult Reading Test (DART)	WCST[16] TMT[7] Figure Recognition (i.e. from the Dutch version of the Kaufman Short Neuropsychological Assessment Procedure)	No gender differences were found as regards sensitivity to Interference, as measured in the Stroop Colour Word Test. Alcohol-dependent women performed better than men on mental flexibility. Men performed better than women on the visual processing task. Irrespective of gender, the consequences of excessive alcohol consumption on cognition were detrimental. Results did not confirm that a longer period of alcohol dependence causes different and more severe cognitive impairment in women than in men.

[16] WCST Wisconsin Card Sorting Test

Author, Publication Year, and Country	Participants, Setting Sample Size	Age Range	Follow-up	Cross-sectional	Psychopathology	Other Relevant Measures	Neuropsychological Measures	Results
Adults								
Lyu and Lee 2012 Health and Retirement Study USA	Population-based sample with 3,888 females and 2,350 males	Mean age: 75.5 years for the female group 74.9 years for the male group	Cross-sectional	Alcohol	About 7.8% of women and 13.7% of men were classified as excessive drinkers. Heavy drinking was defined as drinking on 1 or more days a week and having 3 or more drinks per occasion for males and 2 or more drinks per occasion for females	Problem-drinking history was measured using the CAGE instrument.	Short-term memory, immediate and delayed free recall, and working memory Telephone Interview for Cognitive Status (TICS) test Fluid and crystallized intelligence scores were calculated.	Multivariate analysis showed that, compared with non-excessive drinking, excessive drinking did not have a significant impact on fluid intelligence for either women or men, but it had a significantly negative association with a high crystallized intelligence score among women.

In contrast to findings of adult women´s vulnerability to alcohol compared to men, Alarcon, Nalpas, Pelletier, and Perney (2015) determined that there were no significant gender differences in participants with alcohol-related disorders (the MoCA test). However, a high education level (>12 years) significantly increased the likelihood of having a higher performance score. Compared to controls, significant cognitive deficits were found in tests of visuospatial capacity, attention, fluency, abstraction, and delayed recall in participants with alcohol-related disorders. No gender differences were found. (Alarcon, Nalpas, Pelletier, & Perney, 2015). Furthermore, Sneider et al. (2013) affirmed no gender differences nor interactions with regard to verbal learning and memory amongst binge drinkers and light drinkers (Sneider et al., 2013). Similarly, Green et al. (2012) found no gender differences between participants who engaged in moderate and heavy alcohol use (Green, K., Zebrak, Fothergill, Robertson, & Ensminger, 2012). In a study by Solowij et al. (2011), lifetime cannabis use was associated with poorer episodic memory tests in both men and women cannabis users. This study was not included in Table 2 or Table 3, because it only measured the more acute effects of cannabis and abstinence time was only 20 hours (Solowij et al., 2011).

Alarcon et al. (2015) disclosed that alcohol-related premature brain ageing has spurred considerable research. In their own study, age (average 50 years) was found to be negatively associated with neuropsychological performance; this could be explained by the natural cognitive decline associated with ageing. Although higher education emerged as a protective factor against cognitive impairment in older subjects, cognitive functions dramatically decreased amongst alcohol-related disorders; this was most likely due to chronic alcohol abuse. The test scores of patients who drank heavily (i.e. a mean of 186 g of pure alcohol per day) were significantly lower than those of the controls in Moca´s study, who were 20 years older. The fact that no statistical comparison could be performed precludes any formal conclusions; however, this suggests that a positive association may well exist between the quantity of alcohol consumed and the severity of brain damage. Alarcon et al. (2015) did not find such a correlation, which they assumed was due to the narrow range of high alcohol consumption amongst their patients. However, previous studies (Durazzo, Meyerhoff, & Nixon, 2013; Pennington et al., 2015) have identified such a correlation.

Data obtained in Sabia et al.´s (2014) longitudinal neurological survey demonstrated that heavy alcohol consumption accelerated brain ageing and that, for a given age group, the brain of a person who consumed alcohol was 10 years older than that of a person who did not consume alcohol. Cognitive effects were examined in middle-aged participants (mean age of 56) who engaged in heavy, long-term alcohol consumption (10 years). The results showed that heavy drinking aggravated the weakening of all cognitive domains in men, whilst there was only a weak

association between drinking and impaired executive function in women (Sabia et al., 2014).

Data from the Health and Retirement Study (Lyu & Lee, 2012) confirmed that excessive drinking was associated with lower crystallised intelligence compared to non-excessive drinking amongst women but not amongst men. The authors concluded that women who consumed excessive alcohol may have had depression, which in turn may have weakened their intelligence. Thus, they recommended longitudinally examining the relationship between drinking and cognitive performance in future studies in order to clarify their causal relationship.

Studies of alcohol-dependent men and women (average age of 62.6) found an equal level of cognitive impairment amongst participants of both genders in neuropsychological tests of sensitivity to interference. Men performed better in visual processing, whilst women performed better in mental flexibility, even after controlling for length of alcohol use. Participants of both genders were generally below average compared to controls, suggesting cognitive deterioration after long-term alcohol use (Van den Berg et al., 2017).

Although most studies have suggested that women are more vulnerable to alcohol-induced brain damage than men, the evidence remains unclear. Differences in vulnerability between men and women in these studies can be attributed to several factors. Squeglia et al. (2011) reviewed the following performance differences. First, adolescent girls who engage in binge drinking have greater lifetime alcohol and other substance use. Second, adolescent boys may be more resilient than girls, recruiting more compensative neural systems to achieve task demands. In addition, binge-drinking boys score better than girls on spatial memory tasks, and women have the ability to use verbal compensatory means. Third, gender-specific differences have been observed with regard to neuromaturation, hormonal fluctuations, and alcohol metabolism differences. Brain development in adolescent girls occurs one to two years earlier than in adolescent boys (prefrontal synaptic pruning). Fourth, hormonal-level variability and menstrual cycle phase have been shown to differentially affect performance on spatially related tasks according to gender. Fifth, alcohol-induced fluctuations in hormone levels may explain the dissimilar effects of alcohol on brain activation between genders. Sixth, women have a different gastric metabolism, a higher amount of adipose tissue, or a lower body weight than men. Lastly, abnormalities in brain activation and cognition may precede alcohol use (Squeglia et al., 2011).

Previous studies have not investigated the impact of age of onset for substance abuse when studying differences between adult men and women. Most studies have focused on alcohol use rather than the effects of polysubstance use. However, considering the age of onset for alcohol and substance use amongst adults could clarify the rather contradictory results of previous studies on adults and the elderly.

Van den Berg et al. (2017) investigated the importance of residual confounding factors. When studying gender, ageing, alcohol use, the brain, and the interactions between these variables, residual confounding factors can complicate the results. These residual confounding factors may influence the latter; in other words, there may be other factors associated with the exposure, effect, and risk of developing the disease. This can distort the observed association between the disease and exposure under study. The effects of alcohol on the brain are diverse and influenced by many variables which may not be included in study (co-morbidity with other somatic or psychiatric disorders, genetic background, and eating habits). Patients with AUD may have short attention spans and only be able to perform a limited number of neuropsychological tests. It is possible that different neuropsychological tests yield different results. Finally, if the study sample consists of older AUD inpatients, the results cannot be generalised to outpatients or older, community-dwelling alcohol-dependent people (Van den Berg et al., 2017).

2.5.2.3 Studies of mood disorders

According to Erol and Karpyak (2015), it is difficult to separate cultural (gender-related) and biological (sex-related) components of differences between men and women and the impact of mood changes on alcohol use and misuse. Women are more likely than men to drink heavily when they experience unpleasant emotions, psychological distress, and internal tension. By contrast, men more often report drinking in response to pleasant emotions or social pressure; they expect more positive effects from drinking and report more positive mood states during relapse than women.

Regarding gender differences in co-morbidity, Mellos et al. (2010) found that, in line with clinical and epidemiological studies, the prevalence of personality disorders in alcoholism ranged from 22–40% to 58–78%. The study found that anxiety and mood disorders were the most prevalent comorbid disorders amongst women with AUD, whereas substance abuse and antisocial personality disorder were most frequent amongst men with AUD. In a large sample, women received a diagnosis of borderline personality disorder more often, whereas men had higher rates of antisocial and narcissistic personality disorder (Mellos, Liappas, & Paparrigopoulos, 2010).

According to Gobinath et al. (2017), women are more likely to be diagnosed with depression and comorbid AUD, whilst men are more likely to be diagnosed with bipolar II disorder and comorbid AUD. Alcohol abuse progresses more rapidly in women than in men (Gobinath et al., 2017)

Whittle et al. (2014) emphasised the importance of conducting future longitudinal studies on gender differences in brain development. The authors found that depression was associated with differences in the growth of amygdala and nucleus accumbens volumes in both adolescent boys and girls (Whittle et al., 2014).

Recent evidence has suggested that the relationship between depression and substance use amongst men is more complex than women. Men and women exhibit differences in symptoms of depression and coping mechanisms. These differences have contributed to probable underdiagnosis and treatment in men (Krumm, Checchia, Koesters, Kilian, & Becker, 2017). Men are reluctant to admit depressive symptoms to avoid being considered weak, 'feminine', or submissive by their peers. Self-care is also seen as a sign of weakness. There is evidence that men show exhibit more externalising and atypical symptoms of depression, including irritability, aggression, hostility, substance abuse, and increased risk behaviour than women (Cavanagh, Wilson, Kavanagh & Caputi, 2015), which conventional depression-screening instruments may not be sensitive enough to detect. Considering these factors is important, because weakness and perceived failure in one's role can also lead to depression amongst men. Accordingly, men may have a higher tendency to cope with depression through substance use and addiction.

The New Zealand Mental Health Survey 2003/4 is a nationally representative household survey that involved face-to-face interviews with 12,992 adults aged 16 and older. The survey revealed differences in the type or degree of disability experienced between men and women with mood or anxiety disorders (Scott & Collings, 2010). Men with either mood or anxiety disorders reported significantly more role, social, and cognitive disability than women with either mood or anxiety disorders.

A smaller proportion of women who drink regularly develop alcohol-related problems compared to men. Women who drink heavily have more alcohol-related medical problems and psychiatric disorders than men who drink heavily. In addition, women tend to become alcohol dependent at a later age but have lower rates of alcohol withdrawal symptoms than men. Earlier reports on the more rapid progression of alcoholism in women have been challenged in more recent studies. Women tend to seek treatment earlier and thus have better outcomes than men (Erol & Karpyak, 2015).

2.5.2.4 Studies of personality

Mulder (2002) has noted that personality variables explain a small proportion of the risk of dependence. Vulnerability to alcoholism increases with poorer educational achievement, deviant peers, and general disadvantage. Volkow et al. (2016)

suggested that future studies should help clarify the mechanisms that underlie potential gender differences.

However, research into the MMPI and personality differences between men and women with SUD has so far been scarce. The 24/42 two-point code type is often found among alcohol-using men in treatment, whereas this same code type and the 46/64 code type are often found among alcohol-using women in treatment (Graham, 1993).

In previous studies no unique alcoholic personality or personality measures which are specific to later AUD have been found, although several risk factors have been identified for AUD (Mulder, 2010; Walvoort et al., 2012). These risk factors are impulsivity/novelty seeking and neuroticism/negative emotionality, antisocial behaviour and hyperactivity (Mulder, 2010; Valwoort, 2012).

Taurino et al. (2021) studied the psychological defence mechanisms of men and women with SUD in clinical treatment for over one to three months. They suggested that coping styles, defences, and emotion regulation influence the onset and development of SUD. They also revealed that maladaptive defences are related to a worse psychological functioning and that defensive functioning is associated with personality disorders, and several emotional problems. In the SUD group, gender differences in several MMPI-2 scores were found. Women obtained significantly higher scores on the MMPI-2 Validity F scale and, on clinical scales 1 - Hs, 2 - D, 3 - Hy, 4 - Pd, 6 - Pa, 7 - Pt, 8 - Sc, and 9 - Ma. The researchers affirmed that gender differences act as cross-cultural factors that reinforce or prohibit the use of certain defences via socialization.

In Taurino et al.'s study (2021), participants with a pattern of maladaptive defences had significantly higher mean scores on all personality and psychopathologic variables, except MMPI-2 scales 3 - Hy and 5 - Mf. The researchers combined MMPI-2 with screening instruments of defensive functioning and alexithymia.

Compared with stimulant use disorder patients, AUD patients showed a depressive profile and had higher scores on the MMPI-2 2 - D scale. Analysis of correlations between MMPI-2 personality variables and maladaptive defences in the SUD group revealed significant positive correlations between maladaptive defences in all MMP-2 clinical scales, except MMPI-2 scales 3 - Hy and 5 - Mf.

Taurino et al. (2021) suggested that when confronting distressing material, SUD patients use a chemical way of coping with problems. They found differences among SUD sub-groups – AUD patients, in particular, showed a pattern of depressive symptoms. They argued that AUD patients use less adaptive defences (e.g., acting out, projecting, dissociating, splitting) in the acute phase of the disorder. During the sobriety period, depressive and anxiety symptoms were remitted. The researchers concluded that individuals with higher impairments in identifying feelings and

modulating affective processes tend to apply maladaptive strategies and defences for the regulation of affect in stressful situations.

2.6 Substance use disorder and mood disorders

2.6.1 Neuropsychological performance in co-occurring SUD and mood disorders

Addictive disorders often co-exist alongside mental disorder. Co-morbidity is highly prevalent between SUD and mood and anxiety disorders (Lai, Cleary, Sitharthan, & Hunt, 2015).co-morbid). Mood disorders include depression and Bipolar I Disorder (BD I) and Bipolar II Disorder (BD II). A mood disorder is a mental health problem that primarily affects a person's emotional state. BD I is a psychotic disorder.

Neuropsychological impairments are well represented in patients with mood disorders compared to healthy controls. Several studies and meta-analyses have revealed moderate effect sizes in the domains of processing speed, attention, executive function, learning, memory, and cognitive affective bias (Lam et al., 2014; Tuulio-Henriksson, 2015).

The prevalence of depression in people seeking treatment for AUDs ranges from 25.7% –85%, while patients with alcohol dependence are up to 4.5 times more likely to meet criteria for an affective disorder than non-dependent patients (Hunt, 2015). Co-morbid SUD is present in 70 % of patients with bipolar disorder (BD) (Gold et al., 2018).

Previous studies have shown that the use of alcohol and other substance use were adversely affects BD and further weakens cognitive functions (Cardoso et al., 2015; Levy, Monzani, Stephansky, & Weiss, 2008; Levy & Weiss, 2009; Levy, Manove, & Weiss, 2012; Marshall et al., 2012). Chronic substance use and alcohol have been shown to negatively affect several cognitive domains in BD, including executive functions and memory. For example, Levy et al.´s (2008) study reported that euthymic patients with BD with a history of alcohol dependence showed greater executive dysfunctions compared with patients with BD without a history of use.

Volkow et al. (2016) suggested a bidirectional association between mental illness and SUD. Mental health problems enhance self-medication such that an individual will try to medicate their mental illness through substance use. The association between SUD and mental health is more complex than self-medication. Substance use may trigger mental illness. Prospective studies have shown that substance use precedes mental illness; however, it is difficult to determine whether the co-morbidity is due to self-medication since the substance use started before the mental illness. During its early development, substance use can produce changes that make

individuals vulnerable to mental illness. Substance exposures can change brain development. Without substance abuse, some psychiatric diseases would never have emerged, emerged later, or presented with lower severity (Volkow et al., 2016).

Studies of register-based data of Virtanen´s dissertation (2021) provide evidence of a genetic component to both predispositions to internalising disorders, depression, anxiety, and OCD, and substance misuse across development and during lifetime. Genetic factors explained 76% of the covariance between generalised anxiety/depression and substance misuse, and the remaining 24% was explained by non-shared environmental factors. The association between childhood depression and subsequent substance misuse remained elevated in women even after adjusting for childhood ADHD and conduct disorder, which are strong predictors of substance use problems. In addition, estimates for the association with substance misuse were consistently higher for depressive disorders than for anxiety disorders (Virtanen et al., 2020; Virtanen et al., 2021). Virtanen´s (2021) results suggested that the relationship between internalising disorders and substance misuse partially reflects shared aetiology, but the findings were also consistent with (partially) direct effects between the disorders as proposed by the self-medication hypothesis. It appears that the comorbidity of internalising disorders and substance misuse arises via several mechanisms that are not mutually exclusive.

The co-occurrence of SUD and mental disorders may result in a ’double deficit’ in cognitive functions and have an adverse impact on the course of the patient's illness and neuropsychological performance. Furthermore, co-morbid conditions may have potential differential, additive, or interactive effects on cognitive functions (Donoghue & Doody, 2012).

Hunt et al. (2015) performed a systematic literature review of peer-reviewed published articles on the effects of co-occurring alcohol misuse and depression on neuropsychological functioning. The studies differed in terms of diagnostic tools, neuropsychological assessments, cognitive domains, duration of abstinence, stage of depressive illness, and participant characteristics. A limitation of this systematic review was that a quantitative meta-analysis of the results could not be performed because of the heterogeneous data sets included and the small number of studies that met the criteria for the review. The authors noted that the impact of heterogeneity on the results was difficult to evaluate and precluded interpretation of a combined effect estimate.

The reviewed studies compared the cognitive functioning of individuals with co-occurring alcohol misuse and depression to those with alcohol misuse alone, depression alone, and healthy controls. In addition, the systematic review included studies that described the correlation between depressive symptoms and cognitive functioning. Hunt et al. (2015) identified six studies that reported the neuropsychological profiles of people with co-occurring alcohol misuse and

depression. Severity and the stage of hazardous alcohol use differed between studies; some participants reported current hazardous alcohol use, whilst others were detoxified.

Based on the findings from this systematic review and the existing body of literature that supports evidence of visual memory deficits in independently occurring depression and alcohol misuse, it is recommended that an assessment of visual memory be included in any neuropsychological assessment of co-occurring alcohol misuse and depression (Hunt et al., 2015).

Hunt et al. (2015) found that comorbid groups performed below the norm in measures of executive function but not significantly so. These findings seem inconsistent with the large and accepted body of evidence on cognitive impairment in major depressive disorder and alcohol misuse in the absence of co-morbidity. Nevertheless, two out of the three studies which included direct comparisons between comorbid and singly occurring depression or alcohol groups found that the latter performed in a range that was not significantly below the norm. Hunt et al. (2015) concluded that the cognitive changes that take place with co-occurring alcohol misuse and depression are relatively mild and that cognitive impairments are not an obstacle to starting treatment.

Table 4 presents a summary of studies on comorbid mood disorders and alcohol and substance use, including the duration of abstinence. The studies presented in Table 4 are mainly based on Hunt et al.'s (2015) review. Studies on bipolar disorder have been added separately to the table.

Table 4. Studies on mood disorders and substance use in relation to cognitive performance

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Subgroups	Psychopathology	Other Relevant Sample Data	Neuropsychological Measures	Results
Hermens et al. 2013 Ireland	*N* = 136 Men = 58 %	Mean age = 22	Cross-sectional study	Depression + Binge *n* =43 (32%) Depression *n* = 48 Binge *n* = 24 HC *n* =21	Assessment of people with primary DSM-IV-TR MDD with or without co-occurring binge drinking versus HC with or without binge drinking AUDIT-C>6 to identify binge drinking status DSM-IV-TR MDD diagnosis (i.e. psychiatric interview)		WTAR[1] estimate of premorbid IQ TMT-A[2], TMT-B[2] Visual Learning and MemoryPAL errors[3]; Verbal Learning and Memory; RAVLT[4] Working Memory; SSP[5] Sustained Attention; RVP[6]	Co-occurring binge drinking and depressive disorder was associated with poorer neuropsychological outcome (i.e. visuospatial learning and memory) than binge drinking or depression alone. In terms of cognition, the comorbid group performed within the normal range.

[1] WTAR Wechsler Test of Adult Reading WTAR estimate of premorbid IQ
[2] TMT Trail Making Test, TMT-A, TMT-B
[3] PAL CANTAB/Paired Associates Learning
[4] RAVLT The Rey Auditory Verbal Learning Test
[5] SSP CANTAB/Spatial Span
[6] RVP CANTAB/Rapid Visual Information Processing

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Subgroups	Psychopathology	Other Relevant Sample Data	Neuropsychological Measures	Results
Liu, I-C et al. 2010 Taiwan	Hospital patients Men, *N* = 96 Women, *N* = 27 Detoxified for at least 1 week Among participants, 96.7% received sedatives and hypnotics during a detoxification period, but the use of antidepressants was postponed until the diagnosis of depressive disorder.	Mean age Women = 38.9 Men = 39.6	Cross-sectional	Comorbidity of alcohol use and depression No comorbidity Around 58% of all subjects had a co-existing depressive condition.	Child Behaviour Checklist Adult Self-Report Measures of internalising and externalising psychopathological syndromes Beck Depression Inventory-II Spielberger State Anxiety Inventory No participant scored in the clinical range on any psychopathological or mood measure.	Magnetic resonance imaging was used to examine cortical thickness in adolescent females and males with or without histories of binge drinking.	Barratt Impulsivity Scale; Attentional impulsivity; Motor impulsivity; Non-planning; WAIS-III[7] Verbal IQ Performance IQ WMS-R[8] Working Memory Index Immediate visual memory Delayed visual memory Colour Trails Test	Alcoholics with a co-occurring depressive disorder demonstrate more neurocognitive deficits than alcoholics without comorbidity. Alcohol dependents with a depressive disorder were more impulsive and had a more impaired performance on immediate visual memory than patients without comorbidity. Alcohol dependents generally had low scores on all neuropsychological instruments.

[7] WAIS-III The Wechsler Adult Intelligence Scale, Third Edition
[8] WMS-R The Wechsler Memory Scale Revised

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Sub-groups	Psychopathology	Other Relevant Sample Data	Neuropsychological Measures	Results
Hunt et al. 2009 Australia	*N* = 167 Male (*n* = 93, 55.7%) outpatients who self-referred to the study after seeing advertisements in local media. Participants were not required to abstain from alcohol and other substances to meet entry criteria, but they were requested not to use alcohol or other substances for at least 24 hours before the neuropsychological assessment.	Aged 20–70 (mean = 45.59; SD = 10.67	Cross-sectional	NA	Participants experienced depressive symptoms, as evidenced by BDI-II total scores of ≥17, and had consumed alcohol at hazardous levels in the month prior to the baseline assessment. Hazardous use of alcohol was defined as exceeding the National Health and Medical Research Council (NHMRC) recommended levels (i.e. average of ≥28 standard drinks per week for men and ≥14 per week for women) The depression section of the SCID	Alcohol consumption was assessed using an Alcohol Use Disorders Identification Test (AUDIT), Opiate Treatment Index (OTI), and Severity of Alcohol Dependence Questionnaire (SADQ). A score of 30 on the SADQ was suggested as the cut-off for severe dependence. Current and lifetime diagnoses of alcohol abuse and dependence were also assessed using the alcohol use disorders section of the Structured Clinical Interview for DSM-IVTR (SCID).	WASI[9] Full-Scale IQ; Matrix Reasoning; D-KEFS CWI[10] Inhibition; D-KEFS CWI[10] Inhibition; Switching; Visual and Visuospatial Processing (i.e. Block Design); Verbal Fluency and Language (i.e. Vocabulary, Similarities); D-KEFS[10] (Letter, Category, Category Shifting); Verbal Learning and Memory (i.e.RAVLT[11]) Fluid Intelligence WASI-PIQ[12] IQ and General Knowledge (WASI-FSIQ[13]) Working Memory (WAIS-III[7] /Digit Span)	Despite hazardous alcohol use and severe depressive symptoms, these outpatients generally showed normal cognitive functioning. Severity of depressive symptoms on the BDIII correlated negatively with some measures of cognitive function but did not meet the threshold for significance that the authors set. Near the threshold were Block Design test, WASI-PIQ[12], and WASI-FSIQ[13].

[9] WASI Wechsler Abbreviated Scale of Intelligence
[10] D-KEFS Color Word Interference
[11] RAVLT The Rey Auditory Verbal Learning Test
[12] WASI-PIQ Performance Scale and yield a Performance IQ score; Hunt et al. 2009 Australia
[13] WASI-FSIQ Full Scale Intelligence Quotient

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Sub-groups	Psychopathology	Other Relevant Sample Data	Neuropsychological Measures	Results
Nowakowska et al. 2008 Poland	*N* = 88 Subgroup 1: 13 women and 38 men Subgroup 2: 8 women and 29 men The control group included 30 normal persons (7 women and 23 men) matched according to sex, age, and education to alcohol-dependent patients.	Mean age: 43±9 years	Cross-sectional	Subgroup 1: 51 subjects An assessment was performed directly after discontinuation of alcohol drinking. Subgroup 2: 37 subjects after at least one-year of abstinence Control group consisted of 30 healthy persons.	An outpatient clinic for addiction therapy The diagnosis of alcohol dependence was obtained following the ICD-10 Classification.	SADD and MAST scales Beck Depression Inventory	Executive Functions WCST[14] Working Memory	Severity of depressive symptoms in alcohol use disorders was not correlated with the degree of neuropsychological impairment, suggesting that cognitive function disturbances with alcohol abuse is independent of the degree of depressive symptoms. Compared with healthy subjects, significant disturbances in working memory and executive functions were noted in patients with alcohol dependence, both with short-term and long-term abstinence.

[14] WCST Wisconsin Card Sorting Test

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Sub-groups	Psychopathology	Other Relevant Sample Data	Neuropsychological Measures	Results
Uekermann, Daum, Schlebusch, Wiebel, and Trenckmann 2002 Germany	Alc Men = 18 Women = 12 Dep Men = 15 Women = 13 HC Men = 17 Women = 11 The mean duration of abstinence was 1.98, with SD = 1.56 months with a minimum of 10 days	Alc = 42.60 (9.53) Dep = 44.36 (10. 28) HC = 42.32 (9.78)	Cross-sectional	Alc: *n* = 30 Dep: *n* = 28 HC: *n* = 28 alcoholic depressed (DAlc) = 13 non-depressed (NDAlc) = 18	Alcoholism was diagnosed according the Diagnostic and Statistical Manual (DSM)-IV criteria. Patients with depression but without alcoholism (Dep)received a psychiatric clinic for treatment and were diagnosed by a psychiatrist who was blind to their cognitive data.	Assignment of alcoholic patients into the NDAlc and DAlc groups was based on a median split (*M* = 13) on the Beck Depression Inventory.	A short version of the Wechsler Adult Intelligence Scale (WIP); Digit Span Test; Benton Retention Test; Recognition Memory for Faces; Word lists, immediate and delayed; Story recall; Fragmented Picture Test; Verbal fluency; Cognitive Estimates Test;	There is no significant difference between depressed and non-depressed alcoholics. Deficits are not generally exacerbated by comorbid depressive symptoms. Further studies, however, are desirable to investigate the relationship between executive deficits and depression in alcoholics with evidence □of major depression.
Schafer et al. 1991 Boston, USA	Men*: N* = 171 Alcohol group criteria DSM-III AA or AD Depression group Detoxified (i.e. mean of 10 days of abstinence)	Mean age: 45	At the 3-month follow-up Correlation between depression severity and cognitive function	NA	Depressive symptoms were quantified using the HAMD (Hamilton, 1960) and used in the correlational analysis of severity of depression and cognitive functioning.	Education: Mean = 13 years WAIS Vocabulary estimate of pre-morbid IQ	Processing Speed RCPMB[15]; TMT-A[2], TMT-B[2]; Digit Symbol; Executive Functions RCPMB[15]: Visual and Visuospatial Processing Visual search	Severity of depressive symptoms was an important predictor of cognitive performance in recently detoxified inpatients with alcohol use disorder. Depressive symptom severity accounted for the variance in the Repeatable Cognitive- Perceptual Motor Battery Trails B and Digit Symbol.

[15] RCPMB Repeatable Cognitive-Perceptual-Motor Battery

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Sub-groups	Psychopathology	Other Relevant Sample Data	Neuropsychological Measures	Results
Levy, Manove, and Weiss 2012 USA	*N* = 55 inpatients	Bipolar patients with AD 40.7 (11.3) Bipolar patients without SUD 36.4 (12.2)	At the 3-month follow-up	Patients with co-occurring AD (*n* = 21) Patients without SUD (*n* = 34).	DSM-IV diagnostic criteria for bipolar I disorder	Beck Depression Inventory, Second Edition (BDI-II) (46) score < 15 Beck Hopelessness Scale (BHS) (47) score < 10 Young Mania Rating Scale (YMRS) (48) score < 15.	Five domains of cognitive functioning, namely IQ, attention and working memory, verbal memory, complex visual material processing and visual memory, and executive function. WASI[9]:Vocabulary and Block Design subtests	Dually diagnosed patients performed more poorly on measures of memory, both verbal and nonverbal, and executive functioning than patients without a history of SUD. At the 3-month follow-up, similar discrepancies emerged between the groups. Although cognitive recovery over the course of remission was noted in both groups, patients without SUD exhibited more significant gains than dually diagnosed patients on delayed free recall of the wordlists, stories, and complex figures. More significant gains for patients without SUD were also noted on Part B of the Trail Making Test, which assesses complex attention and cognitive flexibility.

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Sub-groups	Psychopathology	Other Relevant Sample Data	Neuropsychological Measures	Results
Marshall, Walker, Ryan, Kamali, Saundes, Weldon, Adams, McInnis, and Langenecker 2012 USA	N= 256 Controls = 97 Participants were recruited through an outpatient specialty psychiatry clinic, an inpatient psychiatric unit, and advertisements on the web and in a newspaper.	BD with SUD 38.47 (12.02) BD without SUD 39.92 (11.92) Controls 37.74 (14.23)	Cross-sectional	BD with SUD (*n* = 158) BD without SUD (n = 98) Controls (*n* = 97)	Bipolar Disorder (201 Bipolar I Disorder, 36 Bipolar II Disorder, 19 Bipolar Disorder NOS)	DMS-IV diagnostic criteria for SUD Overall, 52.5% (*n* = 83) of participants in the SUD group met diagnostic criteria for only one substance, while 47.5% (*n* = 75) met diagnostic criteria for multiple substances.	ROCF[16] CVLT[17] Purdue Pegboard Test; Emotion Perception Test; Facial Emotion Perception Test; WCST[14] SCWT[18] COWAT[19] Animal Fluency; Digit Symbol test; TMT-A[2], TMT-B[2] Parametric Go/No-Go task	BD patients with a lifetime history of comorbid SUD showed significantly worse visual memory and conceptual reasoning Significant impairment in cognitive functioning exists in Bipolar Disorder, as both BD groups demonstrated poorer performance than the HC group on most cognitive factors.

[16] ROCF The Rey–Osterrieth complex figure
[17] CVLT California Verbal Learning Test
[18] SCWT The Stroop Color and Word Test
[19] COWAT Controlled Oral Word Association Test

Author, Publication Year, and Country	Participants, Setting, and Sample Size	Age Range	Follow-up	Sub-groups	Psychopathology	Other Relevant Sample Data	Neuropsychological Measures	Results
Levy, Monzani, Stephansky, and Weiss 2008 USA	N = 63 hospital inpatients 35 men and 28 women	BP with current AD 35.0 (12.9) BP with remitted AD 46.8. (8.9) BP without SUD 36.1. (12.6)	Cross-sectional	Group 1: Patients meeting DSM-IV diagnostic criteria for alcohol dependence *n* =13 Group 2: Patients with alcohol remission *n* = 9 Group 3: Patients without history of SUD *n* = 41	DSM-IV diagnostic criteria for bipolar I disorder	In the group diagnosed with alcohol dependence in the past 6 months, 2 participants met diagnostic criteria for marijuana abuse, 1 was diagnosed with past cocaine abuse, and 3 were diagnosed with past abuse of both substances. In the fully remitted group, 3 participants met diagnostic criteria for both past marijuana and cocaine abuse (i.e. over 12 months of abstinence), while 1 participant met criteria for past opioid dependence (i.e. over 5 years of abstinence).	IQ estimates Attention and Working Memory (i.e. Digit Span subtest);t; TMT-A[2], TMT-B [2] Letter and Symbol Cancellation Task; Perceptual Organisation and Visual Memory; ROCF[16] Verbal Memory and Logical Memory from WMS-R[20] CVLT[17]; SCWT[18] COWAT[19]; FAS letters format[21] Animal Naming Task WCST[14]	Co-occurring alcohol dependence predicted higher rates of disability status. Neurocognitive impairment showed greater severity in the dually diagnosed groups on measures of executive functioning and memory tests. Significant differences emerged both groups with SUD in the Stroop Test and the Wisconsin Card Sorting Test. Significant differences in visual memory (i.e. Rey Complex Figure Test) in immediate recall and recognition were noted. Significantly lower performance on CVLT-II (i.e. verbal learning) measures of immediate and delayed free recall were observed in the group with current alcohol dependence.

[20] WMS-R The Wechsler Memory Scale Revised

[21] The F-A-S Test assesses phonemic verbal fluency by requesting an individual to orally produce words that begin with the letters F, A and S

Patients who were diagnosed with both BD and SUD performed more poorly on measures of both verbal and nonverbal memory and executive functioning than patients with BD but without a history of SUD (Levy & Weiss, 2009). At a three-month follow-up, similar differences emerged between these two groups. BD patients with a lifetime history of comorbid SUD performed significantly worse in visual memory and conceptual reasoning tests than patients with BD but without SUD (Levy et al., 2012). The results of Marshall et al.´s (2012) study aligned with those of previous studies in that BD patients with SUD had poorer visual memory than controls and patients without BD. Conceptual reasoning and executive functioning (set-shifting) were also weaker in patients with SUD and BD.

A comparison of studies on the comorbidity on depression and alcohol is difficult because these studies examine the severity of depressive symptoms as a continuous measure, whilst depressive symptoms do not necessarily meet the threshold for diagnosis. Participants in the review of Hunt et al. (2009) experienced depressive symptoms, as evidenced by BDI-II total scores of ≥ 17, but not all patients have a diagnosis of depression. On the contrary, participants in studies of patients with bipolar disorder (BD; Gold et al., 2018; Cardoso et al., 2015; Levy, Monzani, Stephansky, & Weiss, 2008; Levy & Weiss, 2009; Levy et al., 2008; Levy, Manove, & Weiss, 2012; Marshall et al., 2012) all have a diagnosis of bipolar disorder.The results of Hunt et al. (2015) seem to confirm that visual impairment is more heavily affected by substance use than verbal impairment and that mood disorders may intensify visual impairment. In addition to visual memory impairment, impairment was detected on the Block Design Test and Performance Intelligence Quotient (WASI-PIQ). However, a limitation of previous studies on comorbid alcohol dependence was that not all patients involved had been diagnosed with depression.

The studies discussed in the current section were mainly cross-sectional in nature. Thus, it is not possible to explore genetic factors, disease severity, and manic episodes in relation to memory and executive disorders. The studies also failed to investigate the effects of specific substances, despite the fact that, for example, nearly half of the patients in the Marshall study (2012) used multiple substances. However, the effect of different substances (e.g. stimulants vs. depressants) and the duration of abuse and dependence may affect cognitive factors in mood disorders. Although further research is necessary, the overall findings from previous studies support the assumption that mood disorders are associated with more persistent and more severe cognitive disorders in BD patients with co-occurring SUD

2.7 Gaps in the existing literature

There is more in-depth understanding of the risk of cognitive impairment associated with an early age of onset of substance use. Studies have investigated alcohol and

substance use dependence in adolescents without mental or neurological disorders or learning disabilities. The aim was to find groups of youth that were as homogeneous as possible in order to study the effects of substance abuse. Observed differences in neuropsychological test performance as well as brain structure and function might have reflected individual differences that preceded substance use (Volkow et al., 2016). Furthermore, the number of substance users in the study populations was small, and brain imaging was not performed (Volkow et al., 2016). In addition, age of onset was often defined in different ways; some studies defined it as the first time that an individual used cannabis, whilst others defined it as the age that an individual initiated regular use, which itself could be defined in a variety of ways across studies (Crane et al., 2015).

Furthermore, few studies controlled for amount of substance use when examining age of initiated use, making it difficult to understand the unique influence of age of initiated use on neuropsychological functioning, as age of initiated use is often confounded with amount of use (i.e. users who started using cannabis at an earlier age consumed more cannabis than those who began later (Crane et al., 2015b). Regarding alcohol use, Hunt et al. (2015) found that severity and stage of hazardous alcohol use differed between studies; some participants engaged in acute used alcohol use, whilst others were detoxified. Abstinence may diminish acute cognitive deficits associated with substance use (Rapeli et al., 2005; Scott, J. C. et al., 2018).

Findings from studies on gender differences in neuropsychological performance and substance use have been controversial. Although most studies have suggested that women are more vulnerable to alcohol-induced brain damage than men, the evidence remains inconclusive. Recent evidence has suggested that there are gender differences in neuropsychological deficits associated with substance use, especially in adolescents. Further research is needed to clarify the mechanisms underlying these potential gender differences (Volkow et al., 2016). Recent gender studies have affirmed that the relationship between mood disorders, personality, and substance use is more complicated (e.g. depression in men manifests differently than in women). Moreover, it is unclear whether the observed changes are heightened by challenges later in life, such as ageing-related cognitive decline in men and women. Evidence indicates that there are associations between gender differences and, for example, cannabis use, but more research is needed to clarify underlying effects (Crane, Schuster, Fusar Poli, & Gonzalez, 2013a; Volkow et al., 2016).

Mood disorders and SUDs have been intensively and separately studied. Despite the clinical importance of comorbid psychiatric symptomatology, only a few studies on neuropsychological performance related to co-occurring mood disorders and SUDs have been conducted (e.g. a quantitative meta-analysis of cognitive function in co-occurring alcohol misuse and depression has not been conducted, as there are only a few studies with homogenous samples). A limitation of studies on comorbid

depression and alcohol is that they examined the relationship between the severity of depressive symptoms as a continuous measure, but depressive symptoms do not necessarily reach the threshold for diagnosis. By contrast, studies on BD and substance abuse involved patients with diagnosed bipolar disease. Participants in the review of Hunt et al. (2009) experienced depressive symptoms, as evidenced by BDI-II total scores of ≥ 17, but not all patients have a diagnosis of depression. On the contrary, participants in studies of patients with bipolar disorder (BD; Gold et al., 2018; Cardoso et al., 2015; Levy, Monzani, Stephansky, & Weiss, 2008; Levy & Weiss, 2009; Levy et al., 2008; Levy, Manove, & Weiss, 2012; Marshall et al., 2012) all have a diagnosis of BD.

3 Aims

Separate studies of this dissertation were developed from the need for clinical research. More research is needed to determine the neuropsychological functions that can be improved by treatment and rehabilitation. According to studies, several factors seem to influence the outcome of rehabilitation: mood disorders and related disorders, age of onset and duration of substance use, length of abstinence, and polysubstance use. Evidence suggests that gender differences in cognitive vulnerability underlie substance abuse. It is possible that preceding individual differences could explain some impairments in previous research. These considerations are important when evaluating factors that influence work ability.

The purpose of this study is to investigate the correlations between (I) age of onset of regular substance use, (II) gender differences, and (III) mood disorders and neuropsychological performance in a sample of hospitalised, middle-aged addiction patients. To this end, the specific research objectives are as follows:

1. To examine the impact of age of onset of regular substance use on neuropsychological performance in patients with a diagnosis of SUD and explore the impact of alternate conditions of substance abuse, particularly single and polysubstance use and background factors (e.g. education level, learning difficulties, and gender), on neuropsychological performance. Based on previous research, it was hypothesised that substance use, especially in adolescence and early adulthood, would impair neuropsychological test results.
2. To study cognitive and personality differences between male and female patients with a diagnosis of SUD and explore the impact of alternate conditions of substance abuse, particularly age of onset of regular substance use, single and polysubstance use, and background factors (e.g. education level and age), on neuropsychological performance. Based on previous studies, it was hypothesised that women are not more vulnerable to substance use-induced neuropsychological deficits and personality differences compared to men.

3. To examine which neuropsychological tests are the most sensitive in distinguishing patients with SUD without mood disorders (SUD-MD) from those with SUD and a mood disorder (SUD+MD); to investigate how the research groups (i.e. SUD-MD and SUD+MD) differ from each other in normative data; and to explore the impact of alternate conditions of substance abuse, particularly age of onset of regular substance use, single and polysubstance use, and background factors (e.g. education level and learning difficulties), on neuropsychological performance. It was hypothesised that comorbidity would affect outcomes such that the neuropsychological performance of SUD+MD patients would be poorer than that of SUD-MD patients.

4 Materials and Methods

4.1 Participants

The current study is cross-sectional in nature. Data were collected from patients at the Järvenpää Addiction Hospital who underwent neuropsychological examination from 2005–2012. A minimum abstinence period of one month was required before testing due to the longer-lasting, sub-acute cognitive, and neural effects of cannabis.

The inclusion criteria for participants were as follows: (1) aged 18–65 years, (2) native Finnish speakers with a substance use diagnosis, and (3) a minimum of one month of abstinence. Meanwhile, the exclusion criteria were as follows: (1) younger than 18 years, (2) HIV-positive or diagnosed with another chronic disease that possibly affects the central nervous system, and (3) a history of neurological disorders, opioid substitution treatment, or epileptic seizures.

Diagnoses were made by experienced psychiatrists according to ICD-10 criteria and based on all available information at the time of discharge. The 19 (21.6%) patients were diagnosed with bipolar disorder (F31), and 69 (78.4%) with depression (F32-34) and mixed anxiety and depressive disorder (F41.2).

Diagnoses of the SUD+MD sample was bipolar disorder (F31), major depressive disorder, single episode, mild (F32.0), major depressive disorder, single episode, moderate (F32.1), major depressive disorder, single episode, severe without psychotic features (F32.2), major depressive disorder, single episode, severe with psychotic features (F32.3), major depressive disorder, single episode, unspecified (F32.9), recurrent major depressive disorder, mild (F33.0), recurrent major depressive disorder, moderate (F33.1), recurrent major depressive disorder, severe without psychotic symptoms (F33.2) recurrent major depressive disorder, in remission (F33.4), persistent mood (affective) disorders (F34.1) and mixed anxiety and depressive disorder (F41.2).

Diagnoses of SUD included harmful use or dependence. 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 polysubstance 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. Alcohol was the most commonly used substance among both monosubstance and polysubstance users.

Data about age of onset for 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 duration of abstinence was determined through laboratory tests.

The study was approved by the ethical committee of the A-Clinic Foundation. Informed consent was obtained from all participants.

4.2 Procedures and neuropsychological and personality assessments

Interviews and neuropsychological testing, included in the study programme, were conducted as part of a normal clinical assessment practice and a treatment plan assessment by the author of this dissertation, who is experienced in using neuropsychological tests. All patients underwent testing after admission once acute depressive symptoms had abated. Each patient was clinically assessed by the clinician responsible for their treatment. Accordingly, a one-month abstinence period was sufficient and practical for neuropsychological assessment, because some of the patients were discharged soon after their one-month stay in the hospital.

The patients underwent detoxification on benzodiazepines and analgesics. There was no mention of any other medication. The psychological testing took approximately two to three hours. The tests were usually conducted in two phases. All testing and scoring of variables was performed by the neuropsychologist (i.e. Irma Höijer) in accordance with standard guidelines.

The protocol assessed cognitive functioning in several domains, including language (premorbid functioning), attention, processing speed, perceptual reasoning, memory, inhibitory capacity, and executive functioning. In addition, personality and learning difficulties were assessed. The neuropsychological tests were constructed from methods that have been widely used in substance abuse research. Some of the tests were performed on only a small number of subjects.

The performance of subjects of different ages was not compared to the mean age group in terms of their calendar age in all tests. WAIS-R subtests of Vocabulary, Block Design, Digit Span Forward, and Digit Span Backward do not have age standards. CogniSpeed tests also do not have age standards, including subtests of Neutral Condition (COL), Congruous Word Condition (CON), and Incongruous Word Condition (IN), Total Stroop, and Stroop Interference. Therefore, additional

analyses of WAIS-R subtests, WMS-R subtests, and CogniSpeed tests were performed by age group. The results of the test variables did not differ from one age group to another. In statistical models age was used as a numerical covariate if there was no age reference group.

Published standards by age group were used for the Digit Symbol, the RPM test and the indices of WMS-R test.

1. Premorbid functioning

   The Vocabulary subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R, Wechsler et al., 1975) was used to assess verbal skill and premorbid functioning. The Vocabulary subtest requires participants to explain the meanings of 34 words, arranged from easy to hard. For each answer, 0, 1, or 2 points are awarded. Answers are given 2 points if the literal meaning or the general use of the comprehension word being tested can be deduced. The Vocabulary test was compared with the normal reference frame of the WAIS-R test. The Vocabulary subtest was used to assess verbal skill and premorbid functioning.

2. Attention

   The Digit Span Forward and Digit Span Backward subtests of the WAIS-R (Wechsler et al., 1975) were used to assess attention. Participants were asked to read number sequences of increasing length and to repeat them after each sequence. Specifically, the Digit Span Backward subtest is sensitive to many kinds of brain damage (Lezak, 1995). The Digit Span Forward and Digit Span Backward subtests compared with the normal reference frame of the WMS-R test.

3. Processing speed

   The Digit Symbol subtest of the WAIS-R (Wechsler et al., 1975) was used to assess processing speed, although the Digit Symbol test may mediate a wide range of simple and complex cognitive processes that are likely to include working memory and executive functions. Digit Symbol is a sensitive and valid test that screens for dysfunctions of the brain and measures of cognitive dysfunction impacted by many domains (Lezak, 1995). The computerised CogniSpeed tasks (Portin et al., 2000) were used to measure simple reaction time (SRT). Reaction time frequently slows with brain disease or injury and disproportionately increases with increasing task complexity (Lezak, 1995). A slowdown in mental processing speed has been frequently reported as a result of dementia and depression (Lezak, 1995). There were no comparable previously conducted CogniSpeed studies with a relevant normal reference frame

except for the Revonsuo (1995) study. In the Revonsuo study (1995), the mean age of the control group was 67.7 (range 62–75).

4. Perceptual reasoning

   The Block Design subtest of the WAIS-R (Wechsler et al., 1975) required participants to view a constructed model or picture in the Stimulus Book and use two-colour blocks to recreate the design within a specified time limit. Block Design is generally considered as the best measure of visuospatial organisation in the Wechsler scales (Lezak, 1995). In addition, participants had to do the RPM. The RPM is a test that evaluates non-verbal performance. It is independent of language, reading, and writing skills. It consists of 60 multiple choice questions, listed in order of increasing difficulty. Respondents are asked to select from a set of eight options the one that completes a given pattern in different matrices. There is no time limit, although the execution time is considered when evaluating results. The tests were originally developed by John C. Raven in 1936. For each age group, N number of correct answers corresponds to a certain percentile score. In Finland, the 1992 edition of the RPM test is available at the Hogrefe Publishing Group.

5. Verbal memory and learning

   The Wechsler Memory Scales – Revised (WMS-R, (Wechsler, D., 1987) include the Verbal Memory Index (VEM), which contains the Logical Memory I and Verbal Paired Associates subtests. Logical Memory I-II consists of two stories that are nearly equivalent in difficulty and equivalent in obtainable score, with an added delayed recall trial. The raw scores in the test are converted into indice of VEM based on the age of the subject.

6. Visual memory and learning

   Visual Memory Index (VIM) of the WMS-R (Wechsler, 1987) contains Figural Memory, Visual Paired Associates I, and Visual Reproduction I subtests. Existing literature supports the idea that visual memory deficits independently occur in depression and alcohol misuse, and it is recommended that an assessment of visual memory be included in any neuropsychological assessment of co-occurring alcohol misuse and depression (Hunt et al., 2015).

7. Delayed memory

   The WMS-R (Wechsler, 1987) includes a Delayed Recall Index (DEL), which consists of Logical Memory II, Visual Paired Associates II, Verbal

Paired Associates II, and Visual Reproduction II subtests. The raw scores in the test are converted into indice of Delayed Recall Index based on the age of the subject.

8. Inhibitory capacity

   The most commonly used inhibition tasks are contained in the Stroop Colour-Word Interference Test. In the present study, inhibitory capacity was assessed using the CogniSpeed version of the Stroop Colour-Word Interference Test (Revonsuo, 1995). The latter includes three subtests: (1) Neutral Condition (COL), (2) Congruous Word Condition (CON), and (3) Incongruous Word Condition (IN). COL and CON are related to automatic and routinised information processing, whilst IN measures conscious and effort-intensive processing. Each task has a practice session of 10 items and a final session of 50 items. In each subtest, the order of the colours was randomised. Two response buttons were coloured red and blue. When the colour and the meaning were incongruent, participants had to suppress word meaning processing. Colour reaction times consisted of three different conditions that differed only in terms of the stimuli's semantic content: neutral, congruous, or incongruous. In every condition, the subjects were asked to only respond to the colour of the letters presented (i.e. red or blue). There were no comparable previously conducted CogniSpeed studies with a relevant normal reference frame except for the Revonsuo (1995) study. In the Revonsuo study (1995), the mean age of the control group was 67.7 (range 62–75).

9. Executive function

   Total Stroop effect refers to the difference between reaction times in CON and IN (Revonsuo, 1995). In manual reaction time tests such as the ones discussed above, the most reliable and consistent indicator of the Stroop effect is the combined effect of facilitation and interference (i.e. the total Stroop effect. Thus, Stroop interference is measured by the difference between reaction times in IN and COL (Revonsuo, 1995). There were no comparable previously conducted CogniSpeed studies with a relevant normal reference frame except for the Revonsuo (1995) study. In the Revonsuo study (1995), the mean age of the control group was 67.7 (range 62–75).

10. Personality

    Personality variables were measured using the following subscales from the MMPI: 1 – Hs Hypochondriasis, 2 – D Depression, 3 – Hy Hysteria, 4 – Pd Psychopathic Deviate, 5 – MF Masculinity-Femininity, 6 – Pa

Paranoia, 7 – Pt Psychasthenia, 8 – Sc Schizophrenia, and 9 – Ma Hypomania (Graham, 1993; Welsh & Dalstrom, 1956). The scoring procedures yield scores for four validity scales and 10 basic clinical or personality scales. Raw scores from the standard validity and clinical scales are transformed into T-scores (mean = 50, SD = 10) using the data provided manual.

Studies have confirmed that the CogniSpeed software is a sensitive instrument for measuring the performances of healthy participants and of participants with brain disease (Lilja, Portin, Hämäläinen, & Salminen, 2001; Portin, Raija et al., 2000; Portin, Raija, 2001).

Neuropsychological assessments of learning disabilities were revised with neuropsychologist who specialises in learning disabilities. Learning disabilities were classified as a single variable that included attention, verbal and nonverbal reasoning, memory problems, dyslexia, and mathematical difficulties. Assessment of attentional difficulties considered the patients' behaviour in test conditions (e.g. short attention span). In an interview, patients were also asked about school success, school breaks, dropouts, and special educational support needs.

4.3 Statistical analyses

Sociodemographic data for the patient groups (i.e. EOAs vs. LOAs; men vs. women SUD-MD vs. SUD+MD) were compared using the Student's t-test, the Mann-Whitney U-test for continuous measurements, and the Chi-square test or Fisher's exact test for categorical variables. For statistical comparisons, $p < 0.05$ was considered to be statistically significant. If the interactions were not statistically significant at the 0.05 level, they were removed from the model.

In study I, intravenous substance users (IV users) comprised a subgroup of polysubstance users. Pearson and Spearman correlations were calculated between age of onset (i.e. regular use, polysubstance use, and IV use) and psychological measures. Spearman's rho correlation was used because the CogniSpeed variables SRT, COL, CON, IN, Total Stroop, and Stroop Interference had non-normal distributions.

Associations between neuropsychological measurements (i.e. Digit Symbol, Block Design, RPM, visual memory and learning, IN, and Stroop interference), regular age of onset, confounding factors [i.e. multiple substance abuse (yes/no], age, education level, and learning difficulties (yes/no)], and their interactions were investigated through an analysis of covariance. Each neuropsychological measurement was analysed separately but removed if it the results were not significant. If the interactions were not statistically significant at the 0.05 level, they

were removed from the model. In this model, age and age of onset of regular use were used as numerical covariates, whilst multiple substance abuse, education level, and learning difficulties were considered as categorical explanatory variables.

In study II, associations between neuropsychological measures, male and female participants, and confounding factors (e.g. age of onset of regular substance use, polysubstance use (yes/no), education level, and learning difficulties) were examined through an analysis of covariance. Analysis of covariance was also used to study associations between personality variables and men and women populations, and confounding factors (e.g. education level, polysubstance use (yes/no) and onset age of regular substance use). Explanatory variables and interactions that did not significantly affect the primary outcome were removed from the analysis. Each neuropsychological measurement was analysed separately. Model-based means were also presented. Logarithmic transformation was used for simple reaction time, IN, and COL to achieve a normal distribution assumption for the residuals.

In study III, an analysis of covariance was used to study associations between neuropsychological measurements, SUD-MD and SUD+MD groups, and confounding factors (i.e. multiple substance abuse (yes/no), age, education level, and learning difficulties). Each neuropsychological measurement was analysed separately. Interactions between mood disorder and explanatory variables were examined but removed if the results were not significant. In these models, age was used as numerical covariate, whereas mood disorder, multiple substance abuse, education level, and learning difficulties were considered as categorical explanatory variables.

Data were analysed using the Statistical Package for Social Sciences (SPSS) software (SPSS Inc., Chicago, IL) and SAS System (version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA).

5 Results

5.1 Age of onset of substance use and neuropsychological performance (Original article I)

5.1.1 Demographic characteristics of early onset abusers (EOA) and late onset abusers (LOA)

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. SUD diagnoses also included alcohol overuse or dependence.
The phrase ´age of onset of regular substance use ´ refers to the age at which a patient reported at least regular weekly use of a substance. Participants were classified according to age of onset of regular substance use to 'early onset abusers' (EOAs; <17 years) and 'late onset abusers' (LOAs; 18> years).

The sociodemographic and clinical characteristics of the study participants are presented in Table 5. The groups significantly differed in terms of demographic and substance use-related variables (p-value < 0.001), which were later controlled in a multivariate analysis. However, there were equal numbers of men and women in both groups.

Table 5. Sociodemographic and substance use-related information for the EOA and LOA populations.

	Total sample N = 164	EOA ≤17 n = 76	LOA ≥18 n = 76
Age	38.7 (10.0)	32.8 (9.6)	43.5 (9.8)
Gender (male)	97 (59.1 %)	45 (59.2 %)	52 (59.1 %)
Level of education Primary School Vocational training College-level education Higher education	 65 (39.6 %) 54 (32.9 %) 28 (17.1 %) 17 (10.4 %)	 45 (59.2 %) 21 (27.6 %) 8 (10.5 %) 2 (2.6 %)	 20 (22.7 %) 33 (37.5 %) 20 (22.7 %) 15 (17.0 %)
Learning difficulties	70 (42.7 %)	44 (57.9 %)	26 (29.5 %)
Age of onset of regular substance use	22.6 (10.4)	14.5 (2.0)	29.2 (9.8)
Polysubstance users	90 (54.9 %)	57 (75.0 %)	33 (37.5 %)

Note. EOA = early onset substance abusers, LOA = late onset substance abusers. Means and standard deviations (SD) for continuous numerical variables and numbers and percentages (%) for categorial variables.

In the overall sample, the distribution of substances used in the single substance group (55%) was as follows: alcohol (41%), sedatives (7%), stimulants (4%), and opioids (3%). The distribution of substances used in the polysubstance 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 polysubstance users generally varied in terms of combinations, which made it difficult to investigate the effects of a single substance.

5.1.2 Correlations between age of onset of regular use and neuropsychological tests

Table 6, Table 7, and Table 8 show the results of primary correlational analyses between age of onset of regular use and neuropsychological tests. Results of Premorbid Intelligence, Processing Speed, and Perceptual Reasoning are presented in Table 6, results of Attention and Memory tests are shown in Table 7, whilst results of CogniSpeed tests for inhibitory capacity are outlined in Table 8. In the primary correlational analyses, significant positive correlations were found between age of onset of regular use and several neuropsychological tests..Spearman’s rho was used

in the statistical analysis of variables SRT, CON, COL, and IN, because these variables were not normally distributed.

Table 6. Results of primary correlational analyses between age of onset of regular use and several neuropsychological tests for premorbid IQ, processing speed, and perceptual reasoning

	Age of onset of regular use			**Age of onset of SUD**			**Age of onset of iv-use**		
Cognitive domain	N	Correlation Pearson Spearman rho	*P* -value	N	Correlation	*P* -value	N	Correlation	*P* -value
Premorbid IQ									
Vocabulary	162	0.17*	0.032	97	0.12	0.24	36	-0.27	0.11
Processing speed									
Digit Symbol Test	100	0.12	0.24	62	-0.12	0.36	21	-0.48**	0.03
Simple reaction time:									
Dominant hand	152	0.28**	<0.001	92	0 .32**	0.002	33	0.04	0.81
Nondominant hand	150	0.27**	<0.001	90	0 .32**	0.002	33	-0.07	0.81
Perceptual reasoning									
Block Design Test	64	-0.02	0.28	39	-0.34*	0.04	14	-0.48	0.08
Raven's Progressive Matrices	149	-0.09	0.87	90	-0.06	0.58	33	-0.46**	0.01

Table 7. Results of primary correlational analyses between age of onset of regular use and several neuropsychological tests for attention, Verbal memory and learning, Visual memory and learning, and Delayed memory

	Age of onset of regular use			**Age of onset of SUD**			**Age of onset of iv-use**		
Cognitive domain	N	Correlation Pearson Spearman rho	*P* -value	N	Correlation	*P* -value	N	Correlation	*P* -value
Attention									
Digit Span Forward	162	0.11	0.15	97	-0.09	0.37	36	-0.04	0.81
Digit Span Backward	161	-0.06	0.45	97	-0.03	0.75	36	0.03	0.87
Verbal memory and learning									
Verbal Memory Index	66	0.22	0.08	35	-0.10	0.57	12	-0.44	0.17
Immediate Logical Memory	66	0.12	0.33	36	-0.02	0.89	12	-0.20	0.54
Delayed Logical Memory	66	0.14	0.27	36	0.05	0.80	12	-0.42	0.18
Immediate Associate Learning	66	0.01	0.92	36	-0.01	0.97	12	-0.20	0.53
Delayed Associate Learning	64	-0.10	0.46	36	-0.06	0.75	36	-0.30	0.37
Visual memory and learning									
Visual Memory Index	64	0 .07	0.56	33	-0.01	0.95	11	-0.02	0.96
Immediate Visual Learning	64	0.08	0.54	34	-0.26	0.14	11	-0.20	0.55
Delayed Visual Learning	64	-0.23	0.07	34	-0.46**	0.007	11	-0.42	0.55
Immediate Visual Reproduction	64	-0.08	0.54	36	0.09	0.61	11	-0.20	0.55
Delayed Visual Reproduction	63	-0.23	0.07	35	-0.02	0.92	11	-0.30	0.78
Delayed memory									
Delayed Memory Index	63	0.06	0.65	34	0.00	1.000	11	-0.39	0.24

Table 8. Results of primary correlational analyses between age of onset of regular use and several neuropsychological tests for inhibitory capacity.

	Age of onset of regular use			**Age of onset of SUD**			**Age of onset of iv-use**		
Cognitive domain	N	Correlation Pearson Spearman rho	*P* -value	N	Correlation	*P* -value	N	Correlation	P-value (= Mann-Whitney U-test)
Inhibitory capacity									
Neutral Condition (COL):									
COL ms	152	0.29**	<0.001	92	0.33**	<0 .001	35	0.08	0.66
COL errors	152	0.11	0.18	92	-0.002	0.44	35	-0.13	0.44
Congruous Word Condition (CON):									
CON ms	152	0.33**	0.02	92	0.35**	<0.001	35	0.003	0.98
CON errors	152	-0.08	0.33	92	-0.13	0.23	35	-0.14	0.42
Incongruous Word Condition (IN):									
IN ms	151	0 .33**	0.002	91	0.30**	0.004	35	0.003	0.98
IN error	151	0.01	0.11	91	-0.09	0.41	35	-0.14	0.42

5.1.3 Analysis of covariance for main effects

For variables that reached significance in the original analysis, group differences were further analysed using ANCOVA whilst adjusting for the confounding factors of education level, learning difficulties, polysubstance use, and age (see Table 9). The results of this analysis are summarised in Table 9.

Table 9. Results of multi-way analysis of covariance for the association between neuropsychological tests and age of onset of regular substance use

Cognitive assessments	Age of onset of regular use	
	F_{df}	P-value
Processing speed Digit Symbol Test (N = 99)	F_{92}=5.00	0.028*
Perceptual reasoning Block Design Test (N = 63)	F_{53}=1.24	0.270
Perceptual reasoning Raven's Progressive Matrices (N = 149)	$F1_{40}$ =6.64	0.011*
Visual memory and learning Delayed Visual Learning (N = 62)	F_{48} =0.02	0.887
Inhibitory capacity IN2 (N = 152)	F_{143} =0.26	0.613

Note: *p <0.05, **p <0.01 and ***p <0.001

With regard to processing speed, EOAs performed worse on the DST than LOAs. Age of onset of regular use was found to be positively related to the DST. This indicates that, the earlier the age of onset of regular use, the slower the performance.

With regard to perceptual reasoning, age of onset of regular substance use was found to have a significant and inverse relationship to perceptual reasoning. This indicates that, the later the age of onset of regular use, the poorer the performance. Compared to EOAs, LOAs performed worse on the RPM test.

5.1.4 Analysis of covariance for covariates and interactions

The covariates were education level (1–4), learning difficulties (yes/no), polysubstance use (yes/no), and age. A more detailed analysis of neuropsychological tests and age of onset of substance use was presented in the original publication I. The results of the multi-way analysis of covariance for the covariates are summarised

in Table 10. There was a positive relation between the Digit Symbol test and the covariable of the education level indicating that the lower the education level, the poorer the performance in the test. Learning disabilities were correlated with lower scores on the RPM test and a lower education level; 64% of patients with learning difficulties had an education level of 1, which corresponds to primary school. Polysubstance users performed worse with regard to visuospatial reasoning on the Block Design Test; the same was not observed amongst single substance users. The Delayed Visual Learning test was impacted by ageing, which weakened memory regardless of age of onset of regular use. The CogniSpeed variable for inhibitory capacity (IN) was also impacted by ageing – the greater a participant's age, the slower their inhibitory capacity.

Table 10. Results of multi-way analysis of covariance for associations between neuropsychological test and covariates.

Cognitive Assessments	Covariables									
	Education level		Learning difficulties		Multiple substance use		[1]Age		Gender	
	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}= 3.24	0.03*	F_{92}= 0.88	0.35	F_{92}= 2.48[3]	0.12	-	-	F_{92}= 1.55.	0.22
Perceptual Reasoning The Block Design test (N=63)	F_{53}= 1.72	0.17	F_{53} = 3.85	0.06	F_{53}= 7.70	0.008	F_{53} = 1.11	0.30	F_{53}= 0.35	0.56
Perceptual Reasoning Raven (N=149)	F_{140} = 1.77	0.16	F_{140} = 13.65	<0.000***	F_{140}= 2.67	0.104	F_{140}= 2.73	0.10	F_{140}= 5.95	0.02*
Visual Memory and Learning Delayed Visual Learning (N=62)	F_{48} = 0.97	0.42	F_{48} = 3.95	0.05	F_{48} = 0.22	0.641	F_{48} = 5.29	0.03*	F_{48} = 1.87	0.18
Inhibitory capacity IN (N=152)	F_{143} = 1.53	0.21	F_{143} = 1.11	0.29	F_{143} = 0.16	0.69	F_{143} = 7.60	0.01**	F_{143}= 0.09	0.77

Note: *p <0.05, **p <0.01 and ***p <0.00. ¯not tested due to minimal clinical interest and limited sample size. [1]Calendar age was also controlled in the model due to the lack of age correction norms. [2]Intravenous use was used as a subgroup of polysubstance use

Where no main significant association between age of onset of regular use and the neuropsychological test was found, the interaction between age of onset of regular use and the covariates were also considered.

The interaction between age and polysubstance use was significantly and negatively correlated with perceptual reasoning, as measured through the Block Design Test. The interaction between age and polysubstance use indicated that the performance of polysubstance users begun to deteriorate with age.

In the least educated group of users (i.e. education level = 1), a later age of onset of regular use had clear negative effects on delayed visual learning. In the other groups (i.e. educational level = 2, 3, or 4), this association was not observed. In the absence of a learning disability, there was a negative association with a later age of onset of regular use and visual learning; if a learning disability was present, no association was observed. The result showed a worse performance in delayed visual memory in a group of LOAs.

No correlations were found with analysis of covariance between Stroop interference and total Stroop and background variables and their interactions.

5.2 Gender differences in cognitive and personality functioning in patients with SUD (Original article II)

5.2.1 Demographic characteristics

No gender differences were found in terms of age, level of education, learning difficulties, or polysubstance use (see Table 11). Age of onset was earlier amongst men than women and duration of substance use was longer amongst men than women. These variables were controlled for in later statistical analyses.

Table 11. Sociodemographic and clinical data for male and female participants

	N	Men N = 97	Women N = 67	Statistical test	Men vs. women *P*-value
Age (mean, *SD*)	164	38.4 (9.7)	38.7 (12.9)	*t*-test	0.86
Education level					
No primary school					
Primary school	164	36 (37.1 %)	29 (43.4 %)		
Vocational training		39 (40.2 %)	15 (22.4 %)		
College-level education		15 (15.5 %)	13 (19.4 %)		
Higher education		7 (7.2 %)	10 (14.9 %)	Chi-square	0.077
Learning difficulties	164	42 (43.4 %)	70 (42.7 %)	Chi-square	0.85
Age of onset of regular substance use	164	20.7 (7.8)	24.9 (12.9)	*t*-test	0.018*
Duration of substance use in years	164	17.8 (8.9)	13.0 (8.6)	*t*-test	0.001***
Polysubstance users	90	53 (54.6 %)	37 (55.2 %)	Chi-square	0.94

Note: *p <0.05, **p <0.01 and ***p <0.001, For continuous numerical variables, means, and standard deviations are presented, whilst counts and percentages are provided for categorical variables

5.2.2 Primary gender differences in neuropsychological tests with normative data

The results of neuropsychological assessments in the men and women groups are summarised in Table 12 and Table 13. Normative reference frames were obtained from the WAIS-R (Wechsler et al., 1975) and WMS-R (Wechsler, 1987), a previous CogniSpeed study (i.e. Revonsuo, 1995), and age-based index of the RPM. There were no comparable previously conducted CogniSpeed studies with a relevant normal reference frame, except for the Revonsuo (1995) study. In the Revonsuo study (1995), the median age of the control group was 67.7 (range 62–75).

Table 12 show the reference frame of the WAIS-R and CogniSpeed subtests and the RPM. The WAIS-R subtests included were the Vocabulary and the Block Design tests. The WAIS-R reference frame for these subtests was the 20–34 age group, which was the only age-based reference frame available. The reference frame for the Digit Symbol test was obtained from the WAIS-IV test, and it was age based. Table 13 show the results of the WMS-R. The reference frame values for the indices Verbal Memory Index, Visual Memory Index, and Delayed Memory Index were all age based. For other subtests of the WMS-R, values for the 36–45 age group were presented. The median age of the men group was 37 (31-46) years, whereas the median age of the women group was 38 (27-50) years.

Additional analyses of the WAIS-R and WMS-R subtests and CogniSpeed tasks by age group and gender were performed. The results of the test variables did not differ from one age group to another. The median and interquartile range for Q1–Q3 were included in the tables to better compare the values of the normal reference range. The tables 12 and 13 shows how the test values of the study group are defined, with Q1–Q3 comprising 75% of the observations. Some of the tests were performed on only a small number of subjects. The group differences were presented as p-values of the T-test based on a previously published study (Original article II).

There were significant differences between men and women in the Vocabulary subtest of the WAIS-R, the DST, and the RPM test (see Table 12) Women performed better on the Vocabulary subtest and the DST, while men performed better on the RPM test, which indicates superior perceptual reasoning. Nevertheless, men's scores were in the normal mean range on the Vocabulary test. However, both male and female participants performed below average on the DST. In CogniSpeed tasks of processing speed, SRT means of both men and women groups were slower than those of normal controls of 67.7 (i.e. range 62–75) years (Revonsuo, 1995). With regard to inhibitory capacity tests, both male and female participants performed similarly to 63- and 64-year-olds in tasks of CON and IN (Revonsuo, 1995).

Results on tests of Visual memory and Learning and Delayed memory were below average amongst both male and female participants. The former group were clinically below average in Visual Memory Index tests (see Table 13)

Table 12. Primary comparisons between men and women of premorbid IQ, processing speed, perceptual reasoning, and inhibitory capacity

		Men ***N*** **= 97**		**Women** ***N*** **= 67**		**Men vs. women** ***p*****-value**
Cognitive domain	Normal reference frame WAIS-R[1] Age group 20-34 WMS IV[2] Revonsuo, 1995[3] Raven, 1992[4]	*N*	Median (interquartile range 25–75%)	*N*	Mean (*SD*)[1] Median (interquartile range 25–75%)[2]	P-value[1] (= t-test) P-value[2] (= Mann-Whitney U-test)
Premorbid IQ						
Vocabulary	8–12[1]	95	8.0 (7-10)	67	10.0 (7-12)	0.026*[1]
Processing speed						
Digit Symbol Test	8–12[2]	54	4.0 (2-6)	46	5.0 (3.8-7.3)	0.012*[1]
Simple reaction time	308 (248-389)[3]	92	368.0 (335.8–454.8)	61	378.0 (325.5–453.0)	0.93[2]
Perceptual reasoning						
Block Design Test	8–12[1]	33	9 (6-10)	31	8.0 (6-11)	0.64[1]
Raven's Progressive Matrices	90–109[4]	88	100.0 (94-112)	60	94.5 (90-101.8)	0.003**[1]
Inhibitory capacity						
Neutral Condition (COL):						
COL ms	614 (445-810)[3]	92	575.5 (493.3714.3)	61	561.0 (484.5–632.0)	0.54[2]
COL errors	1.6% (0-6%)	92	1.0 (0.3–3.0)	61	1.0 (0.0–2.0)	0.051[2]
Congruous Word Condition (CON):						
CON ms	564 (412-753)[3]	92	539.0 (485.8641.5)	61	542.0 (464.5–625.0)	0.40[2]
CON errors	1.6% (0-6%)	92	1.0 (0.0–2.0)	61	1.0 (0.0–2.0)	0.17[2]
Incongruous Word Condition (IN):						
IN ms	678 (446-1311)[3]	91	686.0 (550.0921.0)	61	642.0 (569.0–839.5)	0.88[2]
IN error	1.3 (0-6%)	91	1.0 (0.0–.0)[2]	61	2 (0.0–4.0)	0.55[2]

Table 13. Primary comparisons between men and women of tests of verbal, visual, and delayed learning and memory

		Men *N* = 95		Women *N* = 67		
Cognitive domain	Normal reference frame WMS-R Age group 36–45	*N*	Mean (*SD*)[1] Median (Interquartile range 25%-75%) [2]	*N*	Mean (*SD*)[1] Median (Interquartile range 25%-75%) [2]	*P*-value (= *t*-test)
Verbal memory and learning						
Verbal Memory Index	90–109	42	97.0 (81–103)	25	100.0 (89.5–109.5)	0.21
Immediate Logical Memory	25–26	42	24.0 (17.0–30.5)	25	28.0 (22.5.-32.0)	0.18
Delayed Logical Memory	21–22	41	20.0 (11–25)	35	23.0 (19.5–28.0)	0.87
Immediate Associate Learning	19	42	17.0 (13–20)	25	19.0 (14.5.-22.5)	0.17
Delayed Associate Learning	7–8	41	7 (5–8)	24	7.0 (6.0–8.0)	0.74
Visual memory and learning						
Visual Memory Index	90–109	40	73.5 (59–93.3)	25	83.0 (65.0–99.0)	0.46
Immediate Visual Learning	15	41	10.0 (6–15)	24	13.5. (8.8–17.8)	0.30
Delayed Visual Learning	5–6	40	5 (3–6)	24		0.19
Immediate Visual Reproduction	36	42	35 (29.8–38.0)	25	6.0 (4.0–6.0) 36.0 (32.5–37.5)	0.94
Delayed Visual Reproduction	33–34	41	30.0 (20.5.-37.0)	24	29.0 (25.0–36.8)	0.93
Delayed memory						
Delayed Memory Index	90–109	40	82.5 (55.5–95.8)	25	85.0 (71.0–101.0)	0.23

Note: *p <0.05, **p <0.01 and ***p <0.001

5.2.3 Analysis of covariance for neuropsychological tests

An analysis of covariance was conducted for the neuropsychological tests in order to determine the primary differences between genders. After adjustment (i.e. calendar age, education level, polysubstance use, and years of regular substance use), all differences between the performance of men and women on the neuropsychological tests disappeared, and no interactions with substance use variables (i.e. years of regular substance use of regular use and polysubstance use) or background variables (i.e. education level and learning difficulties) were found.

5.2.4 Analysis of MMPI personality test

5.2.4.1 Primary gender differences on the MMPI personality test

Personality variables were measured using the subscales of the MMPI: Hypochondriasis (1 – Hs), Depression (2 – D), Hysteria (Hy), Psychopathic deviate (Pd 4 – Pd), Masculinity-Femininity (5 – MF), Paranoia (6 – Pa,), Psychasthenia 7 – Pt), Schizophrenia (8 – Sc), Hypomania (9 – Ma), and Social introversion (0 – Si) scales. The validity scales are lie scale (L), infrequency scale (F), and defensiveness scale (K).

Table 14 outlines the primary differences between male and female participants on the MMPI personality test. Male and female participants were found to differ from each other on almost all scales. Gender was significantly associated with the Depression, Psychastenia, Hysteria, Schizophrenia, Hypochondriasis, Paranoia and Masculinity-Femininity, Lie and the Validity scales

Participants of both genders scored high (T = 60-80) for several personality variables compared to the normal reference frame of the MMPI. T-scores of 60 or above were considered with in the clinically significant range. Both genders had elevated scores on the Depression scale, suggesting clinical depression. Depression in men was significantly more severe than that in women. Both genders had elevated scores ion the Hysteria scale, but men scored significantly higher than women. Similarly, in the Psychasthenia, Schizophrenia, Paranoia and Hypochondriasis scales, both genders had clinically significantly elevated scores, although men scored higher than women. In the Masculinity-Femininity scale, the scores of both genders remained at a nonclinical level, but men scored significantly higher than women. Both genders scored clinically high on the Psychopathic Deviate and Paranoia scales.

On the Hypomania scale, women had clinically high scores, whereas men's scores were at a nonclinical level. Nevertheless, the difference between scores was not statistically different. On the contrary, on the Social Introversion scale, men

scored clinically high, while women's scores were at a nonclinical level, although the difference in their scores was not statistically different.

On the validity scale K, both genders scored at a nonclinical level, but women scored higher, implying that they deny symptoms and problems more than men do. Both genders had clinically high F-scores, suggesting that they approach the test-taking task in a different way than what the test authors intended. Notably, in both genders, the T-score was not greater than 100, which did not allow for clear, invalidating responses. The F-scale score (T = 65–79) at this level may indicate clinically severe neurotic or psychotic disorders. Without serious psychopathology, F-scores at this level often describe persons characterized by restlessness and unstableness. Overreporting may be suggested by the elevated results on the F scale, combined with the normal range of scores on L and K, but significant pathology may still be present.

Table 14. Primary differences between male and female participants on MMPI personality variables

	Men ***N* = 95**	**Women** ***N* =67**	**T-test** ***P*-value**
Variable	**Mean (*SD*)**	**Mean (*SD*)**	
1 – Hs	75.85 (16.10)	69.05 (12.61)	0.007**
2 – D	91.89 (18.58)	77.80 (16.65)	0.0001***
3 – Hy	74.21 (13.13)	68.34 (10.64)	0.003**
4 – Pd	80.27 (15.40)	78.19 (13.43)	0.398
5 – MF	63.38 (10.28)	57.97 (14.22)	0.013*
6 – Pa	76.11 (15.68)	71.36 (11.87)	0.038*
7 – Pt,	84.84 (19.01)	73.20 (13.00)	0.0001***
8 – Sc	87.37 (21.79)	75.98 (14.72)	0.0001***
9 – Ma	63.78 (13.52)	67.12 (12.74)	0.136
0 – Si	65.43 (13.26)	63.24 (15.88)	0.383
Validity scales			
Lie L	47.26 (7.36)	50.71 (10.96)	0.023*
Infrequency F	79.28 (16.52)	74.34 (14.48)	0.063
K-correction	50.11 (8.20)	56.17 (13.00)	0.002**

Note: *p <0.05, **p <0.01 and ***p <0.001, Mean and standard deviations for both male and female participants in the MMPI personality variables are presented.

5.2.4.2 Results of multi-way analysis of covariance of the association between MMPI and gender

Personality tests were separately analysed whilst adjusting for education level, polysubstance use, and age of onset of regular substance use. Table 15 outlines the differences between male and female participants and results for the main effects of the multi-way analysis of covariance. Gender was significantly associated with the Depression, Psychastenia, Hysteria, Schizophrenia, Hypochondriasis and Masculinity-Femininity scales. Depression in men was significantly more severe than that in women. Men scored significantly higher than women in Hysteria Scale. Similarly, in the Psychasthenia, Schizophrenia, and Hypochondriasis scales men scored higher than women. In the Masculinity-Femininity scale, men scored significantly higher than women. Both genders scored clinically high on the Psychopathic Deviate and Paranoia scales. On the Hypomania scale, women had clinically high scores, whereas men's scores were at a nonclinical level. Women scored higher than men in the Validity Scale K.

Table 15. Results of multi-way analysis of covariance of the main associations between MMPI personality and gender

MMPI personality variables	Gender differences	
Clinical scales	F_{141}	*P*-value
1 – Hs	6.98	0.0092*
2 – D	18.84	< .0001***
3 – Hy	8.55	0.0040**
4 – Pd	0.27	0.61
5 – MF	4.90	0.028*
6 – Pa	2.87	0.093
7 – Pt	14.20	0.0002**
8 – Sc	11.26	0.0010**
9 – Ma	2.99	0.086
0 – Si	0.88	0.35
Validity scales		
Lie (L)	3.20	0.076
Infrequency (F)	2.33	0.13
K-correction	10.78	0.0013**

Note: *p <0.05, **p <0.01 and ***p <0.001

Even whilst considering education level, age of onset of regular substance use, and polysubstance use as covariables, significant differences between male and

female participants remained (see Table 16). Gender differences and personality variables was not related of education level except Hypomania scale. The values of the Hypomania scale diminished with higher education levels. In addition, considering gender and the covariable of the onset age of regular substance use, participants with early onset of regular substance use had both lower and higher values, which tended to diminish with later onset age. Gender and the covariate of. polysubstance use was associated with higher values of Paranoia, Psychasthenia, and Hypomania scales. Considering gender and age of onset of regular substance use as a covariable, significant differences were found in the validity scale of Lie. A later age of onset of regular use was associated with a higher t-score. Meanwhile, the validity scale of Infrequency significantly correlated with polysubstance use, with polysubstance users scoring higher than patients who did not engage in polysubstance use.

Table 16. Results of multi-way analysis of covariance of associations between MMPI personality variables and covariates

Personality variables	**Education level**		**Age of onset of regular use**		**Polysubstance use**	
Clinical scales	F_{141}	*P*-value	F_{141}	*P*-value	F_{1n1}	*P*-value
1 – Hs Hypochondriasis	0.31	0.82	0.00	0.95	0.49	0.48
2 – D Depression	0.43	0.73	0.62	0.43	0.36	0.55
3 – Hy Hysteria	1.23	0.302	0.16	0.69	2.71	0.102
4 – Pd Psychopathic Deviate	1.41	0.24	1.02	0.32	3.44	0.066
5 – MF MasculinityFemininity	1.12	0.34	5.73	0.018*	0.32	0.57
6 – Pa Paranoia	1.12	0.34	0.00	0.97	5.33	0.023*
7 – Pt Psychasthenia	0.06	0.98	0.04	0.84	4.23	0.041*
8 – Sc Schizophrenia	1.92	0.13	0.02	0.88	3.06	0.082
0 – Si Hypomania	3.41	0.019*	0.18	0.67	9.22	0.0029**
0 – Si Social Introversion	1.35	0.26	0.00	1.00	0.67	0.42
Validity scales						
Lie (L)	0.15	0.93	4.70	0.032*	0.95	0.33
Infrequency (F)	2.41	0.070	0.74	0.39	6.00	0.016*
K-correction	0.91	0.44	0.01	0.90	0.19	0.66

Note: Association is significant at the level 0.05, ** Correlation is significant at the level 0.001, *** Correlation is significant at the level <0.000

5.3 Neuropsychological performance in patients with SUD with and without mood disorders (Original article III)

5.3.1 Demographic characteristics

The group of participants with co-occurring SUD and mood disorder (SUD+MD) included 88 patients, and the group of participants with SUD but without mood disorder (SUD-MD) included 76 patients. Overall, the SUD+MD included 52 (59%) participants who only used one substance (i.e. alcohol, sedatives, stimulants, or opioids) and 36 (41%) participants who used multiple substances (i.e. alcohol, sedatives, cannabis, opioids, stimulants, other psychoactive substances and/or depressants). The SUD-MD group comprised 39 (51%) single substance users and 37 (49%) polysubstance users.

In SUD+MD group, 19 (21.6%) participants were diagnosed with BD and 69 (78.4%) were diagnosed with depression. More clinical information is presented in Table 17, which shows that the two groups were comparable in all variables. There were no differences between groups in the demographic and substance use variables under study, nor in premorbid IQ.

The ages of participants in the SUD-MD group ranged from 19 to 65, with mean age of 37.8 (standard deviation (SD) = 11.9). The ages of participants in the SUD+MD group ranged from 20 to 60, with mean age of 39.1 (SD = 10.3).

Table 17. Clinical Information for the SUD-MD and SUD+MD groups.

	SUD-MD n= 76	**SUD+MD n=88**
Age in years	37.8 (11.9)	39.2 (10.3)
Number of women	34 (50.7 %)	33 (49.3 %)
Premorbid IQ (Vocabulary subtest, WAIS-R)	8.46 (3.10)	9.07 (2.41)
Number of participants with learning difficulties	36 (51.4 %)	34 (48.6 %)
Age of onset of regular substance use in years	21.2 (11.3)	23.5 (1.0)
Duration of substance use in years	16.1 (9.4)	15.7 (8.8)
Duration of polysubstance use in years	8.2 (8.0)	10.7 (7.1)
The age that participants started treatment in years	33.1 (12.3)	36.2 (10.3)
Duration of mood disorder		4.4 (4.5)
Age of onset of affective disorder in years		35.2 (11.1)
Treatment motivation		
Agreed to follow-up care	62 (83.8 %)	74 (84.1 %)
Treatment plan completed	62 (83.8 %)	75 (85.2 %)

Note: For continuous numerical variables means and standard deviations are presented, for categorical variable counts and percentages

5.3.2 Comparisons between the SUD-MD and SUD+MD groups in neuropsychological test results with normative data and Comparisons between the SUD-MD and SUD+MD groups

The results of neuropsychological assessments in the SUD-MD and SUD+MD groups are summarised in Table 18, Table 19, and Table 20. Normative reference frames were obtained from the WAIS-R (Wechsler et al., 1975) and WMS-R (Wechsler, 1987), a previous CogniSpeed study (i.e. Revonsuo, 1995), and age-based index of the RPM. There were no comparable previously conducted CogniSpeed studies with a relevant normal reference frame, except for the Revonsuo (1995) study. In the Revonsuo study (1995), the median age of the control group was 67.7 (range 62–75). The group differences were presented as p-values of the T-test based on a previously published study (Original article III).

The WAIS-R reference frame for these subtests was the 20–34 age group, which was the only age-based reference frame available. The reference frame for the Digit Symbol test was obtained from the WAIS-IV test, and it was age based. For the WMS-R, the reference frame values for the indices Verbal Memory Index, Visual

Memory Index, and Delayed Memory Index were all age based. For other subtests of the WMS-R, values for the 36–45 age group were presented. The median age of the SUD-MD group was 36.0 years, whereas the median age of the SUD+MD group was 40.5 years.

Additional analyses of the WAIS-R and WMS-R subtests and CogniSpeed tasks by age group and mood disorder (yes/no) were performed. The results of the test variables did not differ from one age group to another. The median and interquartile range for Q1–Q3 were included in the tables to better compare the values of the normal reference range. The table shows how the test values of the study group are defined, with Q1–Q3 comprising 75% of the observations. Some of the tests were performed on only a small number of subjects.

The Vocabulary subtest of the WAIS-R was used to assess premorbid IQ. Results for the Vocabulary subtest and the RPM test for both groups were within normal reference frame (see Table 18). This was also the case for the results of the Block Design test for the SUD-MD and SUD+MD groups, although the results for the SUD+MD group were significantly weaker. Notably, performance in the DST was below normal average for both SUD-MD and SUD+MD groups, although the SUD-MD group was significantly faster. The SRT median of both groups was also slower than that in normal controls of 67.7 years. The study groups differed significantly in tests of Digit Symbol, Block Design and processing speed variables of SRT.

In regard to CogniSpeed tasks of inhibitory capacity and executive functions (see Table 19), the medians of IN and Stroop Interference in the SUD+MD group were slower than normal controls of 67 years (Revonsuo, 1995). Stroop Interference values for both groups were also slower than normal controls of 67 years. SUD+MD patients differed significantly from SUD+MD patients in the IN task.

The median scores of the Digit Span Forward, the Digit Span Backward, Visual Memory Index, Delayed Memory Index, and subtest of the Immediate Visual Learning in participants with SUD–MD was found to be below in the normal range (see Table 20). Correspondingly, in SUD+MD patients the median scores of the Digit Span Forward and Backward, Visual Memory Index, Delayed Memory Index and subtests of Delayed Associate Learning, Immediate Visual learning, and Delayed Visual Reproduction were below values of normal reference frame. No significant differences were found between the SUD-MD and SUD+MD groups in measures of attention and memory tasks.

Table 18. Comparisons of neuropsychological measures of premorbid intelligence, processing speed and perceptual reasoning between the groups and normal reference frame added for level evaluation

		SUD-MD		SUD+MD		
Cognitive domain	Normal reference frame WAIS-R subtests; Age group 20-34 WAIS-IV Revonsuo, 1995 The median age of the control group 67.7 (range 62–75)	N	Median (Interquartile range 25–75%)	N	Median (Interquartile range 25–75%)	P-value (T-test)
Premorbid intelligence Vocabulary	8–12 (WAIS-R)	75	9 (6–11)	87	9 (8–11)	0.25
Processing speed Digit Symbol Test	8–12 (WAIS-IV)	42	6 (4–9)	58	4 (2–6)	0.012**
Simple reaction time (SRT), ms	308 (range 248–389) (Revonsuo,1995)	66	346.5 (322.0–445.8)	86	377.0 (346.3–468.8)	0.012**
Perceptual reasoning Block Design Test	8–12 (WAIS-R)	29	9 (6–11)	35	8 (5–9)	0.049*
Raven's Progressive Matrices	90–100 (Raven, 1992)	64	100 (90–111)	85	98 (90.3–105.8)	0.54

Table 19. Comparisons of neuropsychological measures of Inhibitory capacity and executive functions between the groups and normal reference frame added for level evaluation

		SUD-MD		SUD+MD		
Cognitive domain	Normal reference frame Revonsuo, 1995	N		N		P-value (= Mann-Whitney U-test)
Inhibitory capacity						
Neutral Condition (COL)						
COL ms	614 (range 445-810)	66	541.5 (483.5–624.9)	86	578.5 (493.0–708.5)	0.09
errors	1.6% (range 0%-6%)	66	1.0 (0.0.-2.3)	86	1.0 (0.0–3.0)	0.74
Congruous Word Condition (CON)						
CON ms	564 (range 412-753)	66	504.0 (84.0–162.3)	86	548.0 (479.5–642.8)	0.17
errors	1.6% (range 0%-6%)		1.0 (0.0–2.0)	86	1.0 (0.0–2.0)	0.26
Incongruous Word Condition (IN)		65				
IN ms	678 (range 446-1311)	65	631.0 (526.5–784.0)	86	724.5 (582.3–921.0)	0,028**
errors	1.3 % (range 0 %-6 %)		1.0 (0.0–3.0)	86	1.5 (0.0–4.0)	0.41
Executive functions						
Stroop Interference	64 (range -62 -+671)	65	74.00 (29.0–152.5)	85	84.0 (25.0–214.5)	0.35
Total Stroop effect	114 (range 12–604)	65	94.00 (29.5–162.0)	85	119.0 (48.0–241.5)	0.19

Note: *p < 0.05, **p < 0.01 and ***p < 0.001

Table 20. Comparisons of neuropsychological measures of attention and memory between the groups and normal reference frame added for level evaluation.

		SUD-MD		SUD+MD		P-value
Cognitive domain	Normal reference frame 36-45 years WMS-R	N	Median (Interquartile range 25–75 %)	N	Median (Interquartile range 25–75 %)	T-test
Attention						
Digit Span Forward	9	75	6 (5–6)	87	6 (5–7)	0.21
Digit Span Backward	9	75	5 (4–5)	87	5 (4–5)	0.50
Verbal Memory and Learning						
Immediate logical memory	25–26 (22–30)	31	27 (20–33)	35	26 (19–30)	0.68
Delayed logical memory	21–22 (17–27)	30	21 (13–29)	35	22 (15–24)	0.87
Immediate Associate Learning	19 (17–21)	31	18 (14–23)	35	17 (14–20)	0.25
Delayed Associate Learning	7–8	29	7 (5–8)	34	5 (3–6)	0.31
Verbal Memory Index	90–110	30	99 (91–113)	36	98 (81–103)	0.58
Visual Memory and Learning						
Immediate visual learning	15 (14–17)	30	12 (6–15)	34	12 (6–15)	0.93
Delayed visual learning	5–6	29	5 (3–6)	34	5 (3–6)	0.74
Immediate visual reproduction	36 (34–38)	31	37 (33–38)	34	34 (30–38)	0.13
Delayed visual reproduction	33–34 (30–37)	29	31 (23–37)	35	29 (21–36)	0.45
Visual Memory Index	90–110	30	83 (60–104)	34	69 (59–90)	0.11
Delayed Memory						
Delayed Memory Index	90–110	29	86 (62–100)	35	85 (66–95)	0.66

5.3.3 Covariance analyses of neuropsychological tests

For the variables that were deemed significant in the original analysis, group differences were further examined through covariance analyses of neuropsychological tests, adjusting for age, level of education, learning difficulties, and polysubstance use..

The greatest differences were observed between the SUD+MD and SUD-MD groups on the Digit Symbol and Block Design tests. Performance on the DST was most impacted by mood disorders ($F_{91} = 4.90$, $p = 0.029$), adjusting for age ($F_{91} = 3.32$, $p = 0.072$), polysubstance use ($F_{91} = 0.26$, $p = 0.61$), education level ($F_{91} = 1.54$, $p = 0.21$), and learning difficulties ($F_{91}= 1.54$, $df = 91$, $p = 0.22$).

In addition, performance on the Block Design Test exhibited an independent relationship with mood disorders ($F55 = {}_{4.49}$, $p = 0.044$), adjusting for the effects of polysubstance use ($F_{55} = 0.38$, $p = 0.54$), education level ($F_{55} = 1.43$, $p = 0.24$), learning difficulties ($F_{55} = 3.27$, $p = 0.083$) and age ($F_{55} = 3.35$, $p = 0.074$). Although the Block Design Test was administered to for a smaller subset of participants (one third of the overall sample), the difference between the SUD-MD and SUD+MD groups was large and significant.

The relationships between mood disorders and CogniSpeed performance (as measured through SRT and IN) were also examined through covariance analyses. No interactions with mood disorders were found when adjusting for polysubstance use, education level, learning difficulties, and age.

6 Discussion

6.1 Methodological considerations

This thesis consists of three separate studies. The first study explored the impact of the age of onset of regular substance use on neuropsychological test performance. The second study focused on the differences in neuropsychological test performance and personality test variables between men and women diagnosed with substance abuse. The third study examined differences in the neuropsychological tests of two groups – those with a substance use disorder and mood disorders and those with substance use disorder without mood disorders. The data collection method was naturalistic and observational.

The study sample consisted of patients with SUD who were admitted to the Järvenpää Addiction Hospital in a specific time period. Therefore, the study sample accurately represented the clinical substance use population because patients come from hospitals all over Finland.

The study sample was heterogenous with regard to age, education, and substance use diagnoses. It was possible that these covariates correlated with each other. Therefore, interactions between covariates were added to the model. The multicollinearity indices in statistical analyses were tolerable.

Associations between the selected neuropsychological tests and independent factors were carefully controlled for by adjusting for confounding factors and using specific exclusion and inclusion criteria. The selected covariates were education level, learning disabilities, polysubstance use, and calendar age. The effects of SUD on memory are particularly strong amongst participants with fewer years of education (Weinborn, 2011). In the present study, the tests of vocabulary correlated with education.

With regard to age, a study that used the WAIS and CogniSpeed tests to assess healthy individuals aged 39 to 82 years found that performance on the Digit Symbol and Block Design tasks slows with age (Portin, Raija et al., 2000). In this thesis, calendar age was controlled in neuropsychological tests without age correction norms (e.g. CogniSpeed SRT tasks, COL, CON, IN, Block Design Test, and Delayed Visual Learning test).

Learning disabilities was one of the covariates because some impairments may be more related to premorbid factors, such as premorbid cognitive differences (Latvala et al., 2009b; Penick et al., 2010). Learning disabilities, especially childhood ADHD, are associated with alcohol and polysubstance use disorders in adulthood and nicotine use in adolescence (Charach, Yeung, Climans, & Lillie, 2011).

With regard to polysubstance use, this study did not aim to quantify different intoxicants but rather to have a more realistic subsample of substances. The subsample of participants who engaged in polysubstance use was not tested at regular intervals or monitored in detail in terms of different substances and substance use rates. The diagnoses of polysubstance users generally varied in their combination of substances, which made it difficult to investigate the effects of any single substance. Each substance presented a different pattern of cognitive deficits; hence, this was a major limitation of the analysis. Moreover, patients underwent detoxification from benzodiazepine and analgesics.

In this study, the MMPI test was not completely independent of education and variables related to substance use, such as age of onset of substance use and polydrug use. Taurino et al. (2021) speculated that socio-emotional factors influence outcomes of the MMPI-test. It is therefore important to compare further MMPI test responses across cultures and social groups. It is also valuable to combine the MMPI test with other personality surveys and measures, such as in Taurino et al.'s (2021) study. In future research, it would be useful to investigate the associations between personality variables, mood, and neuropsychological test performance similar to what Walvoort (2012) has done.

Several neuropsychological functions were more impaired in SUD and SUD with mood disorders than that in normal reference groups. Notably, it is also likely that hospital patients need more support than, for example, outpatients with substance abuse problems. Outpatients are better able to cope with everyday challenges and work life. By contrast, inpatients were admitted because it was deemed that they would not be able to stay the required month of abstinence without the hospital's structural support. In future research, it is important to evaluate how hospitalized patients differ from those with milder substance abuse problems.

One of the strengths of the present study was the comprehensive and clinically relevant administration of neuropsychological tests, although demanding tests increases missing data. The number of patients allotted to the different neuropsychological tasks varied; it was lower for memory and learning tasks. The aims of the neuropsychological assessments were different for different patients; some assessments were part of a more exhaustive evaluation of working ability, whilst others were part of a more limited therapeutic evaluation. Jokinen (2007) revealed that neurological patients with missing values were older and had, for

example, less education and more neurological impairments (Jokinen, 2007). In this thesis, overall, the amount of missing data was low. No imputations were done. No further analyses of the missing tests were performed as part of this dissertation, because neuropsychological studies were performed to varying extents depending on the purpose of the testing.

The participants consisted of hospital patients who were carefully diagnosed by psychiatrists who specialised in SUD and used ICD-10 criteria. The duration of abstinence was determined through laboratory tests.

6.2 Discussion of the results

6.2.1 Age of onset of substance use and neuropsychological performance (Original article I)

Age of onset of substance use was related to the deterioration of performance in neuropsychological tests of processing speed, perceptual reasoning, and visual memory and learning. Processing speed and age of onset of substance use were significantly associated amongst EOAs; the earlier the substance use began, the slower the processing speed. However, delayed visual learning and perceptual reasoning were more impaired amongst LOAs than EOAs.

The results aligned with those of studies that were long-term in nature and had a larger number of participants, although the number of subjects in this cross-sectional study was modest. The results concord with brain maturation timing and developmental peaks in different parts of brain (Gogtay et al., 2004; Hanson et al., 2011). The regions that are more associated with primary functions (e.g. primary motor cortex) develop earlier than the regions involved in more complex and integrative cognition (i.e. temporal and prefrontal lobe; Gogtay et al., 2004).

The results of Hanson et al.´s (2011) study suggest that the development of learning and memory continues beyond age 20. Increased substance use after a period of lower use in late adolescence or early adulthood appears to have a negative impact on verbal learning and memory and verbal attention. A peak in heavy alcohol and substance use in late adolescence is also associated with a decline in visuospatial memory. Hanson et al. (2011) suggested that group differences in free recall are not primarily a function of differential learning amongst groups but rather reflect difficulty with recalling or recognising information. This result was also found in this study; the delayed visual learning test was more impaired than the immediate visual learning. Delayed visual learning test is related to memory retrieval.

Weaker performance in perceptual reasoning amongst LOAs was understandable due to impaired prefrontal function. Performance in perceptual reasoning can be lower in patients with frontal impairment, because their performance is often

impulsive, careless, and concrete (Lezak, 1995). This result aligns with the research of Joos et al. (2013), who found that early onset participants with AUD generally performed as well as or even better than late onset participants with AUD, especially in visual tests. Hanson et al. (2011) established that neuropsychological functions improve after the cessation of substance use in adolescence, which implies that the frontal and temporal areas and the parietal regions continue to mature beyond adolescence. Significant neurodevelopment occurs in the period between mid-adolescence and the mid-20s; this can be affected by increased substance use in late adolescence. Neural networks and brain reorganisation are modifiable throughout a person's lifespan and are not only limited to early phases or young adulthood (Pfefferbaum, 2014).

In addition, in the current study, poorer performance on the Raven test was associated with learning difficulties. The latter were suggested to be present before the age of onset of substance use, although the effects of substance use can be exaggerated through 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 associated with later alcohol dependence and failure to recover in men included neurological problems, the need for special education at school, and poorer attention measures (e.g. WAIS Digit Span Backward and Forward; Penick et al., 2010).

Amongst predisposing risk factors for SUD, premorbid poor learning and inhibitory capacity have been suggested to be important. Conversely, a high level of education may be a protective factor for cognitive performance in patients with SUD. Processing speed was also related to an individual's level of education. Higher education levels were associated with later age of onset and suggested to be a protective factor that postponed age of onset. The protective effects of higher education and occupation-based social class on cognitive ability have been previously demonstrated in longitudinal studies (Alarcon et al., 2015).

In addition to later age of onset of substance use, ageing seems to aggravate inhibitory capacity. In this study, inhibitory capacity assessed in the CogniSpeed task did not align with the results of Ngyuen-Louie et al. (2017) that earlier and regular alcohol consumption lead to worse executive function (i.e. inhibition ability and Digit Span Backward). Results on measures of executive function have suggested that the impairment of prefrontal function is present before the onset of substance abuse (Squeglia et al., 2014; Tarter et al., 2004). Adolescence is an important phase in the development of executive functions in the brain, but inhibitory control may weaken prior to adolescence and the onset of substance use (Conrod & Nikolaou, 2016; Squeglia,et al., 2014). It is possible that the early onset of substance abuse is

a consequence of problems with executive and attentive functions and poor learning capacity. The findings suggest that, when an individual's capacity to self-regulate is initially poor, substance abuse can exacerbate self-regulation problems.

Some studies have probed into age of onset continuously (Crane et al., 2015; Nguyen Louie et al., 2017; Solowij et al., 2011), while the study of Capella, Benaiges, and Adan (2015) examined the most sensitive measure of age of onset, which is at the age of 16. The results of this thesis support that of previous studies where the association between age of onset of substance use and neuropsychological impairments is a linear and positive variable. In contrast to previous studies (Joos et al., 2013; Kist et al., 2014), age of onset of regular use was treated as a continuous variable. From a statistical perspective, tests for associations are most powerful when using continuous variables, if possible.

Alcohol was the most commonly used substance amongst both single-substance and polysubstance users. Therefore, the results were mainly compared with those of studies that examined cognitive impairment caused by alcohol use and the concomitant use of alcohol and other intoxicants.

6.2.2 Gender differences in cognitive and personality functioning in patients with SUD (Original article II)

This study examined cognitive and personality differences between men and women and assessed the impact of education level, age of onset of regular substance use, and polysubstance use on cognition and personality features in a sample of hospitalised, middle-aged addiction patients with a diagnosis of SUD.

No differences were observed in neuropsychological functioning between men and women After controlling for the effects of education level, duration in years of regular substance use, and polysubstance use, all other differences between male and female participants disappeared, and no correlations or interactions with substance use variables were found. The results do not support the findings of previous studies that women’s cognitive functions are more susceptible to the effects of alcohol and substance use than men’s are (Mulder, 2002; Tuchman, 2010).

Regarding personality variables, there were several differences between male and female participants. Controlling for the impact of education level, age of onset of regular substance use, and polysubstance use, men reported more severe personality and emotional problems than women in scale values of Depression, Psychastenia, Hysteria, Schizophrenia, Hypochondriasis and Masculinity-Femininity. Men had higher scores than women on the Depression scale. On the Psychasthenia scale, men tended to be more anxious, tense, and agitated than women. In the Hypochondriasis and Hysteria scales, men viewed themselves as physically ill more often than women and tended to lack insight on somatic

symptoms or indications of psychological components with regard to their conditions. Similarly, Schizophrenia scale values amongst male participants were significantly higher than amongst female participants, which suggested the possibility of a psychotic disorder, confusion, disorganisation, and disorientation. On the Masculinity-Femininity scale, men exhibited higher values than women, which indicated a lack of stereotypically masculine interests. By contrast, values amongst female participants indicated a tendency towards more stereotypically masculine than feminine interests. Values on the K-correction scale (i.e. a validity scale) were higher amongst female participants, which suggested that they denied their symptoms and problems more than male participants.

In this study, results on gender differences in personality did not align with previous findings on negative emotionality, which suggested that women with high negative emotionality, anxiety, and depression were more susceptible to alcoholism than men (Mellos et al., 2010; Mulder, 2002; Tuchman, 2010). In this study, men exhibited more characteristics of negative emotionality, such as depression, anxiety, tension, and disorganised thinking.

Results of the current study contrast that of to the study of Taurino's (2021) study in which women showed significantly higher scores in MMPI-2 in clinical scales Hypochondriasis, Depression, Hysteria, Psychastenia, and Schizophrenia. In Taurino's study, women also obtained higher scores in the scales Psychopathic Deviate, Paranoia, and Hypomania, whereas data in the current study indicated that these scales do not differ significantly. Researchers have speculated that socio-cultural factors influence the scoring of scales, thereby reinforcing or prohibiting the use of certain defences via socialization patterns.

Results on gender differences in personality in this study also did not support previous findings on paranoia and psychopathic personality characteristics. No significant differences were found between men and women on the Psychopathic Deviate and Paranoia scales. The result regarding the Paranoia Deviate scale contradicts previous findings, which indicated that women were more paranoid than men (Graham, 1993). In fact, participants of both genders had similar scores on this scale – also a finding that differs from previous research (Mellos et al., 2010).

In the present study, personality factors seemed to be independent of education level, except for the Hypomania scale. Values on the Hypomania scale decreased with higher education levels. Participants with higher education levels, however, scored moderately above average. Patients tended to easily grow bored and restless, and their tolerance for frustration was quite low, which suggests that participants of both genders exhibited features of hyperactivity and short attention span.

Moreover, personality factors seemed to be independent of age of onset of regular substance use, except for the Masculinity-Femininity scale. Participants with early onset regular substance use had both lower and higher values on this scale,

which tended to decrease with later onset age. Thus, these results suggest that deviance from traditional masculine and feminine interests may be a risk factor for substance abuse.

In previous studies no unique alcoholic personality or personality measures which are specific to later AUD have been found, although several risk factors have been identified for AUD (Mulder, 2010; Walvoort et al., 2012). These risk factors are impulsivity/novelty seeking and neuroticism/negative emotionality, antisocial behaviour and hyperactivity (Mulder, 2010; Valwoort, 2012). Anxiety and comorbid mood disorders are most prevalent in women with alcohol use disorder (Kessler, 1997; Mulder, 2002; Mellos et al., 2010; Tuchman, 2010; Virtanen, 2021), whereas substance abuse and antisocial personality disorders are most frequent in men (e.g. Kessler, 2010).

Personality traits have been studied in substance abuse research because they are thought to represent endophenotype (Soronen, 2014), which facilitates the identification of genetic factors that underlie psychiatric illnesses. An endophenotype is multifactorial, as it is affected by an individual's genes, their environment, and the interaction between these two factors. Although the heritability of depression is relatively high (i.e. less than 50%), no genes that play a role in the disease have been identified.

Personality traits are strongly associated with depression; of these, the most likely candidate for an endophenotype of depression is neuroticism (Soronen, 2014). For example, Beck's Depression Scale (BDI) and Eysenck’s Personality Inventory (EPI) consider behavioural and neurocognitive performance manifestations as endophenotypes of depression. Belcher et al. (2014) created a heuristic model for the endophenotype of SUD by identifying three personality traits linked to specific brain systems and examining the environment to determine an individual's degree of vulnerability to SUD development. These personality systems are positive emotionality/extraversion (PEM/E), negative emotionality/neuroticism (NEM/N), and high/low constraint (CON). Individuals with low PEM/E, high NEM/N, and low CON are considered to be the most vulnerable (i.e. least resilient) to SUD, whilst individuals with high PEM/E, low NEM/N, and high CON were considered to be the least vulnerable (i.e. most resilient) to SUD (Belcher, Volkow, Moeller, & Ferré, 2014).

Although the MMPI used in this study measured different personality traits than the Multidimensional Personality Questionnaire (MPQ) used in Belcher et al.'s study, results concerning negative emotionality were consistent with those in Belcher et al.'s study. In particular, men with negative emotionality were suggested to have less resilience and more vulnerability to SUD. Women also had elevated negative emotionality. It is likely that cultural environment also increases negative emotionality in men. It is likely that the threshold for men to seek help is higher, that

they delay entering treatment longer, and that the depression they experience is worse compared to women. Few research has been done in Finland and in Nordic countries focusing on gender differences, effects of excessive alcohol use, and mood disorders (Agardh et al., 2017).

An early growth environment is also important for the emotional development of children and adolescents. Graham (1993) did not mention factors related to the early growth environment (e.g., the effect of dysfunctional family relationships on the dimensions of MMPI) but noted that on the Hysteria scale, for example, there is often a rejecting parent in the children's life history. Graham (1993) also mentioned problems with authorities concerning the Psychopathic Deviate and Psychasthenia scales. Similarly, Carlson et al. (2009) affirmed that harsh parental treatment can lead to both misconduct and depression, although neither form of pathology stems solely from parental harshness. The dissertation of Salokangas (2020) affirmed that childhood adversities and trauma experiences are significantly linked to mood and anxiety disorders, suicidality, and alcohol problems. The effect of childhood trauma on alcohol problems is mainly mediated by depression.

Carlson et al. (2009) acknowledged that emotion regulation is at the core of early socioemotional experience. Longitudinal studies have established the association between well-functioning affective attunement in early childhood and adaptive functioning across development. This association also emerged in several SUD studies of SUD risk factors, indicating that dysfunctionality in the early growth environment and intergenerational problems are risk factors for maladaptive defences and substance use.

6.2.3 Neuropsychological performance of patients with SUD with and without mood disorders (Original article III)

After one month of abstinence, patients had clinically recovered from acute symptoms of mood disorder and the acute detrimental effects of substance use. In the SUD+MD group, participants showed reduced visuospatial reasoning performance in the Block Design Test and reduced psychomotor speed in the Digit Symbol Test. These results suggest that mood disorders impact visuospatial reasoning and psychomotor speed more than SUD.

No significant differences were found between the SUD-MD and SUD+MD groups in memory task measures: verbal, visual, and delayed memory. Both groups were equally impaired; visual memory performance was below average in both groups. Clinically, performance on Visual Memory Index was worse in the MD+SUD group than in the SUD-MD group. This suggests that SUD impacts memory more than mood disorders and contradicts the findings of Hunt et al. (2015).

Both the SUD-MD and SUD+MD groups exhibited deficits in processing speed on CogniSpeed tasks compared to healthy controls. The deterioration in performance likely involved the use of a single substance, mostly alcohol. The mean age of SUD-MD patients was 38, whilst the mean age of SUD+MD patients was 39; however, the processing speed of both groups was at the same level as normal 67-year-olds (Revonsuo, 1995).

The results of this study align with those of previous research in which patients with depression experienced problems with psychomotor speed (Bora, Harrison, Ycel, & Pantelis, 2013; Lee, Hermens, Porter, & Redoblado Hodge, 2012) and a deterioration in visuospatial performance (Jeste et al., 1996). The findings also align with those of studies on depression and cognitive functioning in alcoholism (Uekermann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003), BD in alcoholism (Levy et al., 2008), and BD in SUD (Marshall et al., 2012). SUD+MD patients demonstrated more severe and/or widespread neurocognitive deficits than SUD-MD patients. This result is consistent with previous studies that suggested that dual diagnosis of BD and comorbid addictions resulted in more severe symptoms (Balanzá-Martínez, Crespo-Facorro, González-Pinto, & Vieta, 2015) and that there are more severe impairments in the neurocognitive functioning of BD patients with comorbid AUD (Levy et al., 2008; Levy et al., 2012; Marshall et al., 2012; Sanchez-Moreno et al., 2009; van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998). Significant neurocognitive impairment with AUD has also been observed in BD II patients (McElroy et al., 2001; Sole et al., 2012).

The dual-diagnosis BD group exhibited executive deficits, as reflected in a number of completed categories in the Wisconsin Card Sorting Test (WCST; (Levy

et al., 2012; Levy et al., 2008; van Gorp et al., 1998), the Stroop test (Levy et al., 2012; Sanchez-Moreno et al., 2009; Levy et al., 2008), verbal fluency (Levy et al., 2012), Trail Making B (Levy et al., 2012) and conceptual reasoning and set-shifting (Marshall et al., 2012). In addition, patients have demonstrated impairments in verbal memory (Levy et al., 2012; Levy et al., 2008), and visual memory (Levy et al., 2012; Marshall et al., 2012).

In contrast to previous studies, visual memory was found to be below the normal average in both the SUD+MD and SUD-MD groups. Results for Visual Memory Index were clearly clinically below average in the SUD+MD group and slightly below average in the SUD-MD group. Contrary to previous studies, the processing speed task in the present study was most powerfully impacted by mood disorders. In previous studies, educational level and gender were included as covariates in the analysis, but age, learning difficulties, and polysubstance use were not controlled for. In this study, age, education level, learning difficulties, and polysubstance use were controlled for; thus, the potential influence of these variables on neurocognitive results can be ruled out. The clinical groups were balanced with regard to gender.

It is probable that the balancing of study groups and analysis covariates had an impact on the results. For example, all clinical and control subjects were men in Gorp et al.´s (1998) study. Levy et al. (2008) found no group differences with regard to gender or years of education. The dual-diagnosis group in full remission was older than the group of participants with current alcohol dependence, but these discrepancies between study groups were not studied; in fact, they were included as covariates in the statistical analyses. Levy et al. (2012) controlled for hospitalisations and age of onset of alcohol use.

Neurocognitive disorders associated with depression were milder relating to co-occurring depression and substance use. In several studies, only visual memory was impaired in the dual-diagnosis patients. Hunt et al. (2015) found that measures of executive functioning in comorbid groups were below the norm but not significantly so. In this study, a comorbid SUD, alcohol, and mood disorder group demonstrated significantly greater slowing of inhibitory capacity compared to participants who did not have mood disorders.

Only one previous study identified the DST in co-occurring depression and alcohol use (Schafer et al., 1991); another study identified the Block Design Test (Hunt et al., 2009). Poorer functioning in the DST significantly correlated with the increasing severity of depressive symptoms. A relationship was also found between worse depressive symptoms and poorer performance on the Block Design Test. However, a limitation of studies on comorbid depression and alcohol studies is that they examine the relationship between the severity of depressive symptoms as a continuous measure, despite depressive symptoms not necessarily reaching the threshold for diagnosis. Participants in the review of Hunt et al. (2009) experienced

depressive symptoms, as evidenced by BDI-II total scores of ≥ 17, but not all patients have a diagnosis of depression. On the contrary, participants in studies of patients with bipolar disorder (BD; Gold et al., 2018; Cardoso et al., 2015; Levy, Monzani, Stephansky, & Weiss, 2008; Levy & Weiss, 2009; Levy et al., 2008; Levy, Manove, & Weiss, 2012; Marshall et al., 2012) all have a diagnosis of bipolar disorder. This difference may have affected the results.

Difficulties with processing speed and perceptual problems may impact prognosis and treatment. The Digit Symbol and the Block Design tests are fast and sensitive ways to examine treatment effectiveness and monitor treatment progress. For the first neuropsychological assessment, it is useful to use a wider set of tests. Follow-up studies could focus more on these tests, which measure co-occurring alcohol misuse, substance use, and mood disorders. Extensive test batteries are not needed for a retest. The Block Design test is difficult to conceptualize. A patient with the brain damage is unlikely to improve with practice alone (Lezak, 1995).

7 Conclusions

This thesis, which aims to explore neuropsychological performance in a sample of hospitalised, middle-aged addiction patients, considers the impact of alternate conditions of substance abuse, particularly age of onset of regular substance use, single and polysubstance use, and background factors (e.g. education level and learning difficulties) on neuropsychological performance.

First, the impact of age of onset of regular substance use on neuropsychological performance in patients with a diagnosis of SUD were most prominently seen in processing speed, perceptual reasoning, and delayed visual learning, considering alternate conditions of substance abuse, particularly single and polysubstance use and background factors (i.e. education level and learning difficulties). A significant association between processing speed and age of onset of regular substance use was found amongst EOAs – the earlier the age at which substance use began, the slower the processing speed. Processing speed was also related to education level; a higher level of education was associated with faster processing speed. Compared with EOAs, LOAs had weaker performance in the Delayed Visual Memory test, the Raven test for single substance users, and the Block Design test for polysubstance users. Most impaired performance in delayed visual memory was found in the least educated group of LOAs compared to higher educated groups of LOAs.

Second, women were not more vulnerable to substance-induced neuropsychological deficits compared to men. Men exhibited more severe impairment with regard to negative emotionality and personality variables than women. The most prominent personality characteristics that differentiated men from women were depression, psychasthenia, hysteria, schizophrenia, hypochondriasis, and masculinity-femininity, on all scales men scored higher than women. However, participants of both genders experienced more severe negative symptoms compared to normal reference frame of MMPI.

Third, it was found that the neuropsychological tests that were most sensitive for distinguishing patients with SUD without a mood disorder (SUD-MD) from those with SUD and a mood disorder (SUD+MD) were the Digit Symbol and the Block Design tests. Patients with a mood disorder were found to perform slower on the DST than patients without a mood disorder. Moreover, SUD+MD patients scored

lower than SUD-MD patients on the Block Design Test and exhibited more severe and/or widespread neurocognitive deficits and general brain damage than SUD-MD patients, even with the same premorbid cognitive level. These differences were most pronounced in tests of psychomotor speed and visuospatial organisation. In addition, the results of participants in both the SUD-MD and SUD+MD groups differed from those of healthy controls (as represented by normative data). Attention was below average in both groups; the Visual Memory Index and the Delayed Memory Index were the weakest cognitive domains compared to normative data. When juxtaposed against controls, these deficits were notable in their severity.

7.1 Implications for clinical practice and future research

Separate studies of this dissertation were developed from the need for clinical research. More persistently prone to disruption are neuropsychological tests that require rapid completion and tasks that require visual reasoning and learning. As such, psychologists should pay special attention to tests that measure these skills.

More longitudinal research is needed to determine the neuropsychological functions that can be improved by treatment and rehabilitation. According to studies, several factors seem to influence the outcome of rehabilitation: mood disorders and related disorders, age of onset and duration of substance use, length of abstinence, and polysubstance use. It is possible that preceding individual differences, such as inhibitory capacity, education level, and learning difficulties could explain some impairment. These considerations are important when evaluating factors that influence work ability.

The study data affirmed that it is still too early for patients with SUD to return to a work that requires processing speed, visual memory, and visual reasoning after a month of abstinence. Impaired cognitive areas make it difficult to return to work. In learning, both visual memory and verbal memory are important. Both should function normally; any impairment in either visual memory or verbal memory makes learning difficult. Research into the length of abstinence and rehabilitation needed before work resumption requires a longer-term follow-up.

Further research is needed because cognitive rehabilitation in the treatment of SUD requires a more nuanced understanding of associated impairments. Some impairments may not be recoverable with abstinence, especially if age of onset of regular use occurred early (i.e. before ages 17–22). Different substances may have different onset times in adolescence, making their effects on brain development more harmful and irreversible.

Conducting follow-up studies in Finland, especially of young drug users in different samples, is important to determine causal associations in more detail.

Volkow et al. (2016) recommended conducting more longitudinal studies of brain functions in the future because it is possible that the changes observed already existed even before the age of onset of substance use. The results cannot be altogether explained by socioeconomic status and psychiatric factors, although studies have found that lower socioeconomic status is associated with lower dopamine receptor availability – a feature seen in both SUD and other psychopathologies (Kroll et al., 2020). Follow-up studies are also needed because the human brain continues to mature throughout adolescence, and adulthood and neuropsychological functions can improve after the cessation of substance use in adolescence and adulthood.

Individual patterns and trajectories of substance use are associated with neuropsychological performance (e.g. Hanson et al., 2011). Volkow (2020) underlined the importance of personalising the treatment of SUD. Neuropsychological assessments can help to personalise interventions, taking into account individual situations.

The quality of the research population selection impacts results. For example, adolescent substance users have higher rates of early onset behavioural problems (Conrod & Nikolaou, 2016; Niemelä, 2008), adverse early social relationships in childhood (Gerra et al., 2016; Somaini et al., 2011), and poor educational performance and higher rates of school dropout (Crane et al., 2015; Fergusson et al., 2005; Penick et al., 2010; Sjölund et al., 2012), which may confound the association between substance use and neuropsychological performance. Nevertheless, substance use can impair cognitive function, school attainment, and brain development.

Future research is needed to elucidate the role of gender in the development and maintenance of SUD. Evidence suggests that there are gender differences in vulnerability to substance abuse (e.g. Virtanen, 2021). Gender differences precede individual differences, the mechanism of which is an important aspect for further exploration.

In a review, Walvoort et al. (2012) concluded that personality differences in SUD are not independent of cognitive deficits, such as inhibitory dysfunctions. Walvoort et al. (2012) also confirmed that the MMPI typology does not remain stable and that during early abstinence, the MMPI-2 scales tend to reflect symptoms of withdrawal and cognitive recovery, consequently leading to overestimating psychopathology. Therefore, it is also important to investigate the relationship between personality traits and neuropsychological functions.

Several neuropsychological functions were more impaired in SUD and SUD with mood disorders than that in normal reference groups. Similarly, hospital patients need more support than, for example, outpatients with substance abuse problems. Outpatients are better able to cope with everyday challenges and work

life. In contrast, inpatients are often admitted because it is believed that they would not be able to meet the required month of abstinence without the hospital's structural support. In future research, it is important to evaluate how hospitalised patients differ from those with milder substance abuse problems.

In this study, the MMPI test was not completely independent of education and variables related to substance use, such as age of onset of substance use and polydrug use. Taurino et al. (2021) speculated that socio-emotional factors influence outcomes of the MMPI test. It is therefore important to further compare MMPI test responses across cultures and social groups. It is also valuable to combine the MMPI test with other personality surveys and measures such as in Taurino et al.'s (2021) study.

Volkow et al. (2021) emphasised the use of appropriate verbal expressions in diagnostics and treatment planning to reduce the stigma associated with substance use and mental health disorders. Although 'abuse' was once a diagnostic category and still appears as such in some surveys, its removal from the DSM-5 in 2013 reflected a major progressive shift toward conceptualising people with addiction as having a treatable medical condition rather than being guilty of misbehaviour (Volkow, 2021).

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Original Publications

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Onset age of Substance Use and Neuropsychological Performance in Hospital Patients.
Clinical Neuropsychiatry

I

ONSET AGE OF SUBSTANCE USE AND NEUROPSYCHOLOGICAL PERFORMANCE IN HOSPITAL PATIENTS

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

Abstract

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.

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

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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

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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≥ 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.

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 bentzodiatsepines 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 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 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 (β_{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 (β_{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		[1]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

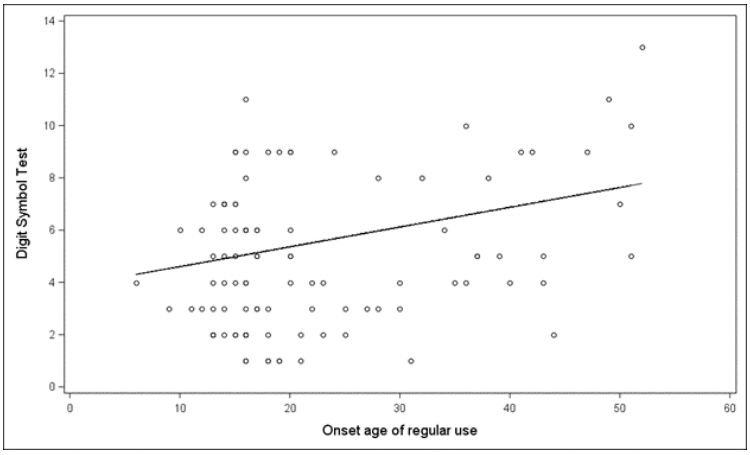
[1]Calendar age was also controlled in the model due to the lack of age correction norms. [2]Intravenous use was used as a subgroup of multidrug use (N=100) (*p <0.05, **p <0.01 and ***p <0.001).

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.

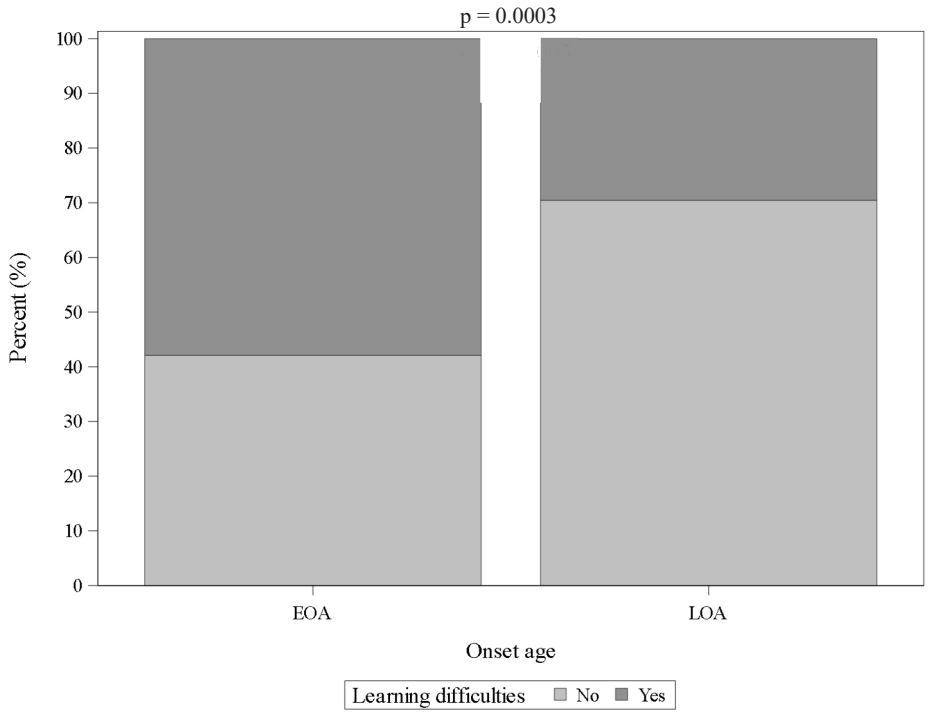
Alcohol was the most commonly used substance among both mono-substance and poly-substance users. We therefore compared the results mainly with studies that have examined the cognitive impairment caused by alcohol use and the concomitant use of alcohol and other intoxicants.

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 support 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 age16 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.

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Gender Differences in Cognitive and Personality Functioning in Patients With Substance Use Disorder

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The study was approved by the ethical committee of the A-Clinic Foundation. 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). Patients had informed consent of the aims of the study, and their participation was voluntary.

All authors have read and approved the manuscript for submission to, have made a substantial contribution to the conception and, design of the study, collection, analysis and interpretation of data, and the writing and intellectual content of the article; and acknowledge that they have exercised due care in ensuring the integrity of this work.

The authors declare no conflict of interest.

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Abstract

Objectives:
Substance abuse is associated with impairments in cognition and many serious physical and behavioral consequences both in men and women. Gender differences, however, are not clear. The aim of this study was to examine gender differences in specific neuropsychological measures and personality variables in a sample of single and polysubstance patients.

Methods:
A total of 164 hospitalized patients—97 men and 67 women—underwent neuropsychological tests of verbal capacity, attention, speed of processing, perceptual reasoning, memory and learning, executive functioning, and inhibitory capacity. Personality was measured using the Minnesota Multiphasic Personality Inventory. Associations between neuropsychological measures, personality variables, and gender differences were studied using multiway analysis of covariance controlled for regular substance use in years, onset age of regular substance use, polysubstance use, and education level.

Results:
After adjustment, all the differences between men and women disappeared in the neuropsychological tests. Men reported higher values of somatisation and emotions of depression and anxiety than women. Men were also more suspicious and elicited more disturbed thinking than women.

Conclusions:
Contrary to previous studies, women are not more vulnerable to the effects of substance use compared with men. Notably, men are more vulnerable to negative emotions than women.

Key Words: substance abuse, gender differences, inpatients, neuropsychological functions, personality

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There is a growing general awareness of substance abuse in women and the importance of gender in medical research and treatment. Biological and psychological differences between men and women may manifest differently in the cognition and personality of those with substance use disorder (SUD). Women have been found to be more susceptible than men to alcohol's effects on behavioral and cognitive functions.[1] Evidence suggest that females are more impaired in tasks of executive functions,[2,3] visual memory,[3] and wechsler adult intelligence scale (WAIS) scores.[4] In contrast, gender does not appear to influence the impairment of cognitive functions in tests of memory, attention, visuospatial ability, and language in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[5] In addition, men and women do not differ in the Montreal Cognitive Assessment (MoCA); there are no differences in visuospatial and executive functions, memory, attention, language, and delayed recall tests.[6]

Differences in personality factors between males and females with alcohol and substance users have been marginally examined. Mulder reviewed personality-based explanations in alcoholism research, interest in which increased in the 1980s. It appeared that patients with alcohol use disorder who also abuse other substances have different personality characteristics from those who do not.[7] Individuals who abuse other substances are younger, more impulsive, disinhibited, and extroverted. Moreover, studies have shown that personality may be an important mediator of the genetic effects of alcoholism. The majority of studies have centered on antisocial personality disorder and conduct disorder, while others have focused on normally distributed personality disorders. Studies have found a clear association between antisocial behavior and alcoholism;

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measures of impulsivity or novelty seeking appeared less predictive. In women, high negative emotionality may predate alcoholism. Nevertheless, personality variables explain a small proportion of the risk of dependence. Vulnerability to alcoholism is increased by poorer educational achievement, deviant peers, and general disadvantage.[7]

The results of a study of the Minnesota Multiphasic Personality Inventory (MMPI) profiles indicated that scale 4 (ie, psychopathic deviance) is likely to be elevated in individuals who abuse substances.[8] Scale 4 is typically not significantly elevated in medical patients. The 24/42 (ie, depression-psychopathic) 2-point code type is found in men with alcohol use disorder. This same code type and the 46/64 (ie, psychopathic-paranoia) code type are often found in women with alcohol use disorder. Neither of these code types is common in other medical patients who do not abuse alcohol.

Gender differences in comorbidity are also important. The prevalence of personality disorders in alcoholism ranges from as low as 22% to 40% to as high as 58% to 78%.[9] Anxiety and mood disorders are the most prevalent comorbid disorders in women with alcohol use disorder, whereas substance abuse and antisocial personality disorders are most frequent in men with alcohol use disorder. In a large sample, women diagnosed with borderline personality disorder more often than men, whereas men had higher rates of antisocial and narcissistic personality disorders than women.[10]

Previous studies have not ruled out the fact that the worst neuropsychological performance of men and women is limited to premorbid cognitive differences and education nor have they considered the impact of the onset age of regular substance use on differences in personality characteristics between men and women. The present study examined (1) the cognitive and personality differences between men and women; (2) the impact of education level, duration of regular substance use, and singlesubstance and polysubstance use on cognition; and (3) the impact of education level, onset age of regular substance use, and singlesubstance and polysubstance use on personality characteristics.

METHODS

Participants

This research is a retrospective cross-sectional study. Data was collected from patients of Järvenpää Addiction Hospital who underwent neuropsychological examination in 2004 to 2012. An abstinence period of one month was required before testing, given the longer-lasting, subacute cognitive, and neural effects of cannabis.

The inclusion criteria were as follows: (1) aged 18 to 65 years, (2) native Finnish speakers with a substance use diagnosis, and (3) minimum of one month of abstinence. Meanwhile, the exclusion criteria were as follows: (1) younger than 18 years old; (2) human immunovirus-positive patients or those having other chronic diseases possibly affecting the central nervous system; and (3) history of neurological disorder, opioid substitution treatment, or epileptic seizures.

The study group consisted of 164 hospitalized patients with SUD, both men ($n = 97$) and women ($n = 67$). No gender differences were found in age, level of education, learning difficulties, or polysubstance use. Duration of regular substance use was significantly longer in men than in women. This variable was controlled in later statistical analyses (Table 1).

The majority of subjects used alcohol as a singlesubstance, with (89.4% among men and 80.0% among women). About half of the men (48%) and more than half of the women (55%) were polysubstance users. The majority of polysubstance users abused alcohol (ie, 80.0% among men and 62.2% among women) in addition to sedatives, cannabis, opioids, and stimulants.

Experienced psychiatrists made the diagnoses following the criteria of ICD-10 based on all available information at the time of discharge. SUD diagnoses also included alcohol overuse or dependence. Data on the years of regular substance use was obtained from medical records, medical examinations, and interviews with a nurse and a social worker.

The study was approved by the ethical committee of the A-Clinic Foundation

TABLE 1. Sociodemographic and Clinical Data of the Men and Women Populations

	N	Men, N = 97, n (%)	Women, N = 67, n (%)	Statistical Test	Men vs. Women *P*
Age (mean, SD)	164	38.39 (9.73)	38.72 (12.77)	*t* test	0.86
Gender	164	97 (59.1)	67 (40.9)	χ^2	0.46
Education level					
No primary school		—	—		
Primary school		36 (37.1)	29 (43.3)		
Vocational training		39 (40.2)	15 (22.4)		
College-level education		15 (15.5)	13 (19.4)		
Higher education	164	7 (7.2)	10 (14.9)	χ^2	0.077
Learning difficulties	164	42 (43.3)	28 (41.8)	χ^2	0.85
Substance use duration, years (mean, SD)	164	17.8 (8.9)	13.0 (8.6)	*t* test	0.001***
Polysubstance users	90	53 (54.6)	37 (55.2)	χ^2	0.94

***$P<0.001$.

(23.1.2013). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation, both institutional and national, and the Helsinki Declaration of 1975, as revised in 2000 (5). Patients had informed consent of the aims of the study, and their participation was voluntary.

MEASURES

Neuropsychological Assessments

Neuropsychological testing was conducted as part of a work clinical assessment and a treatment plan assessment by the first author who is experienced in using the methods. Table 2 presents all neuropsychological measures.

The computerized CogniSpeed tasks[11] were used to measure simple reaction time and automatic and conscious information processing. The Simple Reaction Time subtest of the computerized CogniSpeed test battery was performed first. Inhibitory capacity was assessed by the CogniSpeed version of the Stroop Color-Word Test.[12] The test has 3 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 involves more conscious and effort-intensive processing. The Total Stroop Effect is the difference between reaction times in CON and IN, whereas Stroop Interference is the difference between reaction times in IN and COL.

Studies have confirmed that the CogniSpeed software is a sensitive instrument for measuring the performance of healthy participants and patients with brain disease.[11,13,14]

Personality Assessment

Personality variables were measured using the subscales of the MMPI, namely hypochondriasis, depression, hysteria, psychopathic deviate, masculinity-femininity, paranoia, psychasthenia, schizophrenia, and hypomania scales.[8,15]

Statistical Analyses

The sociodemographic data of the 2 patient groups were compared using the Student *t* test and Mann-Whitney *U* test for continuous measurements and the χ^2 test or the Fisher exact test for categorical variables. For statistical comparisons, $P < 0.05$ was considered statistically significant.

Analysis of covariance was used to study associations between

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TABLE 2. Neuropsychological Measures

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

IQ indicates intelligence quotient; WAIS, wechsler adult intelligence scale.

neuropsychological measures and men and women populations, controlling for education level, regular substance use in years, polysubstance use (yes/no), and calendar age. Analysis of covariance was also used to study associations between personality variables and men and women populations, controlling for education level, polysubstance use (yes/no) and onset age of regular substance use. Explanatory variables and interactions that do not significantly affect the primary outcome were removed from the analysis. Every neuropsychological measurement was analyzed separately. 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 analyzed by using the Statistical Package for Social Sciences software (SPSS Inc., Chicago, IL) and the

SAS System version 9.4 for Windows (SAS Institute Inc., Cary, NC).

RESULTS

Analyses of Covariance of Neuropsychological Tests

The primary differences between men and women in the neuropsychological tests are presented in Table 3.

There were significant differences between men and women in a test of Vocabulary of WAIS-R, the Digit Symbol test, and the Raven test. Women performed better in the Vocabulary test and were faster in the Digit Symbol test, while men performed better in the Raven test indicating better skills in perceptual reasoning. Performance in the Digit Symbol test was, however, below normal average for both men and women. Tests of visual memory and learning and delayed memory were also below average in both men and women. Men were clinically below average in tests of Visual Memory Index. Both men and women were as slow as 63-year and 64-year olds in tasks of Stroop Congruence and Incongruence.[12]

Neuropsychological tests were separately tested, adjusting for calendar age, education level, polysubstance use, and years of regular substance use. Calendar age was adjusted with neuropsychological test without age correction as CogniSpeed tasks of simple reaction time, COL, CON, and IN. In addition, age was adjusted with tests of WAIS-R using original data of raw scores (ie, Digit Span Forward and Backward tests, and Block Design test).

After adjustment, all the differences between men and women disappeared, and there were no correlations nor interactions with substance use variables (ie, duration of regular substance use and multidrug use) or background variables (ie, education level).

Analyses of Covariance of the Personality Test of MMPI

Personality tests were separately tested, adjusting for education level, polysubstance use, and onset age of regular substance use. Men and women differed in almost all scales. Table 4 outlines the primary differences between men and women and the results of multiway analysis of covariance.

The interpretations of the score levels of scales are based on Graham.[8] Both men and women scored moderately high ($T = 60–80$) on all clinical scales. Only women scored below 60 in the masculinity-femininity scale. The elevation of the *F* scale, combined with the normal range scores on *L* and *K*, may suggest overreporting, but significant pathology may still be present.

Gender was significantly associated with depression, psychasthenia, hysteria, schizophrenia, hypochondriasis, and masculinity-femininity. Using education level, onset age of regular substance use, and polysubstance use as covariables, significant differences between men and women remained. With education level as a covariable, significant differences were found in hypomania. With onset age of regular substance use as a covariable, significant differences were found in masculinity-femininity. Accordingly, earlier onset of regular substance use was associated with both lower and higher scores, while *T*-score values tended to diminish with later onset age. With polysubstance use as covariable, significant differences were found in paranoia, psychasthenia, and hypomania. Polysubstance use was also associated with higher paranoia, psychasthenia, and hypomania.

The Validity Scale of *K*-correction correlated significantly with gender. Women scored higher than men. Using onset age of regular use as a covariable, significant differences were found in the validity Scale of Lie. Later onset age of regular use was associated with the higher *T*-score, while the Validity Scale of Infrequency correlated significantly with polysubstance use. Polysubstance users scored higher than patients without polysubstance use.

DISCUSSION

The present study examined cognitive and personality differences between

TABLE 3. Group Comparisons of Neuropsychological Measures

	Men, N = 95		Women, N = 67		
Cognitive Domain	**N**	**Mean (SD); Median (Interquartile Range: 25%-75%)**	**N**	**Mean (SD); Median (Interquartile Range: 25%-75%)**	***P* (*t* test) *P* (Mann-Whitney *U* test)**
Premorbid IQ					
Vocabulary	95	8.36 (2.6)	67	9.33 (2.8)	0.026*
Attention					
Digit span forward	95	5.95 (1.1)	67	6.00 (1.0)	0.76
Digit span backward	95	4.60 (1.1)	67	4.69 (1.0)	0.62
Speed of processing					
Digit symbol	54	4.31 (2.7)	46	5.70 (2.7)	0.012*
Simple reaction time					
Dominant hand	92	368.0 (335.8-454.8)	61	378.0 (325.5-453.0)	0.93
Nondominant hand	89	362.0 (328.0-427.0)	61	389.0 (335.5-467.0)	0.38
Perceptual reasoning					
Block design	33	7.85 (3.6)	31	8.23 (2.8)	0.64
Raven	88	102.67 (14.4)	60	95.82 (11-7)	0.003**
Verbal memory and learning					
Verbal memory index	42	93.62 (16.8)	25	99.00 (17.0)	0.21
Immediate logical memory	42	24.00 (8.9)	25	26.92 (7.6)	0.18
Delayed logical memory	41	19.15 (9.4)	35	23.08 (7.6)	0.87
Immediate associate learning	42	16.40 (4.5)	25	18.12 (5.4)	0.17
Delayed associate learning	41	6.54 (2.9)	24	6.75 (1.5)	0.74
Visual memory and learning					
Visual memory index	40	77.38 (22.0)	25	81.52 (21.6)	0.46
Immediate visual learning	41	10.59 (6.9)	24	12.33 (5.6)	0.30
Delayed visual learning	40	4.18 (1.8)	24	4.79 (1.9)	0.19
Immediate visual reproduction	42	34.38 (5.4)	25	34.48 (3.9)	0.94
Delayed visual reproduction	41	28.32 (9.9)	24	28.08 (9.0)	0.93
Delayed memory					
Delayed memory index	40	79.43 (22.8)	25	86.08 (18.9)	0.23
Inhibitory capacity					
Neutral Condition (COL)					
COL ms	92	575.5 (493.3-714.3)	61	561.0 (484.5-632.0)	0.54
COL errors	92	1.0 (0.3-3.0)	61	1.0 (0.0-2.0)	0.05
Congruous Word Condition (CON)					
CON ms	92	539.0 (485.8-641.5)	61	542.0 (464.5-625.0)	0.40
CON errors	92	1.0 (0.0-2.0)	61	1.0 (0.0-2.0)	0.17

TABLE 3. (*continued*)

Cognitive Domain	Men, N = 95 N	Men, N = 95 Mean (SD); Median (Interquartile Range: 25%-75%)	Women, N = 67 N	Women, N = 67 Mean (SD); Median (Interquartile Range: 25%-75%)	*P* (*t* test) *P* (Mann-Whitney *U* test)
Incongruous Word Condition (IN)					
IN ms	91	686.0 (550.0-921.0)	61	642.0 (569.0-839.5)	0.88
IN errors	91	1.0 (0.0-4.0)	61	2 (0.0-4.0)	0.55

*$P<0.05$.
**$P<0.01$.
IQ indicates intelligence quotient.

men and women; assessed the impact of education level, duration of regular substance use in years, and singlesubstance and polysubstance use on cognition; and evaluated the impact of education level, onset age of regular substance use, and singlesubstance and polysubstance use on personality features in a sample of hospitalized addiction patients with a diagnosis of SUD.

Men and women did not differ in any of the sociodemographic variables studied. Moreover, they did differ in clinical variables. The duration of regular substance use among men was longer than that of women. The effect of this variable was controlled in the statistical analyses.

Significant differences between men and women in the primary neuropsychological tests were observed. Women had better vocabulary, and they were faster than men in the test of psychomotor speed. In contrast, men performed better than women in perceptual reasoning. After controlling the effects of education level, duration of regular substance use, polysubstance use, and calendar age, all the differences between men and women disappeared, and there were no correlations nor interactions with substance use variables. The results do not support the findings of previous studies that women's cognitive functions are more susceptible to the effects of alcohol and substance use than men's.

Several differences were noted between men and women in personality variables. Controlling for the impact of education level, onset age of regular substance use, and polysubstance use, men reported more severe personality and emotional problems than women in the scale values of depression, psychasthenia, hysteria, schizophrenia, hypochondriasis, and masculinity-femininity. Men also had higher scores than women in the depression scale. In the psychasthenia scale, men tended to be more anxious, tense, and agitated than women. In the hypochondriasis and hysteria scales, men perceived themselves more often than women as physically ill, and they tended to lack insight into the somatic symptoms or indications of the psychological components of their conditions. Similarly, men's schizophrenia scale values were significantly higher than women's values, suggesting the possibility of psychotic disorder, confusion, disorganization, and disorientation. In the masculinity-femininity scale, men had higher values than women, indicating a lack of stereotypically masculine interests. Women's values were indicative of interests that tended to be stereotypically more masculine than feminine. *K*-correction scale values (ie, a validity scale) were higher in women, suggesting that women denied symptoms and problems more than men do.

Personality differences between male and female participants in this study did not support previous findings concerning negative emotionality. Previous studies have found that women with high negative emotionality, anxiety, and depression are more susceptible to alcoholism than men.[7,9,16] In this

TABLE 4. Results of Multiway Analysis of Covariance of the Associations Between Personality Variables of Minnesota Multiphasic Personality Inventory, Gender, and Covariables

	Gender Differences		Gender and Covariables							
Personality Variables	**Men, N = 97**	**Women, N = 67**	**Gender**		**Education Level**		**Onset Age of Regular Use**		**Polysubstance Use**	
Clinical Scales	**Mean (SD)**	**Mean (SD)**	F_{141}	***P***	F_{141}	***P***	F_{141}	***P***	F_{1n1}	***P***
Hypochondriasis (Hs)	75.85 (16.10)	69.05 (12.61)	6.98	0.0092*	0.31	0.82	0.00	0.95	0.49	0.48
Depression (D)	91.89 (18.58)	77.80 (16.65)	18.84	<0.0001***	0.43	0.73	0.62	0.43	0.36	0.55
Hysteria (Hy)	74.21 (13.13)	68.34 (10.64)	8.55	0.0040**	1.23	0.302	0.16	0.69	2.71	0.102
Psychopathic Deviate (Pd)	80.27 (15.40)	78.19 (13.43)	0.27	0.61	1.41	0.24	1.02	0.32	3.44	0.066
Masculinity-Femininity (Mf)	63.38 (10.28)	57.97 (14.22)	4.90	0.028*	1.12	0.34	5.73	0.018*	0.32	0.57
Paranoia (Pa)	76.11 (15.68)	71.36 (11,87)	2.87	0.093	1.12	0.34	0.00	0.97	5.33	0.023*
Psychasthenia (Pt)	84.84 (19.01)	73.20 (13.00)	14.20	0.0002**	0.06	0.98	0.04	0.84	4.23	0.041*
Schizophrenia (Sc)	87.37 (21.79)	75.98 (14.72)	11.26	0.0010**	1.92	0.13	0.02	0.88	3.06	0.082
Hypomania (Ma)	63.78 (13.52)	67.12 (12.74)	2.99	0.086	3.41	0.019*	0.18	0.67	9.22	0.0029**
Social Introversion (Si)	65.43 (13.26)	63.24 (15.88)	0.88	0.35	1.35	0.26	0.00	1.00	0.67	0.42
Validity scales										
Lie (L)	47.26 (7.36)	50.71 (10.96)	3.20	0.076	0.15	0.93	4.70	0.032*	0.95	0.33
Infrequency (F)	79.28 (16.52)	74.34 (14.48)	2.33	0.13	2.41	0.070	0.74	0.39	6.00	0.016*
K-correction	50.11 (8.20)	56.17 (13.00)	10.78	0.0013**	0.91	0.44	0.01	0.90	0.19	0.66

*Correlation is significant at the level 0.05.
**Correlation is significant at the level 0.001.
***Correlation is significant at the level <0.000.

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study, men had more characteristics of negative emotionality, such as depression, anxiety, tension, and disorganized thinking. Expectations of men in their roles as the main breadwinner of the family remained strong. Failure in these expectations caused more anxiety and depression in men than in women.

Similarly, personality differences between male and female participants in this study did not align with previous findings concerning paranoia and psychopathic personality characteristics. There was no significant difference between men and women in scales of psychopathic deviate and paranoia. The result of the paranoia scale was unlike previous findings, that women are more paranoid than men.[8] In fact, both genders were equal in their scores of psychopathic deviances, and this finding differs from that in previous studies.[9]

Polysubstance users had more serious problems in the paranoia and hypomania scales irrespective of gender differences. The values of the paranoia scale were extremely high in the polysubstance group. Moreover, the values of the hypomania scale correlated with polysubstance use, diminishing with higher education levels. Notably, subjects with higher education levels had moderately higher scores compared with the overall average.

Findings from the present study revealed that men have more serious problems regulating emotions, although women also had moderately high values in most scales. Both groups produced higher than normal values on the depression, psychopathic deviate, paranoia, anxiety, thinking disturbances, and hypomania scales. Their profiles were interpreted as indicating increased tendencies toward acting-out behavior, high levels of stress and psychological discomfort, interpersonal guardedness, and hostility. Both genders had difficulties regulating their emotions and behaviors, although men found it more difficult to do so.

The personality factors in this study appeared independent of education level except the hypomania scale. The values of the hypomania scale diminished with higher education levels. Subjects with higher education levels had moderately higher values compared with the average level. Patients tended to be bored and restless easily. Moreover, their frustration tolerance was low, suggesting that both genders have features of hyperactivity and short attention span.

The personality factors also appeared independent of onset age of regular substance use, except the masculinity-femininity scale. Participant groups with early onset of regular substance use had both lower and higher values, which tended to diminish with later onset age. The results suggest that deviance from traditional masculinity and femininity interests may be a risk factor for substance abuse.

The present study demonstrated qualitative differences in emotion regulation between male and female substance-dependent individuals. However, knowledge of gender differences in emotional brain development is still limited. Emotional and personality disturbances associated with substance use are suggested to be based on earlier proneness to negative emotionality and social deviance in men and women.[7,17,18]

Regarding treatment, prognosis is unfavorable for both men and women because of their lack of insight into and resistance to the psychological components of their condition. As such, it may be useful to combine self-report inventory tests with more advanced methods for personality research, for example, the schema-focused approach[18] and the Rorschach Comprehensive System.[17] These methods can help patients to recognize persistent, maladaptive patterns of thinking, feeling, and behaving. It is also important to openly discuss and evaluate affect dysregulation and impulse control problems targeting relapse of substance use. Although personality disorders are said to explain only a small proportion of the use of intoxicants, it is essential to identify related disturbances in regulating feelings and behaviors during treatment. Moreover, our findings of personality and emotional variables enable to develop cost-effective screening procedures for clinical use in SUDs.

Limitations and Advantages

One limitation of this study is that we were unable to investigate the effects of specific substances, as nearly half of the participants abused multiple substances. Each substance of abuse presents

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with a diverse pattern of cognitive deficits. 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.[19] We expected that our study sample would be more realistic than those in studies that tracked the effects of various drugs with specified amounts. The different substance use groups were not analyzed separately, mainly to avoid type II error in multiple testing. The data collection method was naturalistic and observational. As noted in the multiway analysis of covariance, the significance of polysubstance use in this study was generally negligible. The results suggest that using only one substance, mostly alcohol, is sufficient to impair performance level.

Another weakness is that our sample size was moderate. The number of patients in the neuropsychological tests varied, being smaller in memory and learning tasks. Patients' effort to complete time-consuming neuropsychological tests also varied.

Moreover, the new MMPI-2 version has not been translated and standardized in Finnish, so we used the primary MMPI.[15] The MMPI-2 is similar in many ways to the original MMPI. Much of the research concerning the interpretation of the original MMPI still applies directly to the MMPI-2. We also used the interpretation of Graham,[18] as it includes further discussion of similarities and differences between the original MMPI and the MMPI-2. We also used the old version of WAIS (WAIS-R) in the assessment of intellectual capacity since the study started in 2004 when WAIS-III was not yet translated and standardized for use by psychologists in Finland. Likewise, WMS-R was used as a 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 this study is the carefully diagnosed hospital participants. They were diagnosed by psychiatrists specialized in substance abuse disorder and mood disorder using ICD-10 criteria for the diagnosis of each condition. The duration of abstinence was stated in laboratory tests.

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ARTICLE

Neuropsychological performance in patients with substance use disorder with and without mood disorders

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ABSTRACT

Background: Mood disorders commonly co-occur in patients with substance use disorders (SUD). This combination may increase the risk of pathological effects and impair cognitive functioning.
Aim: The aim of the study was to examine the effects of mood and substance use disorders on specific neuropsychological measures.
Methods: The participants comprised 164 hospitalised patients, 88 with (SUD + MD) and 76 (SUD–MD) without mood disorders, ranging in age from 19 to 65 years. Their diagnostic assessment was based on a psychiatric interview (ICD-10). Neuropsychological tests were carried out after a minimum of one month of abstinence.
Results: Processing speed ($p = 0.029$), and perceptual reasoning ($p = 0.039$) were more impaired in the SUD + MD group than in the SUD–MD group. An Analysis of covariance (ANCOVA) controlled for age, education level, learning difficulties and polysubstance use revealed that the groups were most powerfully separated by the Digit Symbol test and the Block Design test.
Conclusions: Patients with substance abuse and mood disorders seem to have more deficits in speed processing and perceptual reasoning than substance abuse patients without mood disorders. These processing speed difficulties and perceptual problems may impact prognosis and treatment. The Digit Symbol test and the Block Design test are a fast and sensitive ways to examine treatment effectiveness and monitor treatment progress.

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Substance abuse; mood disorders; inpatients; neuropsychological functions; diagnostic differentiation

Introduction

Substance use disorder (SUD) is widely recognised as a complex, chronic disease. Substance abuse has been defined as using two or more different psychoactive substances (alcohol or illicit drugs) simultaneously or sequentially leading to clinically significant psychobiological problems [1]. Addictive disorders often coexist with mental disorders. Co-morbidity is highly prevalent between SUD and mood disorders, including depression and bipolar disorders (BD) [2].

Neuropsychological studies have revealed neurocognitive deficits both in patients with SUD and/or mood disorders. Studies of SUD have identified deficits in attention and information processing [3–5], and executive, visuospatial, and memory functioning [3,6–10]. Impaired performance especially in tests of attention, executive function and memory have been found in patients with mood disorders [11–19]. Dually-diagnosed patients with bipolar disorder and SUD performed more poorly on measures of memory (both verbal and nonverbal) and executive functioning than patients without a history of SUD [20,21]. At a 3-month follow-up, similar discrepancies emerged between the groups [21]. BD patients with a lifetime history of comorbid SUD showed significantly worse visual memory and conceptual reasoning above and beyond the dysfunction observed in these factors in BD without SUD [22]. Hunt et al. [23] systematically reviewed the literature examining the effects of co-occurring alcohol misuse and depression on neuropsychological functioning from peer-reviewed published articles. The findings of this review and the study of Marshall et al. [22] support the view that measures of visual memory should be included in future neuropsychological studies of co-occurring alcohol misuse, SUD, and mood disorders.

Co-occurring SUD with mental disorders may result in a 'double deficit' [24] in cognitive functions and have an adverse impact on their course of illness and neuropsychological performance. Furthermore, co-morbid conditions may have potential differential, additive, or interactive effects on cognitive functions [22,23].

Some studies have been examined cognitive performance with co-occurring mood and substance use disorders [20,22,23]. Yet, there is little information about the cognitive function in polysubstance users with mood disorders. The main aim of the present study was to examine the combined effect of intoxicating substance abuse and mood disorders on cognitive functioning. We assessed the neuropsychological performance in patients with SUD and a mood disorder (SUD + MD) and SUD without mood disorders (SUD–MD). We hypothesised that patients with SUD + MD would perform worse in cognitive tests than SUD–MD

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patients. We compared the research groups to normative data and to each other. It was investigated which neuropsychological tests were the most sensitive to distinguish SUD–MD and SUD + MD patients from each other in the monitoring of treatment progress.

Methods

Participants

This is a retrospective study. The database was collected from patients at the Järvenpää Addiction Hospital during the 2004–2012 period who underwent neuropsychological examination. A minimum of a 1-month period of abstinence was required before testing because of cannabis given its long-lasting, sub-acute cognitive and neural effects.

Diagnoses of SUD and/or mood disorders were assigned according to the ICD-10 criteria. A consensus research analysis was carried out without knowing the patients test scores by experienced psychiatrists. Diagnoses of SUD and/or mood disorders were based on semi-structured clinical interview and all the information gathered during patient's stay in hospital. The diagnostic procedure was carried out by clinicians (psychiatrists), who were responsible for patient's treatment.

Substance use disorder (SUD) diagnoses also consisted of alcohol overuse or dependence. The co-occurring SUD and mood disorder group (SUD + MD) consisted of 88 patients and group of SUD patients without mood disorders (SUD–MD) consisted of 76 patients. The SUD + MD group comprised 52 (59%) single substance (alcohol, sedatives, stimulants or opioids) users, and 36 (41%) polysubstance (alcohol, sedatives, cannabis, opioids, stimulants, other psychoactive substances and/or depressants) users. The SUD–MD group comprised 39 (51%) single substance users, and 37 (49%) polysubstance users.

19 (21.6%) patients were diagnosed with bipolar disorder, and 69 (78.4%) with depression. More clinical information is presented in Table 1. No significant statistical differences between the groups were found.

The inclusion criteria were the following: the studied participants were aged 18–65 years, were native Finnish speakers with a substance use diagnosis and a minimum of 1 month's abstinence. The exclusion criteria for all participants were if they were less than 18 years of age, HIV-positive, or had another chronic disease possibly affecting the central nervous system, or had a history of neurological disorders, opioid substitution treatment or epileptic seizures.

The study was approved by the ethical committee of the A-Clinic Foundation, and informed consent was obtained from all participants.

Procedures and instruments

Neuropsychological testing was made as part of a work clinical assessment and assessment for treatment plans by the first author who is experienced in using the methods. All patients underwent testing after admission once the acute depressive symptoms had abated and clinically assessed by the clinician responsible for the patient's treatment to allow for testing. It was assessed that one-month abstinence was enough for neuropsychological assessment and practically useful because some of the patients were discharged soon after a one-month stay in hospital.

Diagnoses of SUD and/or mood disorders were based on semi-structured clinical interview and all the information gathered during a patient's stay in hospital. The diagnostic procedure was carried out by experienced clinicians

Table 1. Clinical Information for the SUD–MD and SUD + MD groups; for continuous numerical variables means and standard deviations are presented, for categorical variable counts and percentages (*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$).

	SUD–MD $N = 76$	SUD + MD $N = 88$	Statistical analysis	p Value
Age (mean, SD)	37.8 (11.9)	39.1 (10.3)	t Test	0.42
Gender			χ^2	0.35
Men	42 (43.3%)	55 (56.7%)		
Women	34 (50.7%)	33 (49.3%)		
Learning difficulties			χ^2	0.26
Yes	36 (51.4%)	34 (48.6%)		
No	40 (42.6%)	54 (57.6%)		
Onset of substance use age	16.2 (7.6)	16.3 (5.9)	t-Test	0.97
Onset of regular substance use	21.2 (11.3)	23.5 (1.0)	t Test	0.17
Substance use duration (years)	16.1 (9.4)	15.7 (8.8)	t Test	0.78
Multidrug use in years	8.2 (8.0)	10.7 (7.1)	t Test	0.07
Onset of injection drug abuse	19.9 (5.3)	23.3 (6.6)	t Test	0.12
Duration of injection abuse	4.5 (6.0)	5.7 (3.7)	t Test	0.55
Treatment onset age	33.1 (12.3)	36.2 (10.3)	t Test	0.09
Treatment duration, years	7.4 (14.0)	4.0 (4.0)	t Test	0.052
Depression score (MMPI)	79.2 (17.7)	91.5 (18.4)	t Test	0.001□□□
Affection disorder data (only males)				
Duration of disorder		4.4 (4.5)		
Onset age of affective disorder		35.2 (11.1)		
Treatment motivation				
Agreed follow-up care			Fisher's exact test	1.00
Yes	62 (83.8%)	74 (84.1%)		
No	12 (16.2%)	14 (15.9%)		
Treatment plan completed				
Yes	62 (83.8%)	75 (85.2%)	Fisher's exact test	0.83
No	12 (16.2%)	13 (14.8%)		

Table 2. Neuropsychological measures.

Cognitive domain	Test	Score units
Premorbid IQ	Vocabulary (WAIS-R [25])	Standard score
Attention	Digit span forward	Total raw score, max 12
	Digit span backward	Total raw score, max 12
Speed of processing	Digit symbol (WAIS-R [25])	Standard score
	Simple reaction time (CogniSpeed; [28])	Time to complete (ms)
Perceptual reasoning	Block design (WAIS-R [25])	Standard score
	Raven standard matrices [27]	
Verbal memory and learning	Verbal subtests of the WMS-R [26]	Verbal memory index
	Immediate logical memory	Total raw score, max 50
	Delayed recall of logical memory	Total raw score, max 50
	Immediate associate learning	Total raw score, max 24
	Delayed recall of associate learning	Total raw score, max 8
Visual memory and learning	Visual subtests of (WMS-R [26])	Visual memory index
	Immediate visual learning	Total raw score, max 18
	Delayed recall of visual learning	Total raw score, max 6
	Immediate visual reproduction	Total raw score, max 41
	Delayed recall of visual reproduction	Total raw score, max 41
Delayed memory	(WMS-R [26])	Delayed memory index
Inhibitory capacity	CogniSpeed version of the Stroop color-word test [30]	Time to complete (ms), and number of errors
	Neutral condition, COL	
	Congruous word condition, CON	
	Incongruous word condition, IN2	
Executive function	CogniSpeed version of the Stroop Color-word test [30]	Time to complete (ms)
Total Stroop		
(IN2-CON)		
Stroop		
Interference		
(IN2-COL)		

(psychiatrists), who were responsible for a patient's treatment, according to the ICD-10 criteria.

The patients had undergone detoxification from benzodiazepines and analgesics. There was no mention of any other medication. The psychological testing took about 2–3 h, and usually tests were done in two phases. All the testing and scoring of the variables was done by the neuropsychologist (Irma Höijer) in accordance with the standard guidelines.

Neuropsychological measures are presented in Table 2.

The neuropsychological test battery consisted of the following tests: Wechsler Intelligence Scale-Revised (WAIS-R [25]) subtests of Vocabulary, Digit Span Forward, Digit Span Backward, Block Design, and Digit Symbol; Wechsler Memory Scale-Revised (WMS-R; [26]) subtests of Immediate Logical Memory, Delayed recall of Logical Memory, Immediate Associate Learning, Delayed recall of Associate Learning, Immediate Visual Learning, Delayed recall of Visual Learning, Immediate Visual Reproduction, Delayed recall of Visual Reproduction, Visual Reproduction, and Delayed Memory; Raven Standard Matrices [27]; CogniSpeed tests [28] subtests of Simple reaction time, Stroop Color-Word Test of Neutral Condition, (COL), Congruous Word Condition (CON), and Incongruous Word Condition (IN2).

The vocabulary subtest of the WAIS-R [25] was used to assess premorbid IQ. Neuropsychological assessments of the learning disabilities were co-worked with experienced neuropsychologists specialised in learning disabilities. Learning disabilities were classified as one variable (Learning problems Yes/No). They consisted of attention, verbal and nonverbal reasoning, memory problems, dyslexia and mathematical difficulties. Assessment of learning disabilities comprised the ability of verbal reasoning, verbal learning ability, memory and attention. Assessment of attentional difficulties consider the behaviour of the test conditions (e.g. a short attention span). In addition, in an interview, subjects were asked about school success, school breaks, dropping out and the need for special educational support. Less frequently, it was possible to get written information about the earlier developmental stages, for example, symptoms of hyperactivity in childhood.

The computerised CogniSpeed tasks [29] were used to measure simple reaction time, automatic and conscious information processing. Simple reaction time subtest of the computerised CogniSpeed test battery performed first. Inhibitory capacity was assessed by the CogniSpeed version of the Stroop Color-Word Test [30]. The test consists of three subtests: (1) Neutral Condition (COL) and (2) Congruous Word Condition CON and (3) Incongruous Word Condition (IN2). COL and CON are related to more automatic and routinized information processing. Incongruous Word Condition (IN2) measures more conscious and effort-intensive processing. Each task begins with a practice session of 10 items and a final session of 50 items. In each subtest, the order of the colors was randomised. The two response buttons were coloured red and blue. When the color and the meaning were incongruent, suppression of word meaning processing was demanded. The Color Reaction times consist of three different conditions, which differ only with regard to the semantic content of the stimuli, neutral, congruous, or incongruous. In every condition, the subjects were asked to respond only to the colour of the letters presented (red or blue).

As part of the Stroop test COL was always performed first. On the computer screen, a coloured eight-character line" nnnnnnnn" appeared. The color of the line was either red or blue. The subject was told to keep the dominant index finger resting between the two reaction keys, lightly touching both. When the stimulus appeared on the screen, the subject was

administered to pushing the key with same color as quickly as possible. When the subject was ready for the next stimulus, the subject pushed the long "space2" key with the left hand. After a delay, the next stimulus appeared on the screen. The actual test was preceded by a practice set of 10 items. It was renewed if the subject had difficulties in learning the task.

CON was similar to the COL explained above, apart from the stimuli. Instead of the meaningless line of letters, the colored letter string formed a color word congruous with the ink color of the letters in the word. That is, the blue letters formed the word 'blue' and the red letters formed the word 'red'.

IN2 was similar to the COL apart from the stimuli. The colored line in this task consisted of a color word which is incongruous with the ink color of the letters in the word. In other words, the blue letters formed the word 'red' and the letters formed the word 'blue'.

CogniSpeed software has been found to be a sensitive instrument in measuring the performances of healthy participants and of patients with brain disease [29,31,32].

Total Stroop Effect is the difference between reaction times in the Congruous Word condition (CON) and the Incongruous Word condition [33]. In manual reaction time tests such as the present ones, the most reliable and consistent indicator of the Stroop effect proved to be the combined effect of facilitation and interference, the total Stroop effect. Stroop Interference is the difference between reaction times in the Incongruous Word condition and the Neutral condition (COL) [33].

In addition, depression was measured by the Minnesota Multiphasic Personality Inventory (MMPI) [34] self-report personality inventory depression (D)-scale. The MMPI is not a neuropsychological test. It is used in neuropsychological assessments to identify the presence of psychiatric disorders and "emotional" factors. MMPI was not used as a part of psychiatric diagnosis.

Statistical analyses

Where the two patient groups alone 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, as appropriate $p < 0.05$ (two-tailed) was considered statistically significant. Associations between neuropsychological measurement [Simple reaction time, Digit Symbol, Block Design, Inhibitory Capacity (IN2)] and SUD–MD and SUD + MD group, and confounding factors (multiple substance abuse (yes/no), age, education level and learning difficulties) were studied with analysis of covariance. Every neuropsychological measurement was analysed separately (Table 3). Interactions between mood disorder and explanatory variables were examined but removed in case on non-significant result. In these models, age was used as numerical covariate and mood disorder, multiple substance abuse, education level and learning difficulties as categorical explanatory variables.

In each of these four ANCOVA tests [simple reaction time, digit symbol, block design, inhibitory capacity (IN2)] we started with following model:

$$\begin{aligned}&\text{mood disorder} + \text{multiple substance abuse}\\ &+ \text{education level} + \text{age} + \text{learning difficulties}\\ &+ \text{mood disorder} \times \text{multiple substance abuse}\\ &+ \text{mood disorder} \times \text{education level}\\ &+ \text{mood disorder} \times \text{age}\\ &+ \text{mood disorder} \times \text{learning difficulties}.\end{aligned}$$

If the interactions were not statistically significant at a level of 0.05, we removed the interaction from the model.

We studied the possibility of multicollinearity by looking at the association between mood disorder and other explanatory variables. None of these association reached a significance level of 0.05.

Those explanatory variables and interactions that do not significantly affect the primary outcome were removed from the analysis. Logarithmic transformation was used for simple reaction time, IN2 and COL to achieve normal distribution assumption for residuals.

The data were analysed by using SPSS software (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL) and with SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and clinical variables

There were no statistically significant differences between groups (*t* test and x^2) (Table 1). As expected, the depression score as assessed by the MMPI, was significantly elevated in the SUD + MD group.

Table 3. Multi-way analysis of covariance of relationship between test performance and substance use disorder (SUD) with mood disorder (MD); association between neuropsychological test, mood disorder and confounders.

Neuropsychological tests	Difference between SUD–MD SUD + MD groups			Confounding factors							
				Education level		Learning difficulties		Polysubstance use		Age	
	F_{DF}[a]	*p* Value	Effect size (Cohen's *d*)	F_{DF}	*p* Value	F_{DF}	*p* Value	F_{DF}	*p* Value	F_{DF}	*p* Value
Simple reaction time	2.52_{144}	0.11	−0.34	1.01_{144}	0.39	0.31_{144}	0.58	1.03_{144}	0.78	1.73_{144}	0.19
Digit symbol	4.90_{91}	0.029	0.52	1.54_{91}	0.21	1.54_{91}	0.22	0.26_{91}	0.61	3.32_{91}	0.072
Block design	4.49_{55}	0.039	0.51	1.43_{55}	0.24	3.27_{55}	0.076	0.38_{55}	0.54	3.35_{55}	0.073
Inhibitory capacity (IN2)	3.09_{143}	0.081	−0.37	1.67_{143}	0.18	1.99_{143}	0.16	0.08_{143}	0.78	11.21_{143}	0.0010

[a]FDF=*F* test statistics value together with degrees of freedom (DF).

Table 4. Group comparisons of neuropsychological measures (*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$).

	SUD–MD		SUD + MD		
Cognitive domain	*N*	Mean (SD)[a] Median (Interquartile range 25–75%)[b]	*N*	Mean (SD)[a] Median (Interquartile range 25–75%)[b]	*p* Value[a] (=*t* test) *p* Value[b] (=Mann–Whitney *U* test)
Premorbid IQ					
Vocabulary	75	8.49 (3.1)[a]	87	9.0 (2.4)[a]	0.25[a]
Attention					
Digit span forward	75	5.87 (1.1)[a]	87	6.08 (1.0)[a]	0.21[a]
Digit span backward	75	4.57 (1.1)[a]	87	4.69 (1.1)[a]	0.50[a]
Speed of processing					
Digit symbol	42	8.40 (2.7)[a]	58	7.05 (2.5)[a]	0.012[a]**
Simple reaction time:					
Dominant hand	66	346.5 (322.0–445.8)[b]	86	377.0 (346.3–468.8)[b]	0.012[b]**
Nondominant hand	65	338.0 (321.5–484.0)[b]	85	387.0 (342.3–468.8)[b]	0.0081[b]**
Perceptual reasoning					
Block design	29	8.90 (3.1)[a]	35	7.31 (3.1)[a]	0.049[×a]
Raven	64	100.72 (14.7)[a]	85	99.3 (13.0)[a]	0.54[a]
Verbal memory and learning					
Verbal memory index	30	96.83 (18.2)[a]	36	94.50 (16.2)[a]	0.58[a]
Immediate logical memory	31	25.80 (9.3)[a]	35	24.91 (8.3)[a]	0.68[a]
Delayed logical memory	30	20.77 (9.5)[a]	35	20.40 (8.6)[a]	0.87[a]
Immediate associate learning	31	17.81 (4.8)[a]	35	16.40 (5.0)[a]	0.25[a]
Delayed associate learning	29	4.37 (1.9)[a]	34	4.52 (1.7)[a]	0.31[a]
Visual memory and learning					
Visual memory index	30	84.0 (23.1)[a]	34	75.38 (19.8)[a]	0.11[a]
Immediate visual learning	30	11.27 (5.3)[a]	34	11.41 (7.4)[a]	0.93[a]
Delayed visual learning	29	4.38 (1.9)[a]	34	4.52 (1.7)[a]	0.74[a]
Immediate visual reproduction	31	35.39 (4.2)[a]	35	33.54 (5.3)[a]	0.13[a]
Delayed visual reproduction	29	29.14 (8.4)[a]	35	27.29 (10.5)[a]	0.45[a]
Delayed memory					
Delayed memory index	29	83.48 (23.7)[a]	35	81.03 (20.0)[a]	0.66[a]
Inhibitory capacity					
Neutral condition (COL):					
COL ms	66	541.5 (483.5–624.0)[b]	86	578.5 (493.0–708.5)[b]	0.09[b]
COL errors	66	1.0 (0.0–2.3)[b]	86	1.0 (0.0–3.0)[b]	0.74[b]
Congruous word condition (CON):					
CON ms	66	504.0 (84.0–162.3)[b]	86	548.0 (479.5–642.8)[b]	0.17[b]
CON errors	66	1.0 (0.0–2.0)[b]	86	1.0 (0.0–2.0)[b]	0.26[b]
Incongruous word condition (IN2):					
IN2 ms	65	631.0 (526.5–784.0)[b]	86	724.5 (582.3–921.0)[b]	0.028[b]**
IN2 errors	65	1.0 (0.0–3.0)[b]	86	1.5 (0.0–4.0)[b]	0.41[b]
Executive functions					
Stroop interference	65	74.00 (29.0–152.5)	85	84.0 (25.0–214.5)	0.35[b]
Total Stroop	65	94.00 (29.5–162.0)	85	119.0 (48.0–241.5)	0.19[b]

Neuropsychological performance vs. normative data

The results of neuropsychological assessments are summarized in Table 4. Normative data were obtained from WAIS-R and WMS-R norms of the normal age group and previous CogniSpeed research.

Using a simple diagnostic criterion of classifying a case as impaired if performance fell more than 1 standard deviation below the population mean (<84) and as normal if it fell above that point (>85), there were some clinical differences in performance between the groups and normative data. Except for the mean averages of visual and delayed memory the performance in patients with SUD–MD was found to be in the normal range. In CogniSpeed tasks of processing speed, the Simple Reaction Time (SRT) means of the group were slower than in normal controls of 47.7 (2.3) years [35], whose normal average value for simple reaction time (SRT) is 290 (33) ms [35] and slower than in normal controls of 67.7 (range 62–75) years, whose normal average for SRT was 308 (39) ms.

The means of processing speed, perceptual reasoning, visual and delayed memory fell below one standard deviation of the population mean in the SUD + MD group. In CogniSpeed tasks of processing speed the simple reaction time (SRT) means of the group were slower than in normal controls of 67.7 (range 62–75) years, whose mean for SRT was 308 (39). The means of COL, CON and IN2 were below normal controls of 67 years [33]. Normative data of the average reaction time in COL reaction time was 614 ms (range 445–810). The error percentage was 1.6%, range 0-6%. Normative data in CON reaction time was 564 ms (range 446–1311). The error percentage was 1.6, range 0–6%. The average reaction time in IN2 reaction time was 678 ms (range 446–1311). The error percentage was 1.3%, range 0–6%. In Incongruous Word Condition (IN2) there were more error reactions than in normal controls of 67 years.

SUD–MD vs. SUD + MD

The study groups differed significantly in tests of Digit Symbol, Block Design and processing speed variables of simple reaction time and Incongruous Word condition (IN2) (Table 4).

For the variables that reached significance in the original analysis, group differences were further analysed by the ANCOVA adjusting for confounding factors of education level, learning difficulties, polysubstance use and age (Table 3).

The Digit Symbol test was impacted most powerfully by the mood disorders adjusting for the confounders. Respectively, the Block Design test has quite independent relationship with mood disorders adjusting for the effects of the confounders. Although the Block Design tests were made only for a smaller sample size (1/3 of the whole sample), the difference between the groups SUD–MD and SUD + MD was large and significant. No interactions with mood disorders were found between variables of age, level of education, learning difficulties and multiple drug use. No significant associations were found with simple reaction time (SRT) and inhibitory capacity (IN2) with mood disorders adjusting for confounding variables age, level of education, learning difficulties and polysubstance use.

Duration of illness and age correlate strongly with each other (r=.241, $p < 0.002$). Replacing age by duration of illness did not change the result. We preferred to use age as a confounding factor because, in addition to the effect of age, it also includes possible effect of duration of abuse. In analyses with MMPI depressive symptoms as a confounding factor, effect of diagnosis (SUD–MD vs. SUD + MD) expectedly lost its statistical significance. Although the SUD + MD patients had recovered from their clinically manifest depressive symptoms, they still (as expected) reported depressive symptoms in MMPI clearly more than the SUD–MD patients.

Discussion

The aim of the present study was to evaluate the neuropsychological performance in patients with SUD with mood disorders (SUD + MD) and without mood disorders (SUD–MD). In SUD + MD patients, we observed reduced performance of visuospatial reasoning (Block Design) and psychomotor speed (Digit Symbol).

The results of this study were similar to previous studies in which patients with depression had problems concerning psychomotor speed [11,16] and weakening of visuospatial performance [14].

The findings were also in accordance with previous results from studies about depression and cognitive functioning in alcoholism [23,36], bipolar disorder in alcoholism [21] and bipolar disorder in SUD [22]. SUD + MD patients showed more severe and/or widespread neurocognitive deficits than SUD–MD patients.

Substance abuse is associated with structural brain changes that are associated with neurocognitive deficits. Depending on the severity of alcohol abuse and other physical problems, such as vitamin deficiency, alcoholism may cause multiple white and grey matter damages in the brain, like in mammillary bodies, periaqueductal gray matter, and tissue surrounding the third ventricle, hippocampus, thalamus, orbitofrontal cortices, cerebellum and frontal cortex [37]. Opioid-dependent individuals seem to have gray matter deficits in several regions that play a key role in cognitive and affective processing. Defects in the fronto-cerebellar system might be responsible for impulsivity, compulsive behaviours, and affective disturbances and the fronto-insular system for the cognitive and decision-making impairments [38]. Compared with healthy controls, smaller hippocampal volumes and changes in the amygdala and striatum as well as decreased fractional anisotropy have frequently been found in marijuana users [39].

Also in patients with depression, abnormalities in brain structures have been found. Both in unipolar and bipolar depression, abnormalities in the cerebral brain regions typically consist of decreased frontal or prefrontal cortical volumes [40] as well as in frontotemporal, including hippocampal structures, and limbic circuits relating to deficits in hippocampus-dependent recollection memory [41].

Addiction is seen as a chronic brain disorder associated with impaired function of the frontal areas [42]. The frontal lobe functions include executive functions and problem solving. Fernández-Serrano et al. [43] studied the neuropsychological consequences of alcohol and drug abuse on a broad range of executive functions, comprising measures of fluency, working memory, analogical reasoning, interference, cognitive flexibility, decision-making and self-regulation. Decrements were observed in substance-dependent individuals (SDIs) with a median abstinence duration of 8 months regarded as a long-term effect. In addition to alcohol, the main drugs motivating treatment were cannabis, cocaine and heroin. The results revealed that SDIs had significantly poorer performance than the healthy control across all of the executive domains assessed. Severity of alcohol use is associated with verbal fluency and decision-making decrements. Quantity of cannabis and cocaine use have common detrimental effects on verbal working memory, analogical reasoning and decision-making measures. Duration of cocaine and heroin use have common detrimental effects on visual–spatial shifting measures. Fernández Serrano et al. [43] found specific effects of duration of cannabis use on visual–spatial working memory, and of duration of cocaine use on response inhibition. Deficits in working memory, reasoning, fluency and cognitive flexibility may be associated with difficulties in retaining complex instructions, selecting relevant information and generalising specific learning [43].

Findings from prospective research provide evidence that earlier onset cannabis abuse would be associated with worse cognitive deficits [44]. After adjusting for multiple relevant covariates cannabis use was associated with persistent deficits in executive function and processing speed and a decline in full-scale IQ after controlling for education. In addition, the study showed impairment of learning and memory. Cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users.

The review of Hunt et al. [23] is the first to our knowledge to identify and systematically examine the accumulated body of research on cognitive functioning in people with co-occurring alcohol misuse and depression. The findings were mixed as to whether the addition of co-occurring depression exacerbates neurocognitive deficits in alcohol-misusing samples.

There were few significant differences in neuropsychological test performance other than some notable findings concerning visual memory. The six studies of the review differed in diagnostic tools, neuropsychological assessments, cognitive domains, duration of abstinence from alcohol, stage of depressive illness and participant characteristics. The impact of this heterogeneity on the results precluded interpretation of a combined effect estimate.

In the review, only one of the studies identified used the Digit Symbol test [45], and one study used the Block Design test [46]. However, poorer functioning on the Digit Symbol test correlated significantly with increasing severity of depressive symptoms and there was a trend relationship between worse depressive symptoms and poorer Block Design performance. Both tests are often used as part of the Wechsler Intelligence Scale. Much neuropsychological research has focused on these tests under the assumption that these scores would reflect the impairment of general brain damage. Especially the Digit Symbol test tends to be affected regardless of the locus of the lesion [47].

The result of this study is consistent with study of Hunt et al. [46]. The SUD + MD and SUD–MD were powerfully separated by the Block Design test. Lower Block Design performance has been found in SUD patients [48] and those with psychotic depression [14]. The results of this study are also consistent with previous study of Schafer et al. [45] with regard to the Digit Symbol test. The Digit Symbol test powerfully separated the SUD + MD and SUD–MD groups. The Digit Symbol test is a processing speed task that measures how quickly different types of cognitive processing operations can be performed. Normal aging is accompanied by a slight decrease in performance after 60 in cognitive tests for speed and flexibility [32]. Slowness in information processing speed is a disorder associated with many neurological diseases and brain injuries, mood disorders, and in substance abuse disorders. The clinical test methods for assessing mental processing speed are typically either computer-aided reaction time tasks or paper-and-pencil tests that may also require psychomotor functioning to some extent.

Memory functions have been frequently affected in patients with mood disorders [16] and in those who have mood disorders with SUD, especially visual memory [21–23]. Smoking abstinence results in visuospatial working memory disabilities in male smoker patients with schizophrenia, including delayed recall and recognition biases [49].

In this study, an unexpected finding was that no significant differences were found between groups in measures of memory tasks (verbal, visual and delayed memory). Both groups were equally impaired, although the Visual Memory Index in the MD + SUD group was clinically more inferior compared to the average than in the SUD–MD group. These results suggest that SUD impacts memory more than mood disorders. It is worth mentioning that neuropsychological tests were conducted after clinical recovery from depression and from the acute detrimental effects of substance use which had not damaged much memory functions. In our study, visual memory was below average in both study groups. There was no statistically significant difference between the study groups, although clinically the performance of the SUD–MD group was a little below average [84.0 (23.1)] and the SUD + MD group was clearly below average [75.4 (19.8)].

In this study, processing speed was also measured by CogniSpeed tasks (simple reaction time, IN2). Both groups – SUD–MD and SUD + MD – had deficits in processing speed compared to healthy controls. The single substance used (mostly alcohol) was probably involved in test performance deterioration. The mean age of the SUD–MD patients was 38 and the mean age of the SUD + MD patients was 39, but processing speed of both groups was at the same level as normal 67-year olds.

Limitations and advantages

The limitation of the study is the grouping of patients using a range of substances together and the grouping a range of mood disorders together. The sample size was moderate and mood disorders consisted of several categories of disorders that probably have different severity. The different substance use groups were not analysed separately. Each substance of abuse and each mood disorder presents with a quite a diverse pattern of cognitive deficits, and this is a major limitation of the analysis. The data collection method was naturalistic and observational. It is impossible to recruit matched control groups, which is a fundamental shortcoming of observational research and cannot be solved by merely adding covariates to the analysis [50]. The different substance use groups were not analysed separately mainly to avoid type II error of multiple testing. In the multi-way analysis of covariance, the significance of multidrug use in this study was generally negligible, and results suggested that using only one substance (mostly alcohol) is sufficient to impair performance.

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

We used norms of tests standardized on a Finnish adult sample to compare patients with healthy controls. Test failures or test score discrepancies have been treated as signs of organicity [47]. Unfortunately, we did not have control groups of MD without SUD and healthy controls. This puts a clear limitation for more advanced analyses and conclusions.

A major strength is carefully diagnosed hospital participants. Patients were diagnosed by psychiatrists specialised in substance abuse disorder and mood disorder using ICD-10 criteria for the diagnosis of each condition. The duration of

abstinence was stated by laboratory tests. The study highlighted the usefulness of the Digit Symbol and Block Design tests in neuropsychological research. These are easy, simple to use and save time. They seem to be important in differential diagnoses, and regardless of the diagnosis, they work well.

As Hunt et al. [23] note, it is difficult to recruit participants with comorbid alcohol misuse and to fully understand the impact of the combined presentation of the two conditions. Prospective studies are desirable, but it is hard to motivate hospital patients to engage in for long-term follow-up. Outpatient volunteers may have protective factors related to their cognitive functioning and their ability to remain in the community compared to research participants. 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 [51].

Nevertheless, more research with careful administration of inclusion and exclusion criteria is warranted. Substance abuse seems to result in a 'double deficit' [24] in cognitive functions in those with mood disorders, which may have an adverse impact on their course of illness and functional outcome of neuropsychological performance. Considering the high co-occurrence of substance use disorder and mood disorders, and the cognitive impairments associated with mood disorders, early diagnosis of mood disorder is important. A follow-up study suggests that neuropsychological dysfunction of both mood disorders and SUD may be prognostic of a more chronic and severe disorder [21].

Conclusions

Patients with substance abuse and mood disorders seem to have more deficits in speed processing and perceptual reasoning than substance abuse patients without mood disorders. These processing speed difficulties and perceptual problems may impact prognosis and treatment. The Digit Symbol test and the Block Design test are a fast and sensitive ways to examine treatment effectiveness and monitor treatment progress. For the first neuropsychological assessment, it is useful to use a wider set of tests; the follow-up studies can focus more on these tests, which measure co-occurring alcohol misuse, substance use, and mood disorders. Extensive test batteries are not needed for a retest.

Ethical approval

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).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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