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.

Keywords: 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 lead- ing to clinically significant psychobiological problems [1]. Addictive disorders often coexist with mental disorders. Comorbidity 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 disor- ders. Studies of SUD have identified deficits in attention and information processing [3–5], and executive, visuospa- tial, 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 neuropsycholog- ical 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 patients. We compared the research groups to norma- tive 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 absti- nence 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 patient`s 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 pa- tient'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 psy- choactive 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 informa- tion is presented in Table 1. No significant statistical differences between the groups were found.

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%)		

	SUD–MD $N = 76$	SUD + MD $N = 88$	Statistical analysis	p Value
Learning difficulties			0.26	
		χ^2		
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%)		

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 (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 guide- lines.

Neuropsychological measures are presented in Table 2.

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)		

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; Wechs- ler Memory Scale-Revised (WMS-R; [26]) subtests of Immediate Logical Memory, Delayed recall of Logical Memo- ry, 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 disabili-

ties comprised the ability of verbal reasoning, verbal learning ability, memory and attention. Assessment of attention- al 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, symp- toms of hyperactivity in childhood.

The computerised CogniSpeed tasks [29] were used to measure simple reaction time, automatic and conscious in- formation processing. Simple reaction time subtest of the computerised CogniSpeed test battery performed first. In- hibitory 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 ses- sion 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 partic- ipants 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 In- congruous Word condition [33]. In manual reaction time tests such as the present ones, the most reliable and consis- tent 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 Neu- tral condition (COL) [33].

In addition, depression was measured by the Minnesota Multiphasic Personality Inventory (MMPI) [34] self-re- port personality inventory depression (D)-scale. The MMPI is not a neuropsychological test. It is used in neuropsy- chological 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 varia- bles were used. For statistical comparisons, as appropriate $p < 0.05$ (two-tailed) was considered statistically signifi- cant. Associations between neuropsychological measurement [Simple reaction time, Digit Symbol, Block Design, In- hibitory 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 neuropsycho- logical measurement was analysed separately (Table 3). Interactions between mood disorder and explanatory varia- bles were examined but removed in case on non-significant result. In these models, age was used as numerical covari-

ate and mood disorder, multiple substance abuse, education level and learning difficulties as categorical explanatory variables.

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
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).

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

mood disorder + multiple substance abuse + education level + age + learning difficulties + mood disorder × multiple substan

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.

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.

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

Cognitive domain	SUD–MD		SUD + MD		
	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[x][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]

Cognitive domain	SUD–MD		SUD + MD		
	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)
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]

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 devia- tion 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 (Ta- ble 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 sam- ple), 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 dis- orders 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 confound-

ing 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 function- ing 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 cor- tex [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, com- pulsive 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 fron- tal 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 mem- ory, analogical reasoning and decision-making measures. Duration of cocaine and heroin use have common detrimen- tal effects on visual–spatial shifting measures. Fernández Serrano et al. [43] found specific effects of duration of can- nabis use on visual–spatial working memory, and of duration of cocaine use on response inhibition. Deficits in work- ing 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 persis- tent 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-mis- using samples. There were few significant differences in neuropsychological test performance other than some nota- ble 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 se- verity 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 neuropsycho- logical 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 powerful- ly 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 pro- cessing 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 be- low 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 multi- drug 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 con- trol 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 dura- tion 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 mo- tivate hospital patients to engage in for long-term follow-up. Outpatient volunteers may have protective factors rela- ted to their cognitive functioning and their ability to remain in the community compared to research participants. Eld- erly 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 sensi- tive ways to examine treatment effectiveness and monitor treatment progress. For the first neuropsychological assess- ment, 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 [AQ7]statement

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

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