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Cognitive changes in patients with acute phase psychosis—Effects of illicit drug use

Siri Helle [a,*], Rolf Gjestad [a], Erik Johnsen [a,b], Rune Andreas Kroken [a], Hugo A. Jørgensen [b], Else-Marie Løberg [a,c]

[a] Division of Psychiatry, Haukeland University Hospital, Sandviksleitet 1, N-5035 Bergen, Norway
[b] Department of Clinical Medicine, University of Bergen, Norway
[c] Department of Clinical Psychology, University of Bergen, Norway

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ABSTRACT

Illicit drug use may influence cognition in non-affective psychosis. Previous studies have shown better cognition in psychosis with illicit drug use as compared to psychosis only. Possibly, illicit drug using patients have more transient drug-related cognitive deficits. Thus, the aim of the present study was to examine cognitive change the first weeks after admission to a psychiatric emergency ward, expecting more cognitive improvement at follow-up in the illicit drug group as compared to psychosis only. Patients with acute non-affective psychosis with (26%) and without illicit drug use were examined at baseline ($n=123$) and follow-up ($n=67$), with alternative forms of the Repeatable Battery for the Assessment of Neuropsychological Status. Latent Growth Curve models, controlling for cognition at baseline and age differences between the groups, were used to analyze cognitive change. The illicit drug using patients showed the largest improvement in cognition, especially among the youngest patients. Younger patients with non-affective psychosis and illicit drug use showed more cognitive improvement the first weeks after acute psychosis as compared to psychosis only. This suggests that the illicit drug users constitute a sub-group with less stable cognitive deficits and less cognitive vulnerability.

1. Introduction

Extensive use of illicit drugs is common in patients with non-affective psychosis, typically about 40–50% of patients with psychosis report lifetime substance use disorder (Regier et al., 1990; Kovasznay et al., 1997; Blanchard et al., 2000; Margolese et al., 2004). The range of reported substance use disorder is large in psychosis, however, from 10% to 70%, depending on methodological differences and population characteristics (Jimenez-Castro et al., 2011). Rates of cannabis use have been found to be especially high; a review reported that median rate for current cannabis use disorder was 28.6% in first-episode and 22.0% for more long-lasting non-affective psychosis (Koskinen et al., 2010). Substance use in psychosis has been associated with more hospitalizations, non-adherence, heightened suicide risk and adverse long-term clinical outcomes compared to patients with psychosis who do not use illicit drugs (Talamo et al., 2006; Zammit et al., 2008; Schmidt et al., 2011; Large et al., 2014; Sara et al., 2014; Tarricone et al., 2014). Some of the most frequently used illicit drugs, cannabis and stimulants (Ringen et al., 2008; Helseth et al., 2009; Koskinen et al., 2010), may induce transient positive psychosis symptoms and cognitive alterations (Curran et al., 2004; D'Souza et al., 2005, 2009; Smith et al., 2009).

A majority of patients with schizophrenia and non-affective psychoses have clinical significant cognitive deficits (Keefe and Fenton, 2007; Palmer et al., 2009; Lewandowski et al., 2011), often depicted as a vulnerability factor that is present also before the development of psychosis (Woodberry et al., 2008) and in high-risk populations (Brewer et al., 2005; Woodberry et al., 2010). It is likely, however, that the use of illicit drugs influences cognition in psychosis. Experimental studies have shown that the most prominent psychoactive substance in cannabis, Delta-9-tetrahydrocannabinol (THC), have an especially strong negative effect on cognition in individuals with psychosis (D'Souza et al., 2005; Henquet et al., 2006). Most studies, have found better cognitive functioning in psychosis patients with lifetime or previous illicit drug use as compared to psychosis alone (Potvin et al., 2008; Løberg and Hugdahl, 2009; Rabin et al., 2011; Yucel et al., 2012), although this has not been consistently shown in all studies (e.g. Wobrock et al., 2013). Furthermore, for cannabis, superior cognitive functioning in

* Corresponding author. Tel.: +47 48 02 02 87.
E-mail address: siri.helle@helse-bergen.no (S. Helle).

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the illicit drug using group has been reported in first episode psychosis patients (Rodriguez-Sanchez et al., 2010; Cunha et al., 2013) and at 10-year follow-up after onset of psychosis (Stirling et al., 2005), and replicated by means of functional Magnetic Resonance Imaging (fMRI) (Løberg et al., 2012). Whilst intake of THC has been associated with transient cognitive deficits (D'Souza et al., 2005, 2009), mixed results for the intake of stimulants have been reported with both better (Barch and Carter, 2005; Bahorik et al., 2013) and worse (Meijer et al., 2012) cognitive performance in non-affective psychosis. It is likely that the effect of both cannabis and stimulants use on cognition in patients with non-affective psychosis is time-related (Løberg and Hugdahl, 2009). Possibly, current illicit drug use, like cannabis, influence cognition more negatively, while previous drug use is a marker of a different pathway to psychosis. The illicit drug using psychotic patients may constitute a sub-group with less cognitive vulnerability (Løberg et al., 2012; Ferraro et al., 2013); illicit drug use may have a more temporary influence on cognition, generating a short-term cognitive and psychotic breakdown (Løberg and Hugdahl, 2009). Thus, illicit drug use, like cannabis, may create transient deficits in cognition paralleling the period of acute psychosis.

To test this hypothesis, it is necessary to examine the change of cognitive functioning from the time of an acute psychotic breakthrough to the stabilization of psychotic symptoms in patients with and without drug use. Furthermore, the drug using group should be abstinent from illicit drugs in the follow-up period to enable possible cognitive improvement. To accomplish this, only patients with symptoms of acute psychosis admitted to a psychiatric in-patient emergency department were included, and the patients were followed while hospitalized to minimize use of illicit drugs. By 4–6 weeks most of the long-term effects of illicit drug use should be minimized, and most psychosis symptoms responding to treatment (Sherwood et al., 2006; Szoke et al., 2008). Follow-up was therefore set to time of discharge from the acute ward or after 6 weeks at the latest, if not discharged earlier. This was allowed for both a naturalistic prognostic design and a reduction of variability in regard to time to follow-up. Furthermore, a brief neuropsychological screening instrument with alternative forms; the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), was used to minimize potential practice effects (Randolph, 1998; Gold et al., 1999; Beglinger et al., 2005). Earlier longitudinal studies on cognitive functioning have usually not addressed the issue of practice effects sufficiently (Goldberg et al., 2007, 2010). Practice effects can be particularly evident when there are short time intervals between repeated neuropsychological testing, and the effect seems to be strongest from baseline to the second testing (Hausknecht et al., 2007; Bartels et al., 2010). Latent Growth Curve modeling was chosen to examine cognitive trajectories from baseline to follow-up in order to minimize the effect of missing data, controlling for the baseline level in cognitive functioning and varying test–retest intervals.

The aim of the present study was to compare cognitive changes in non-affective psychosis patients with illicit drug use to cognitive changes in non-affective psychosis patients with no illicit drug use after an acute psychotic episode. It was hypothesized that the drug group would show more improvement in cognitive functioning from time of admission to a psychiatric emergency ward to time of discharge from the acute ward or after 6 weeks at the latest.

2. Methods

2.1. Study design

All patients were recruited from an acute psychiatric emergency ward at Haukeland University Hospital, Bergen, Norway, through an extensive clinical research project; the Bergen Psychosis Project (BPP). This project was a 24-month, prospective, rater-blind, pragmatic, randomized, head-to-head comparison of the effectiveness of risperidone, olanzapine, quetiapine, and ziprasidone (see Johnsen et al. (2010), for details). Thus, all patients were candidates for oral antipsychotic drug therapy. The present study used data from the period the patients were in-patients at the psychiatric emergency ward. Baseline was defined as the time of admittance to the ward, and follow-up was defined as time of discharge from the acute ward or after 6 weeks at the latest, if not discharged earlier, except for three patients that for practical reasons were followed-up between 7 and 11 weeks. The mean time period from baseline to follow-up was 4 weeks ($M=4.03$, S.D.$=2.13$, $Mdn=3.71$). The first inclusion of patients to the present study took place the 9th of March 2004 and the last patient was included the 13th of January 2009. The project was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. The Regional Committee for Medical Research Ethics allowed eligible patients to be included before informed consent was provided, thus entailing a clinically relevant representation in the study.

2.2. Subjects

2.2.1. Inclusion criteria and sample characteristics

Criteria for inclusion were symptoms of active non-affective psychosis, determined by a score of four or over on one or more of the items Delusions, Hallucinatory behavior, Grandiosity, Suspiciousness/Persecution, or Unusual thought content from the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989). Patients with affective psychoses and drug-induced psychosis were excluded, and all patients met the ICD-10 diagnostic criteria (WHO, 2004) for schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder and non-organic psychotic disorder. The diagnoses were determined by psychiatrists or specialists in clinical psychology. Patients were excluded if they were not able to understand Norwegian, had a history of head injury or mental retardation. In addition, patients under the influence of illicit drugs during testing were excluded. There were 123 patients at baseline and 67 patients at follow-up. Demographic, clinical and cognitive characteristics by group and time of assessment are provided in Table 1.

2.2.2. Drug groups

Information on illicit drug use was based on the Clinician Drug Use Scale (CDUS) and alcohol use was based on the Clinician Alcohol Use Scale (CAUS) (Drake et al., 1990). The scales have similar structures. The drug use scale rates clinically significant illicit drug use in severe mental illness on a scale from 1 to 5 ranging from abstinence (1), use without impairment (2), abuse (3), dependent (4), and severe dependence (5) the last 6 months (Drake et al., 1996). The patients' drug use in the present study was rated by a trained psychiatrist, and the threshold was set at "use without impairment". The psychiatrist used all available information over the 6 last months when evaluating the illicit drug use. The Clinical Drug Use scale has shown excellent reliability and increase of validity when multiple sources are used for rating severity of drug use, in addition to high sensitivity and specificity (Drake et al., 1990). Patients were split into two groups at baseline according to the presence of drug use. A psychosis group without drug use ($n=91$), and a group with both psychosis and concurrent drug use ($n=32$). To further decrease false negative drug users all the patients' clinical records were carefully examined by a trained psychiatric research nurse for use of cannabis as a marker of drug use, as it is possible that cannabis use could be underreported (Bahorik et al., 2014). All 32 patients in the psychosis group with drug use had a lifetime history of cannabis use. In addition, the distribution of additional drug use as reported by use of Drug Use Scale was the following: stimulants; $n=6$, stimulants, sedatives, hypnotic, anxiolytic; $n=3$, opiates and stimulants; $n=2$, stimulants, sedatives, hypnotic, anxiolytic, opiates; $n=1$. There were 72 urine tests administrated at baseline, seven of these patients tested positive on cannabis, two on amphetamines and one on opiates, 33 on benzodiazepines. As part of the admission to the psychiatric emergency ward, hospital staff examines the patients' property in search for substances. Urine tests are administrated if an in-patient appears intoxicated or is suspected to have been using illicit drugs. In the psychosis groups with and without illicit drug use the distribution of the ICD-10 primary psychosis diagnosis was the following at baseline: schizophrenia spectrum; 62.5%, 39.5%, acute and transient psychotic disorders; 34.4%, 49.5%, and non-organic psychotic disorders; 3.1%, 11.0%, respectively. At 1 month follow-up the distribution of psychosis diagnosis was similar to baseline distribution in the psychosis groups without and with illicit drug use: schizophrenia spectrum; 62.6%, 38.5%, acute and transient psychotic disorders; 31.2%, 51.9%, non-organic psychotic disorder; 6.2%, 9.6%.

2.3. Assessments

2.3.1. Cognitive assessments

To assess cognitive impairments the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, 1998) was administrated at baseline and follow-up to assess cognitive impairments in patients with psychosis by trained psychiatric research nurses. RBANS is a cognitive screening instrument that can be used to examine cognitive change when administrated successively

Table 1
Mean (S.D.) demographic, clinical and cognitive data by group.

	Baseline		Follow-up	
	Without drug use $n=91$	With drug use $n=32$	Without drug use $n=51$	With drug use $n=16$
Group distribution %	74.0%	26.0%	76.1%	23.9%
Men %	61.5%	84.4% *	58.8%	87.5% *
Age	37.83 (12.82)	26.54 (6.23)***	37.78 (13.41)	25.74 (5.48)***
Education (years)	13.01 (3.12)	12.42 (2.83)	12.92 (2.99)	13.30 (3.37)
Clinician Drug Use Scale	1.02 (0.14)	2.23 (0.95)***		
Clinician Alcohol Use Scale	1.83 (0.52)	2.16 (0.45) *		
Medication (DDD)			1.16 (0.57)	0.94 (0.45)
PANSS				
Delusions	4.66 (1.10)	4.47 (1.14)	3.00 (1.44)	3.13 (1.09)
Unusual thought content	2.42 (1.49)	2.72 (1.73)	1.47 (0.88)	1.88 (1.09)
Hallucinatory behavior	3.43 (1.74)	4.03 (1.40)	2.25 (1.66)	2.06 (1.12)
Grandiosity	1.43 (1.09)	2.19 (1.64) *	1.08 (0.56)	1.94 (1.57)*
Suspiciousness	4.29 (1.59)	4.13 (1.29)	2.67 (1.60)	2.63 (1.26)
Positive scale	19.66 (3.93)	21.34 (5.38)	12.86 (4.36)	14.38 (4.33)
Negative scale	19.67 (7.37)	19.09 (8.66)	14.80 (6.44)	16.13 (7.03)
Gen. psychopath.scale	33.67 (6.08)	36.06 (7.13)	25.88 (7.09)	25.81 (2.97)
Total	73.00 (12.61)	76.50 (16.38)	53.55 (15.35)	56.31 (9.26)
GAF function score	31.01 (5.03)	30.84 (3.99)	39.44 (8.50)	37.00 (4.72)
RBANS *t*-scores				
Immediate memory	35.95 (11.20)	34.48 (9.07)	40.02 (10.84)	38.33 (10.52)
Visuospatial/constructional	47.52 (12.64)	48.55 (12.83)	48.45 (12.08)	47.80 (12.42)
Language	40.82 (7.77)	38.52 (8.61)	46.27 (7.77)	46.20 (10.58)
Attention	30.32 (9.36)	27.61 (7.59)	34.49 (9.26)	33.07 (11.85)
Delayed Memory	38.57 (12.61)	36.42 (11.82)	41.96 (12.21)	40.27 (12.93)
Total	35.10 (10.04)	33.32 (8.69)	42.24 (7.52)	41.13 (8.37)

Note. S.D.=Standard Deviation. DDD=Defined Daily Dose. PANSS=The Positive and Negative Syndrome Scale for Schizophrenia. GAF=Global Assessment of Functioning Scale. RBANS=The Repeatable Battery for the Assessment of Neuropsychological Status.

* Significant at the $P<0.005$ level.

*** $P<0.001$.

since it has alternative forms. It takes about 30 min to administrate the 12 subtests that make up the test battery, making it suitable also for acute psychotic patients who may have less endurance in a test situation. RBANS measures the following domains: Immediate Memory, Visuospatial/Constructional Ability, Language, Attention, Delayed Memory, as well as a global measure, Total Scale (Randolph, 1998). These cognitive functions are of particular interest in psychosis research, and it has been demonstrated that RBANS, as a screening instrument, has good sensitivity to typical cognitive deficits in schizophrenia, in addition to good validity and reliability (Gold et al., 1999; Hobart et al., 1999; Wilk et al., 2004; Holzer et al., 2007). RBANS Total Scale has the best test–retest reliability as opposed to the specific domains, except from Attention, which also have demonstrated good test–retest reliability (Gold et al., 1999; Wilk et al., 2002). The RBANS total *t*-score was therefore chosen for the analyses.

2.3.2. Clinical assessments

All clinical assessments were performed at baseline and follow-up by trained psychiatrists. Symptoms were assessed with the PANSS (Kay et al., 1989), and there were no systematic differences among the raters as shown by excellent inter-rater reliability coefficients (0.92). Global Assessment of Functioning scale-Split Version, Function Scale (GAF-F) was used as an estimate of general functioning (Karterud et al., 1998).

2.4. Statistical analysis

SPSS version 20 was used for descriptive statistics, cross-tabulations with χ^2-test, and *t*-tests of group differences (SPSS, 2011). Latent Growth Curve models were analyzed with the Mplus program, version 7.11 (Muthén and Muthén, 2013). ANOVA repeated measure is based on the listwise deletion method, assumes equal test–retest intervals and individual variations in change are not addressed (Nayak Savla et al., 2006). Latent Growth Curve modeling was used to analyse individual and mean level and change in RBANS total *t*-score. This is a critical feature as cognitive functioning in patients with schizophrenia is heterogeneous and patients may have different cognitive development trajectories; some patients' performance on neuropsychological tests is stable, whilst others' performance change over time (Barnett et al., 2007; Lewandowski et al., 2011). Change between two measurement time points, as in the present study, is a difference score model (Raykov, 1993; Duncan et al., 2006). Individual changes over time may be non-linear. This is, however, not possible to explore within the present design. Therefore the estimated model assumes linearity, which also is illustrated in the model generated figure. Because of only two measurement points the residuals had to be pre-specified in order to identify the model (Stoolmiller, 1995). Mplus allows unequal individual time-spaced observations to be analyzed (Muthén and Muthén, 2013), and the measurement of time was specified as weeks. This makes it particular advantageous when examining cognitive changes over time in the present naturalistic design. The default estimator for Latent Growth Curve modeling is maximum likelihood with robust standard errors (MLR), which is robust for non-normal data (Muthén and Muthén, 2008; Kline, 2010).

Mplus models may use all available data and will in this way minimize the effect of missing data (Duncan and Duncan, 2004; Bollen and Curran, 2006). Out of 32 subjects in the drug use group and 91 subjects in the group without drug use, 16 and 51 contributed at the follow-up occasion. The full information data analysis method used give improved statistical power and generalizability to the results relative to what would be the case if the ordinary listwise deletion method had been used for data analysis. This means that all patients at baseline gave information to the baseline part of the statistical model. Besides, the contribution rate at follow-up is very similar in the two groups (non-drug: 56% and drug: 50%). The standard Latent Growth Curve models assume missing data to be missing at random (Muthén and Muthén, 2013). In order to examine the validity of this assumption, independent *t*-tests were used to examine possibly differences in all baseline demographic, clinical, and cognitive characteristics in the sample that was retested and those that dropped out from the study. The only differences that emerged were in relation to a significantly higher score on Delayed Memory and Attention for the retested sample, ($M=40.82$, S.D.$=11.53$; $M=31.21$, S.D.$=8.99$), as compared to drop-outs ($M=35.00$, S.D.$=12.68$; $M=27.89$, S.D.$=8.72$), respectively, $t(116)>2.03$, $P<0.05$ for both comparisons. The overall lack of differences in demographic, clinical, and cognitive characteristics between the follow-up group and patients *t* baseline only indicates that the drop-outs are "missing at random" (McKnight et al., 2007).

Unconditional Latent Growth Curve models were first analyzed, then Group (Psychosis group with and without drug use), Age and the interaction term between Group and Age were entered as predictors. A dummy contrast variable was used for group comparison (Pedhazur and Schmelkin, 1991). The interaction term between Group and Age was included into the statistical model in order to account for the age difference (mean and variance) in the two groups and to explore if differences between the groups were found to be dependent on the age levels (Cohen et al., 2003). Integrating interaction terms into the model is standard procedure in order to account for heteroscedasticity (Cohen et al., 2003). The Age variable was kept as a continuous variable, as categorizing the variable results in reduced statistical power (Royston et al., 2006) and small sample sizes in subgroups. If not contributing statistically significant, the interaction terms and the Age variable were removed from the models in a backward hierarchical procedure

(Cohen et al., 2003). The Gender and the Gender × Group interaction variables were tested in an additional model. The triple interaction between Group, Age, and Gender was included to even more fully account for the data heterogeneity with regard to group differences. The term tests for gender-specific group differences at different age levels. Multicolinearity in interaction analyses was solved by mean centering of the age variable (Pedhazur and Schmelkin, 1991; Cohen et al., 2003).

3. Results

3.1. Demographic, clinical, and cognitive characteristics

The demographic, clinical, and cognitive characteristics from Table 1 were satisfactorily normal distributed to allow for the use of parametric analyses. To examine group differences for these variables at baseline, chi-square tests and *t*-tests were used for the categorical and continuous variables, respectively, see Table 1 for details. The groups differed in regard to Gender and Age, χ^2 (1, $N=123$)=5.62, $P<0.05$, and $t(108)=6.57$, $P<0.001$, respectively. There were more men in the psychosis group with illicit drug use compared to the psychosis group without, and patients in the psychosis group with illicit drug use ($M=26.54$, S.D.=6.23) were younger than the non-users ($M=37.83$, S.D.=12.82). In addition, at baseline the psychosis group with illicit drug use had a higher score on Grandiosity ($M=2.19$, S.D.=1.64), $t(41)=2.44$, $P<0.05$, compared to psychosis group without illicit drug use ($M=1.43$, S.D.=1.09). The psychosis group with illicit drug use had significantly higher ratings on the Clinical Drug Use Scale ($M=2.23$, S.D.=0.95), $t(30)=6.98$, $P<0.001$, and Clinical Alcohol Use Scale ($M=2.16$, S.D.=0.45), $t(12)=3.16$, $P<0.05$, compared to the group without (CDUS; $M=1.02$, S.D.=0.14), (CAUS: $M=1.83$, S.D.=0.52). There were no differences in the distribution of a schizophrenia spectrum diagnosis and an acute transient diagnosis in the respective groups χ^2 (1, $N=112$)=2.85, $P<0.05$.

3.2. Change in cognition

In the unconditional growth curve model (without inclusion of predictors) the mean baseline score was 34.71 ($P<0.05$) and the mean change was 1.10 ($P<0.05$). In addition, there was statistically significant individual variation at the baseline level (intercept) (92.40, $P<0.05$) and in cognitive change per week (slope) (7.36, $P<0.05$). A negative relation between baseline level and change per week emerged (covariance: −7.50, $r=-0.29$, $P<0.05$), which indicates a steeper increase in RBANS total *t*-scores among patients displaying a lower baseline score on RBANS total (estimated increase at different baseline levels: mean: 1.11; minus 1 S.D.: 1.89; and plus 1 S.D.: 0.33). This finding supports the need for statistical analyses controlling for this effect.

The Fig. 1 presents the model estimated results from the Latent Growth Curve models, illustrating the cognitive change in the two groups over time and dependent on Age. To illustrate how cognitive change across different age levels varies in the two groups, ages 25, 35 and 45 are represented as different lines. This model, which controlled for RBANS total *t*-score at baseline, showed a larger increase of the total *t*-score per week in the psychosis patients with illicit drug use (group effect: $b=2.00$, $P<0.05$), especially among younger patients (Group × Age interaction: $b=-0.29$, $P<0.05$).

The analyses including Gender and Gender interaction with Group and Age did not give any statistically significant results. The re-estimated model without the triple interaction gave the following results for the change factor: Group: $b=2.53$ ($P<0.05$); Age: $b=-0.02$ ($P>0.05$); Group × Age: $b=-0.29$ ($P<0.05$); Gender: $b=1.20$ ($P>0.05$); and Group × Gender: $b=-1.25$ ($P>0.05$).

To better understand the effect of age on cognitive change in the psychosis group with illicit drug use, additional statistical analyses were performed, focusing on symptoms, type of illicit drug use and diagnosis as potential confounders. Pearson correlation analyses were used to examine how age in the psychosis group with illicit drug use was related to symptoms as measured by the PANSS subscales. Simple linear regression analyses were used to examine how Age was related to multiple drug use versus single drug use, and having a schizophrenia diagnosis as opposed to an acute or transient psychosis diagnosis in the psychosis group with illicit drug use. There were negative associations between Age and the PANSS negative subscale, $r=-0.37$; PANSS general psychopathological subscale, $r=-0.38$; and PANSS total score, $r=-0.38$, at baseline, all $P<0.05$. No associations emerged between Age and Type of drug use and Diagnosis (having a schizophrenia diagnosis as opposed to an acute psychosis diagnosis).

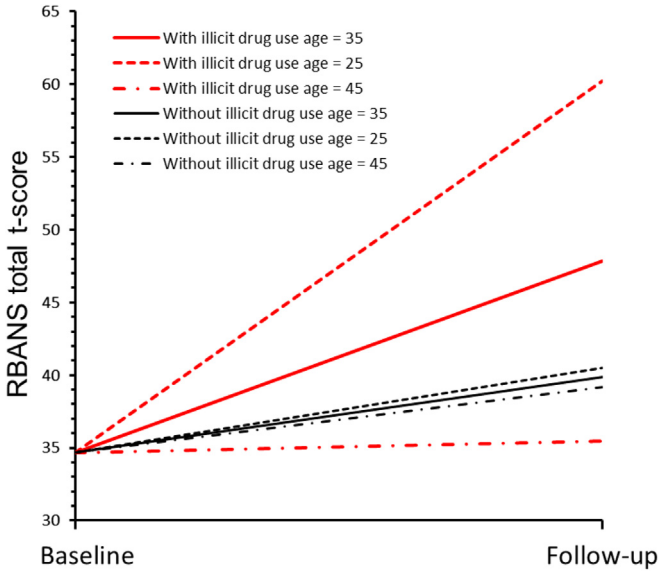

Fig. 1. Model estimated change in RBANS total *t*-score from baseline to follow-up in the psychosis groups with and without illicit drug use by age.

4. Discussion

A general cognitive improvement emerged in non-affective psychosis with and without illicit drug use in the first month after an acute psychotic episode. As hypothesized, the psychosis group with illicit drug use showed the largest increase in performance on the global measure of cognitive functioning from baseline to follow-up, especially among the youngest patients in this group. No significant differences in cognitive functioning were found at baseline between the groups in this study. However, a larger increase in cognitive functioning emerged in the psychosis group with illicit drug use as compared to the group without from admission to follow-up. This indicates that the cognitive recovery process is more prominent in the illicit drug using psychosis group in the acute phase as opposed to the non-affective psychosis only group. Possibly, patients with non-affective psychosis and a history of illicit drug use, like for instance cannabis, originally have a superior cognitive functioning (Løberg and Hugdahl, 2009; Yucel et al., 2012). Conceivably, use of illicit drugs can induce transient cognitive deficits, mimicking the cognitive vulnerability that characterizes patients with schizophrenia at group level (Løberg and Hugdahl, 2009). The results from this study, with larger cognitive changes in the psychosis group with illicit drug use, are in line with this assumption. Thus, the cognitive deficits

initially in the acute psychosis phase may be attributed to the effects of illicit drugs, like cannabis.

The analyzed interaction model accounted for age differences in the two groups and showed the group difference to be stronger for younger patients. This means that the younger patients in the psychosis group with illicit drug use had the largest cognitive change in the acute phase, and younger age was not related to polydrug use or having a schizophrenia diagnoses as opposed to an acute and transient psychosis diagnosis in the psychosis group with illicit drug use group. A plausible explanation for a larger cognitive change among the younger illicit drug using patients is that their neurocognitive set-up is more resilient and flexible; their younger brains may have a larger capacity for plasticity (Kolb and Robbin, 2011). Accordingly, the recovery process of the brain functioning in the acute phase is larger among these patients. However, one cannot rule out the possibility of a selection bias. Theoretically the younger patients in this study could represent a better functioning cognition sub-group. The association between younger age and higher scores on the PANSS negative and general psychopathology subscales, and thus higher PANSS total scores, in the psychosis group with illicit drug use, implies that the younger illicit drug using patients have more, not less, symptoms at admission. However, in spite of more symptoms at baseline the youngest illicit drug using patients have the most improvement on the neuropsychological tests in the acute phase. Interestingly, this effect of age has been reported previously; a meta-analysis by Potvin et al. (2008) found that the effect of better global cognition in schizophrenia patients with mixed substance use or cannabis use decreased with increased age. Thus, it is important to be aware of the effect of age in relation to cognitive functioning when drawing conclusions about cognition.

Use of illicit drugs like cannabis and amphetamines, may have led to disturbances in dopaminergic and endogenous cannabinoid system and transient cognitive deficits, which ultimately have resulted in expression of a psychotic disorder (Di Forti et al., 2007; Bossong and Niesink, 2010; Kuepper et al., 2010). This is supported by the fact that having a drug use disorder, in particular cannabis and amphetamines use disorder (Callaghan et al., 2012), or earlier cannabis use, is a risk factor for developing schizophrenia in a dose dependent manner (Andreasson et al., 1987; Henquet et al., 2005; Moore et al., 2007). Thus, illicit drug-using patients may have become psychotic through an alternative etiological pathway Løberg and Hugdahl, 2009; Løberg et al., 2012). Supporting this, less neurological soft signs (Bersani et al., 2002; Stirling et al., 2005; Ruiz-Veguilla et al., 2012) and better social and leisure functioning and more social contacts among drug using patients with schizophrenia, as compared to psychosis patients without illicit drug use, have also been found (Salyers and Mueser, 2001). In addition, non-affective psychosis patients with cannabis use seem to have a higher premorbid IQ compared to those without illicit drug use (Leeson et al., 2012). Furthermore, studies have generally reported an earlier onset of psychosis among cannabis using patients with schizophrenia (Large et al., 2011; Leeson et al., 2012; Myles et al., 2012; Di Forti et al., 2013; Donoghue et al., 2014), also suggesting an alternative etiological pathway. Use of illicit drugs, like cannabis and amphetamines seems to have an additive negative effect on brain functioning, and in some individuals the threshold for developing psychosis is lowered, presumably depending on the brains ability to tolerate the effects of drugs, amount of drugs taken and genetic and cognitive vulnerability.

The present study is a naturalistic prospective study integrated in clinical practice. This increases the generalizability and clinical relevance of the study, while at the same time decreases the ability to control for confounders and the ability to create a more homogenous drug user group, since multiple drug use seems to be the norm. It may therefore be difficult to attribute the differential effects on cognition to a particular illicit drug. Confounders have been minimized by controlling for group differences by statistical procedures, but it is a weakness of this study that age onset of psychosis and number of psychotic episodes were not recorded, this was also the case with frequency and duration of illicit drug use. Methodological strengths of the present study were particularly that the patients were hospitalized during the follow-up to minimize drug use and that that neuropsychological screening instrument had alternative forms to avoid practice effects. The present study did not include a control group of healthy individuals.

Cognitive functioning has been shown to predict functional everyday outcomes, like work participation, better than positive symptoms (Green, 1996; Ventura et al., 2009). RBANS total score has also been shown to be strongly related to work participation in patients with schizophrenia (Gold et al., 1999). Even though a general cognitive improvement took place in both groups, indicating that neuropsychological functioning in the acute psychosis phase is not stable, better cognition in particularly the younger psychosis patients that are using illicit drugs emerged. This may have positive clinical implications, suggesting a potential for better functional outcome. It seems plausible however, that a better prognosis is dependent on abstinence from illicit drugs (Mullin et al., 2012; Gupta et al., 2013). In line with this, worse cognitive functioning has been associated with continuous use of illicit drugs in psychosis (Rabin et al., 2012). A parallel focus on illicit drug use in the treatment of psychosis is therefore beneficial also with cognition in mind.

Declaration of interests

Author E.J. has received honoraria for lectures given in meetings arranged by Bristol-Myers Squibb, Eli Lilly, and AstraZeneca, has consulted for Eli Lilly, and has been reimbursed by Eli Lilly and Janssen Cilag for attending conferences. Author H.A.J. has been reimbursed by Eli Lilly for contribution to a brochure. Author E.-M. Løberg have received honoraria from Pearson Assessment for consulting on the development of the Norwegian version of the RBANS.

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