



Duration of untreated psychosis and cognitive functioning

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ARTICLE INFO

Article history:

Received 15 June 2012

Received in revised form 7 December 2012

Accepted 19 December 2012

Available online 8 February 2013

Keywords:

First episode psychosis (FEP)

At risk mental state (ARMS)

Neuropsychology

Cognitive deterioration

Duration of untreated illness

Duration of untreated psychosis

ABSTRACT

Background: Studies examining the influence of duration of untreated psychosis (DUP) or duration of untreated illness (DUI) on cognition vary with regard to results and methods. This study is the first in this field to include an at risk mental state with later transition to psychosis (ARMS-T) sample and to analyse how the DUI relates to their cognitive functioning. Because methodological operationalization of cognitive functioning in previous studies is highly heterogeneous, we aimed to compare different approaches.

Method: 60 first episode psychosis (FEP) patients and 24 ARMS-T patients were examined. Associations between DUP, DUI and neurocognitive performance were tested by three different operationalizations of cognition: as the raw outcome measure of different neuropsychological tests, as outcome scores which were normed on a sample of 75 healthy participants, and as the deterioration index (DI).

Results: There were no significant correlations between DUP or DUI and outcome of neuropsychological tests in both normed and raw scores. When adjusted for covariates, DUP and DUI also did not significantly predict any cognitive performance. There was no significant relationship between DUP or DUI and the DI index. However, longer DUP and DUI were significantly associated with stronger negative symptoms.

Conclusions: This study could not confirm an association between duration of untreated psychosis or duration of untreated illness and neurocognitive performance in the ARMS-T and FEP samples. This could be because schizophrenic psychoses are neurodevelopmental disorders in which most cognitive deficits exist long before the onset of psychiatric symptoms.

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1. Introduction

Duration of untreated psychosis (DUP) is defined as the time from appearance of the first psychotic symptom to initiation of adequate neuroleptic treatment (Marshall et al., 2005). Shorter DUP is associated with better clinical outcome (Marshall et al., 2005) and greater response to antipsychotic treatment (Perkins et al., 2005).

The specific association between DUP and cognitive deficits at treatment initiation has been analysed in several studies and gained importance based on the hypothesis that psychosis might have a “toxic effect” on the brain (Wyatt, 1991). However, among 18 studies which have so far examined this association, only 6 found a positive association whereas 13 did not (Supplementary Table 1). The studies vary with regard to methods and operationalization of DUP, which makes these data difficult to interpret. Some of these studies also considered the relationship of cognitive deficits with duration of untreated illness (DUI), which is usually defined as the DUP plus any period of prodromal symptoms (e.g. Barnes et al., 2000).

Most of the existing studies analysed the association between DUP and cognitive functioning by relating DUP to different neuropsychological tests and IQ measures at the time of treatment initiation (e.g. Goldberg et al., 2009). However, Amminger et al. (2002b) argued that only the difference to a patient's premorbid abilities would provide a meaningful measure for deterioration. Consequently, they made use of the deterioration index (DI; Bilder et al., 1985), assessing the discrepancy between “hold” and “non-hold” cognitive functions. In accordance with the above hypothesis, Amminger et al. (2002a) found that DUP was positively associated with DI, but not with morbid cognitive functioning, which was replicated by Gaynor et al. (2009).

Because methodological operationalization of cognitive functioning in studies examining the relationship between DUP and cognitive decline is highly heterogeneous, we aimed to compare different approaches in order to detect whether differences in methodological approaches could have led to inconsistencies between earlier studies. Specifically, we analysed the relationship between DUP, DUI and cognitive deterioration in three different ways: first, we operationalized cognitive functioning as raw outcome measure of different neuropsychological tests as done in most similar studies. Second, we analysed the relationship between DUP, DUI, and cognitive deficits using neuropsychological outcome scores normed on a sample of 75 healthy participants with the same socio-demographic characteristics. Thirdly, deterioration was

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assessed by the DI in a similar way as in Amminger et al. (2002a) and Gaynor et al. (2009).

Of the studies listed in Supplementary Table 1, only four have also looked at the interrelationship between DUI (other than DUP) and cognition. None of them found significant correlations. A difference between the effect of DUP versus DUI on cognitive performance might be expected in the way that cognitive performance could be affected more strongly by DUP than by DUI because later stages of the disease process (i.e. stages with psychotic symptoms) are likely to be more toxic to the brain than earlier stages.

This study is the first to include 24 at risk mental state (ARMS) individuals with later transition to psychosis (ARMS-T) and to examine how the DUI relates to their cognitive functioning at presentation to our clinic. The inclusion of an ARMS sample with only unspecific prodromal signs but later transition to psychosis can help to clarify the influence of first psychiatric symptoms on cognition, eventually detecting that untreated first psychiatric symptoms are associated with cognition before the outbreak of psychosis. However, based on previous studies with first episode psychosis (FEP) patients reporting no relationship between DUI and cognition (e.g. Barnes et al., 2000; Norman et al., 2001), we expected no relationship between DUI and cognitive functioning in this patient group, which could mean that cognitive deficits occur prior to the onset of psychiatric symptoms.

2. Methods

2.1. Setting and recruitment

This study was part of the Basel (Früherkennung von Psychosen) (FePsy) study (Riecher-Rössler et al., 2007, 2009), which aims to improve the early detection of psychosis. Participants were recruited into the study via a specialised early detection outpatient clinic at the Psychiatric Outpatient Department Basel. The study was approved by the Ethics Committee of Basel, Switzerland (EKBB), and written informed consent was obtained from the participants.

2.2. Screening procedure

The Basel Screening Instrument for Psychosis (BSIP) was used (Riecher-Rössler et al., 2008) to assess participants and identify them as individuals with an at risk mental state (ARMS), first episode psychosis (FEP) patients, or “not at risk for psychosis” (i.e. other psychiatric diseases). Inclusion as ARMS required one or more of the following: (a) “attenuated” psychotic symptoms, (b) brief limited intermittent psychotic symptoms (BLIPS), (c) a first degree relative with a psychotic disorder plus at least two indicators of a clinical change, such as marked decline in social or occupational functioning, or (d) minimal amount and combination of unspecific risk factors according to the BSIP (Riecher-Rössler et al., 2008). FEP patients had to fulfil the transition criteria for psychosis according to Yung et al. (1998), but did not have to fulfil the time criteria of a diagnosis according to ICD or DSM. Subjects treated with antipsychotics for >3 weeks or who had exceeded a 2500 mg cumulative chlorpromazine equivalent dose and subjects with a clearly diagnosed organic, substance induced as well as affective psychosis were excluded.

2.3. Participants

In this study, we present data of 84 patients from the Basel FePsy study for which information about DUP, DUI, and neuropsychological performance could be obtained. 28 patients from the FePsy study had to be excluded from this study due to missing data regarding DUP, DUI or neuropsychology. 60 of the patients were identified as FEP patients. 24 ARMS individuals were included, who later made the transition to frank psychosis (ARMS-T) according to the PACE criteria (Yung et al., 1998). This sample overlaps with previous samples reported on

from the FePsy study (Gschwandtner et al., 2003; Pflueger et al., 2007; Riecher-Rössler et al., 2009).

A sample of 75 healthy participants was used for the normalisation of the neuropsychological tests. They were recruited from a commercial school, hospital staff, and through advertisements. Exclusion criteria were as follows: a current or former psychiatric disorder or neurological disease, serious medical condition, substance abuse, or a family history of psychiatric disorder.

2.4. Duration of untreated illness/duration of untreated psychosis

The duration of untreated illness (DUI) was defined as the time period between first self-perceived signs or symptoms of a change in well-being and first contact with our early detection service. The duration of untreated psychosis (DUP) was defined as time period between the appearance of the first positive psychotic symptom and first contact with our early detection service. The DUP was only assessed in FEP patients as it was almost zero in our ARMS-T patients due to our close follow-up during the at-risk-mental-state and prompt treatment at transition. The DUI and DUP were determined by using the Basel Interview for Psychosis (BIP) (Riecher-Rössler et al., in preparation), which is a semistructured interview allowing an exact description of the onset of all symptoms. Exact recall is facilitated by a personal time grid regarding important life events, which is first established with each patient. Both DUP and DUI were established by considering the patients' subjective response but also including other clinical information resources such as for instance information from family members and medical histories.

2.5. Neurocognitive measures

The neuropsychological test-battery was mainly based on computer-administered tests, so that nearly all measures provided reaction times and numbers of errors (omissions/false alarms). The assessment of the participants was conducted by fully qualified psychologists and well-trained, supervised advanced students of psychology and was conducted at time of first contact with our service for both ARMS and FEP.

2.5.1. Intelligence

- The Mehrfachwahl-Wortschatz-Test (MWT-A; Lehrl, 1991) and the Leistungsprüfsystem, scale 3 (LPS) (Horn, 1983), are well established German intelligence scales for assessing verbal and non-verbal (abstract reasoning) abilities.

2.5.2. Executive function

- The computer-administered Tower of Hanoi (ToH; Gediga and Schöttke, 1994) is a task demanding sequential anticipation of the consequences of one's actions. The execution of action needs to be guided by planned and goal-oriented behaviour.
- The computer-administered Wisconsin Card Sorting Test (WCST; Drühe-Wienholt and Wienholt, 1998; Heaton et al., 1993) demands flexible shifts between three cognitive sets in order to avoid perseveration errors. The execution of action is controlled by a task-related feedback.
- The Go/No-Go subtest of the Tests for Attentional Performance (TAP; Zimmermann and Fimm, 1993) requires the inhibition of responses provoked by visually similar, but non-target stimuli.

2.5.3. Working memory

- The Working Memory subtest of the Tests for Attentional Performance (TAP; Zimmermann and Fimm, 1993) forces the subject to match visually presented stimuli in terms of a 2-back task. Whether the subject succeeds depends on the subject's ability to concentrate on tasks which impose a permanent cognitive load.

2.5.4. Attention

■ The Continuous Performance Test (CPT-OX; Rosvold et al., 1956) measures vigilance in terms of sustained visual attention. Four letters are consecutively displayed in a pseudo-randomized order. Whenever a prime (O) precedes the target (X) a pushbutton needs to be pressed.

It permits the computation of indices which reflect performance changes between the first and the second part of the task. The CPT-OX version is therefore equivalent to the CPT-AX.

2.6. DI index

The DI index (Bilder et al., 1992) is based on the assumption that a large discrepancy between a subject's best and poorest cognition performance suggests cognitive loss. The DI index by Bilder et al. (1992) is calculated by assessing the difference between the Wechsler Adult Intelligence Scale-R (Wechsler, 1981) subtests: Information and Vocabulary ("hold-tests") to the Digit symbol ("non-hold" test) according to the following formula: "hold-tests" – "non-hold tests"/"hold-tests". In our study, we used the MWT-A (Lehrl, 1991) test as "hold-test", which has been shown to be a useful measure of premorbid IQ (Lehrl et al., 1995). The LPS, scale 3 (Horn, 1983) which is a German intelligence scale for assessing non-verbal abstract reasoning abilities, was used as "non-hold" test. Consequently, the DI index in our study was computed as follows:

$$DI = \frac{(MWT-A)-(LPS)}{(MWT-A)}.$$

2.7. Psychopathology measures

Positive symptoms were assessed with the 4 items: hallucinations, suspiciousness, unusual thought content, and conceptual disorganisation of the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993). Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983).

2.8. Cannabis use

Cannabis use was determined by the Basel Interview for Psychosis (BIP) (Riecher-Rössler et al., in preparation) and was assessed both for ARMS and FEP patients at study inclusion. The BIP contains two items assessing the frequency of past and present cannabis consumption. Frequency of cannabis use is assessed by these items on a five-point ordinal scale using the following response categories: daily, several times a week, several times a month, less than several times a month, and not at all. For the present analyses, only current cannabis use was considered.

2.9. Statistical analysis

All analyses were performed using SPSS version 19. Associations between DUP, DUI and neurocognitive performance were tested with and without adjusting for confounding variables and with three different operationalizations of neurocognitive performance. Due to a strong positive skew in both DUP and DUI, Spearman's rank correlation was used in the unadjusted analyses and log transformed DUP/DUI in the adjusted analyses (i.e. multiple regressions). Adjustments were performed for the influence of age, gender, years of education, antipsychotic medication, cannabis use, BPRS positive symptom score, and SANS total score.

For the first operationalization of neurocognitive performance, we calculated composite scores for each subtest of the neuropsychological test battery. The composites were the averages of the z-transformed

performance scores (i.e. reaction-time, omissions, false-alarms) of each test. For the second operationalization, we used composite scores that were the averages of the normed performance scores of each test. Scores were normed on our sample of 75 healthy participants according to the following procedure: first, the distribution of the residuals of each score in the normative sample was made approximately Gaussian by applying the Box–Cox transformation for linear models (Box and Cox, 1964) if the score was uncensored and the Box–Cox transformation for Tobit models (Han and Kronmal, 2004) if the score was censored. Second, an optimal model was selected among six possible models with the following predictor sets: intercept only, age, gender, education, age + education, age + sex, age + education + sex, age + education + sex + age–sex–interaction. Again, Tobit and linear regression models were used for censored and uncensored scores, respectively. Optimal models were selected by using the predicted residual sum-of-squares (PRESS) statistic (Allen, 1974), which measures the predictive performance of a model in leave-out-cross-validation. Finally, normed values were calculated according to the following formula: (transformed raw score – predicted from best model)/residual standard error of best model.

For the third operationalization of neurocognitive decline, a DI index was calculated as described above.

P-values < 0.05 were considered significant. However, for hypothesis tests using the first and second operationalization of neurocognitive decline, which comprised seven different outcome measures, we divided the alpha level by seven to account for multiple testing.

3. Results

3.1. Sample characteristics and confounding factors

The patients included in this study did not differ from those who were excluded regarding age, gender, education, total SANS, BPRS positive symptom and BPRS total score (Table 1). There were also no significant differences between the ARMS-T and the FEP group included in the study regarding age ($p=0.05$), gender ($p=0.80$), education ($p=0.59$), cannabis use ($p=0.77$) and SANS total score ($p=0.69$). However, FEP patients had higher BPRS positive symptoms score ($p<0.001$) and were significantly more likely to be medicated with antipsychotics ($p=0.04$). 3 (12.5%) ARMS-T and 23 (38.3%) FEP subjects had been receiving antipsychotic treatment at assessment time.

3.2. Duration of untreated illness and duration of untreated psychosis

The median DUI was 36 months (mean: 56.7 months, SD: 68.67 months, IQR: 75.0). DUI did not differ significantly between FEP and ARMS-T (Mann–Whitney- U : 741; $p=0.839$), nor between men and women (Mann–Whitney- U : 725.5; $p=0.581$). The median DUP, which by definition could only be assessed in FEP patients, was 12 months with a mean of 36.8 months (SD: 56.43, IQR: 53.75) months. The large difference between mean and median DUP was due to a positively skewed distribution (skewness: 2.70, kurtosis: 8.39), caused by a small number of outliers. Regarding gender differences, the median value of DUP for men was 12 months (mean: 40.8 months; SD: 62.67; IQR: 56.75), while the median value of DUP for women was 11 months (mean: 28.8 months; SD: 41.55; IQR: 46.00), which was statistically non-significant (Mann–Whitney- U : 368; $p=0.62$). Fig. 1 shows the DUP and DUI distributions in the different subgroups.

There were no significant Spearman's rank correlations between DUP or DUI and cannabis use, years of education and BPRS total score. There was a significant correlation between DUP and SANS global score ($\rho=0.23$, $p=0.024$) as well as a significant correlation between DUI and SANS global score ($\rho=0.20$, $p=0.034$).

Table 1
Socio-demographic characteristics^a of ARMS-T and FEP.

	ARMS-T ^b incl. (n = 24)		ARMS-T ^c exclud. (n = 3)		Significance value
Men	n = 16	(66.7%)	n = 1	(33.3%)	p = 0.54
Women	n = 8	(33.3%)	n = 2	(66.7%)	
Age	26.6	(6.9)	21.0	(3.1)	p = 0.06
Education (in years)	11.1	(2.5)	9.3	(1.2)	p = 0.10
BPRS total	41.0	(9.8)	50.6	(35.6)	p = 0.69
BPRS positive symptoms	7.5	(2.2)	9.3	(6.7)	p = 0.67
SANS total	28.3	(18.1)	17.3	(6.9)	p = 0.09
Neuroleptic medication	3	(12.5%)	0	(0.0%)	p = 1.00
MWT IQ	109.3	(12.9)	111.0	(.)	
	FEP ^b incl. (n = 60)		FEP ^c exclud. (n = 25)		Significance value
Men	n = 40	(66.7%)	n = 14	(56.0%)	p = 0.49
Women	n = 20	(33.3%)	n = 11	(44.0%)	
Age	30.1	(8.2)	29.3	(9.4)	p = 0.72
Education (in years)	11.4	(3.2)	10.4	(2.6)	p = 0.14
BPRS total	52.2	(13.4)	51.3	(13.3)	p = 0.80
BPRS positive symptoms	12.4	(3.6)	11.4	(4.2)	p = 0.33
SANS total	26.5	(17.6)	22.0	(19.4)	p = 0.37
Neuroleptic medication	23	(38.3%)	6	(35.3%)	p = 0.96
MWT IQ	107.6	(15.7)	106.8	(16.0)	p = 0.87

ARMS-T, at risk mental state with transition to psychosis; FEP, first episode of psychosis.

Fisher's exact test for categorical variables, t-test for continuous variables.

^a Unless indicated otherwise values are given as means with SD in brackets.

^b With DUP/DUI and neuropsychological information.

^c Without DUP/DUI and/or neuropsychological information.

3.3. DUP, DUI and neuropsychological tests

Table 2 lists Spearman's rank correlations of DUP and DUI with the normed composite scores and composite scores based on z-transformed scores of the neuropsychological tests for the whole group of FEP and ARMS-T patients.

There were no significant correlations between DUI or DUP and normed composite scores or composite scores based on z-transformed scores of neuropsychological tests, even when no adjustment for multiple testing was applied (Table 2). The results did not change when the

Table 2

Spearman's rank correlations for duration of untreated psychosis (DUP) and duration of untreated illness (DUI) and normed composite scores/composite scores based on z-transformed scores of neuropsychological tests for the whole sample.

	DUI ^a	DUI ^b	DUP ^a	DUP ^b
MWT-A	−0.09	−0.04	0.02	−0.04
LPS	0.15	0.15	0.23	0.23
ToH	0.01	0.00	−0.05	−0.06
WCST	−0.09	−0.12	−0.18	−0.14
TAP go/no go	0.04	0.01	0.07	0.06
TAP wm	0.07	0.08	0.19	0.16
CPT-OX	−0.11	0.10	−0.12	0.13

MWT-A = Mehrfachwahl-Wortschatz; LPS = Leistungsprüfsystem, scale 3; ToH = Tower of Hanoi; WCST = Wisconsin Card Sorting System; TAP go/no go = Go/No-Go subtest of the Tests for Attentional Performance; TAP wm = Working Memory subtest of the TAP; CPT-OX = Continuous Performance Test.

^a Correlations with normed composite scores.

^b Correlations with composite scores based on z-transformed scores.

analysis was performed separately for ARMS-T and FEP (Table 3). When the correlational analyses were repeated with the single variables (not composite scores), there was one significant correlation between time per move in the Tower of Hanoi and DUP ($\rho = 0.25$, $p = 0.41$) in the normed scores; however, this significance ceased when corrected for multiple testing.

In the confounder-adjusted analyses (i.e. multiple regression models) with normed composite scores, DUP was only associated with one neurocognitive outcome variable, namely, non-verbal intelligence as measured by the LPS ($p = 0.03$), but the association was relatively weak ($\beta = 0.28$), not in the expected direction, and did not remain significant after correction for multiple testing ($p = 0.15$). The same was true for DUI, which showed one positive association with LPS ($\beta = 0.23$; $p = 0.03$) that did not survive correction for multiple testing (adjusted $p = 0.22$). As can be seen from Fig. 2, only age, years of education and SANS total score were significantly associated with any outcome when adjusted for potential confounders and multiple testing. The results of the confounder-adjusted analyses did not change when repeated with composite scores based on z-transformed scores.

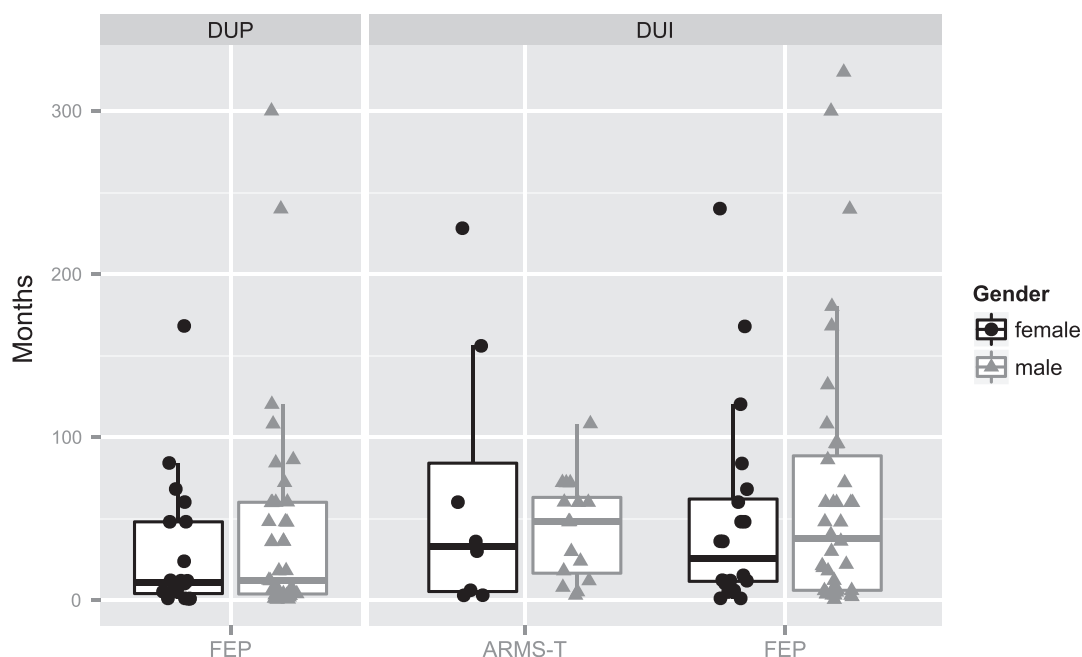


Fig. 1. Duration of untreated illness (DUI) and duration of untreated psychosis (DUP).

Table 3

Spearman's rank correlations duration of untreated psychosis (DUP) and duration of untreated illness (DUI) and normed composite scores/composite scores based on z-transformed scores of neuropsychological tests separately by ARMS-T and FEP patients.

	ARMS		FEP		DUP ^a	DUP ^b
	DUI ^a	DUI ^b	DUI ^a	DUI ^b		
MWT-A	0.15	0.25	−0.18	−0.12	0.02	−0.04
LPS	0.22	0.22	0.09	0.09	0.23	0.23
ToH	0.30	0.33	−0.12	−0.15	−0.05	−0.06
WCST	0.30	0.18	−0.22	−0.22	−0.18	−0.14
TAP go/no go	0.03	−0.01	0.05	0.01	0.07	0.06
TAP wm	0.00	0.06	0.10	0.09	0.19	0.16
CPT-OX	0.05	0.00	−0.17	0.14	−0.12	0.13

ARMS-T, at risk mental state with transition to psychosis; FEP, first episode of psychosis. MWT-A = Mehrfachwahl-Wortschatz; LPS = Leistungsprüfsystem, scale 3; ToH = Tower of Hanoi; WCST = Wisconsin Card Sorting System; TAP go/no go = Go/No-Go subtest of the Tests for Attentional Performance; TAP wm = Working Memory subtest of the TAP; CPT-OX = Continuous Performance Test.

^a Correlations with normed composite scores.

^b Correlations with composite scores based on z-transformed scores.

3.4. DUP, DUI and the deterioration index

The median value for the deterioration index (DI) was 0.01 (mean: −0.01; SD: 0.17). DI scores did not differ between ARMS-T and FEP ($T = -1.09$; $p = 0.28$) and between women and men ($T = 1.74$; $p = 0.09$). There was a significant correlation between DI and age ($r = 0.31$; $p = 0.004$) as well as DI and BPRS score ($r = 0.24$; $p = 0.021$), but no significant correlations between DI and DUI, DUP, SANS total score, gender, years of education, and cannabis use. In a multiple regression model, where DI was entered as the dependent variable and DUP, BPRS positive symptom score, SANS total score, gender, years of education, cannabis use and antipsychotic medication as predictors, only age predicted a stronger cognitive decline (standardised regression coefficient $\beta = 0.271$; $p = 0.019$).

4. Discussion

The aim of this study was to investigate the relationship between DUP, DUI and neurocognitive performance in a sample of 60 FEP and

24 ARMS patients with later transition to psychosis (ARMS-T). We compared three ways of operationalizing cognitive functioning but neither of the approaches detected a relationship between cognitive deficits and DUP or DUI.

4.1. Length of DUP or DUI and influencing factors

The mean and median DUP of our study (148 weeks/48 weeks) were somewhat higher than those reported in most other studies (for review, see Norman et al., 2001). This might be explained by the way our onset of DUP was defined; DUP started when the first positive psychotic symptom occurred but not a full blown psychotic episode. Therefore, our DUP already started when the first “attenuated” or “brief-limited-intermittent” psychotic symptoms were subjectively experienced. But even if it is true that a prolonged DUP or DUI might be associated with cognitive deterioration, this deterioration itself might have contributed to a recall bias. However, the fact that we also integrated other clinical information such as information from family members/medical histories in order to establish DUP should have helped to reduce this bias.

The duration of untreated illness reported in our study is in line with other studies. The median DUI was 36 months (SD: 68.6) for the whole study sample, and DUI varied widely, which is similar to results described earlier (Häfner et al., 1998; Riecher-Rössler et al., 2006).

Longer DUP and DUI were significantly associated with stronger negative symptoms. This is in line with most other studies as shown in the review by Marshall et al. (2005) which reported a significant association between DUP and several outcome measures including negative symptoms. In the meta-analysis of Perkins et al. (2005), duration of untreated psychosis was even only associated with negative, but not with positive symptoms. In one study finding a significant association between DUP and cognition, this finding ceased to be significant when it was controlled for negative symptoms (Ammeringer et al., 2002a), suggesting that the influence of DUP on cognition is confounded or mediated by negative symptoms.

4.2. DUP, DUI and cognitive impairment

In this study, we could not detect significant relationships between DUP, DUI, and cognitive functioning, neither when cognitive functioning

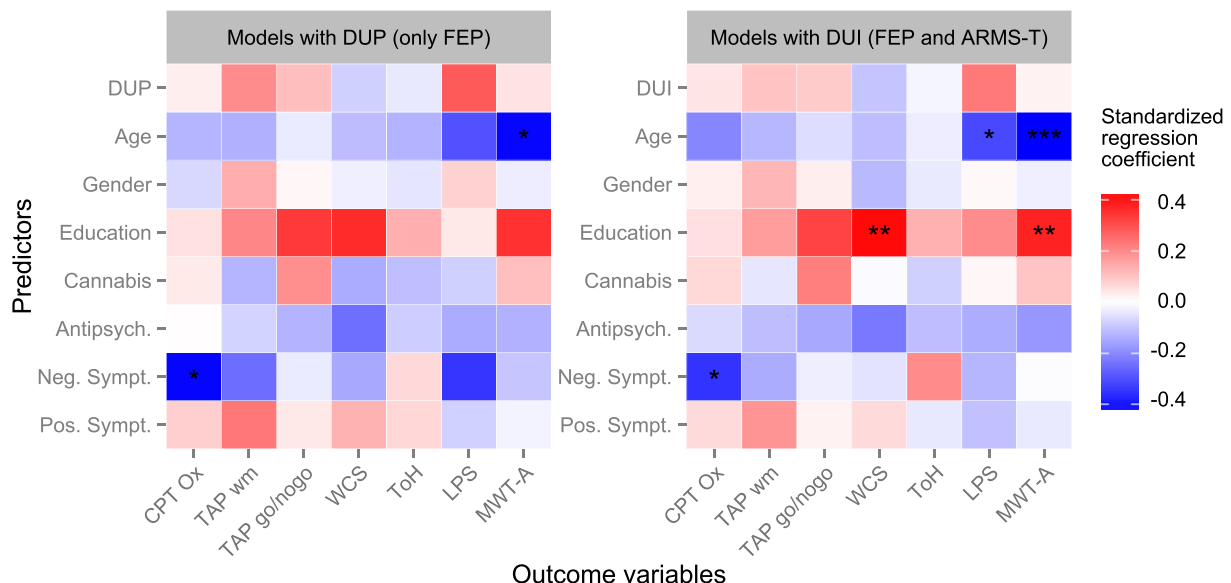


Fig. 2. Predictors of cognition: cognitive test scores as dependent variables and log DUP/log DUI, age, gender, education, cannabis consumption, SANS negative and BPRS positive symptoms as independent variables. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ after adjustment for multiple testing.

was looked at as raw outcome measure of neuropsychological tests, as a deterioration index, nor as the deviation of the performance of patients compared to the performance of healthy controls. As shown in the Supplementary Table 1, this is in line with many other studies: among 18 studies examining this relationship, only 5 found a positive relationship between DUP, DUI and cognition.

The following theories could explain this:

There are several studies suggesting schizophrenic psychoses are neurodevelopmental disorders and that the origins of these are to be found in childhood (Jones et al., 1994). A recent 45-year follow-up report from a Copenhagen birth cohort showed that individuals who developed schizophrenic psychoses reached developmental milestones later than a control-group (Sorensen et al., 2010). These data confirm that the cognitive deficits in schizophrenic psychoses by far precede the onset of psychiatric and especially psychotic symptoms and therefore there might be no connection between the duration of untreated psychosis and cognitive performance. Rather, certain cognitive deficits might underlie the vulnerability to psychosis in a least a subgroup of patients.

An alternative explanation was proposed by Goldberg et al. (2009); the development of psychosis and neurocognitive deficits is based on two different psychological mechanisms: psychotic experiences might be the consequence of a learning process and are thus stabilized over time (Kapur, 2003). Hence they get the more difficult to treat, the longer they are being consolidated, which would explain the frequently reported correlation between DUP and treatment response (e.g. Perkins et al., 2005). In contrast to the development of psychotic experiences, moment-to-moment information processing is not learned. Therefore, DUP and cognition might not be related to each other (Goldberg et al., 2009). Using the approach of Amminger et al. (2002a) and applying the deterioration index (DI) by Wechsler (1958), our study could not replicate the finding of a positive relationship between DUP and this index. This might be because we used a different test to calculate the DI than Amminger et al. (2002a). But as mentioned above; several studies suggest that schizophrenia is a neurodevelopmental disorder (e.g. Lewis and Levitt, 2002). Therefore, the concept of a premorbid IQ and a deterioration index seems inapplicable. It has additionally been criticized that the reliability of the DI is limited because the use of “premorbid” intellectual ability is problematic in cases of a long-standing learning problem (e.g. dyslexia) or in cases where damage to brain regions directly involved in those functions is present (e.g. Cipolotti and Warrington, 1995). In view of these arguments challenging the reliability of the DI, our results with it do not seem further surprising.

4.3. Strengths/limitations

The strengths of our study were that – in contrast to all other studies – we included not only a FEP sample, but also an ARMS sample with later transition to psychosis and analysed how the DUI relates to their cognitive functioning. Additionally, we used different operationalizations for cognitive decline.

A limitation is the modest sample size of this difficult-to-collect patient sample, which leads to limited statistical power. Furthermore, the used neuropsychological test versions imposed only a moderate cognitive load, which led to strong ceiling effects in some scores. This might have accounted for the lacking association between DUP, DUI and cognition. Additionally, we did not include a measure of

verbal memory, which has been shown to be an important marker of an at risk mental state (e.g. Brewer et al., 2005; Lin et al., 2011; Fusar-Poli et al., 2012; Valli et al., 2012).

4.4. Conclusions

This study could not – even when operationalizing cognition in different ways – confirm an association between duration of untreated psychosis or duration of untreated illness and neurocognition in FEP patients or ARMS-T individuals, suggesting that the cognitive decline that occurs before and during the transition to psychosis is not further worsened with increasing duration of untreated psychosis and/or prodromal phase or that cognitive deficits occur prior to the onset of psychiatric symptoms (e.g. already in childhood). However, as the relationship between DUP and treatment outcome is well established and as there might be other consequences of delayed treatment, this should not weaken the rationale for early detection and intervention strategies in patients with a first psychotic episode. Future studies in this field should focus on the association between DUP, DUI and longitudinal changes of cognition and also encompass factors such as very early cognitive developmental abnormalities.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2012.12.016>.

Role of funding source

This project is supported by the Swiss National Science Foundation no. 3200-057216.99, no. 3200-057216.99 and no. PBB5B-106936 and the Nora van Meeuwen-Haeffliger Stiftung, Basel (CH).

Contributors

A. Riecher designed and supervised the study and the writing of the paper. C. Rapp did the statistical analyses and wrote the manuscript. E. Studerus supervised the statistical analyses and the writing of the manuscript. Hilal Bugra helped drafting the article. Jacqueline Aston, Corinne Tamagni, Anna Walter, Marlon Pflueger and Stefan Borgwardt reviewed the manuscript and provided important intellectual content.

Conflict of interest

All authors report no financial interests or potential conflicts of interest with respect to this study.

Acknowledgements

We would like to thank Roya Zaborsky, MD, who participated in the recruitment and assessment of patients. We would also like to thank Claudine Pfister and Martina Klemm for their help in preparing the manuscript.

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