Duration of untreated psychosis and cognitive functioning

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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.