



Neurocognition and recovery in first episode psychosis

Gunnar Faber^{a,*}, Henderikus G.O.M. Smid^b, Arthur R. Van Gool^a, Lex Wunderink^c,
Durk Wiersma^b, Robert J. van den Bosch^b

^a Yulius, Mental Health Institute, Hellingeng 21, 3311 GZ Dordrecht, The Netherlands

^b Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

^c GGZ-Friesland, Mental Health Institute, Leeuwarden, The Netherlands

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ABSTRACT

Cognitive functioning has been found to be a predictor of functional outcome of schizophrenia. It is unclear, however, whether clinical recovery can be predicted by scores on specific cognitive domains. The predictive value of specific neurocognitive domains and other clinical variables for symptomatic and functional outcome and clinical recovery after a 2-year follow-up is explored in a group of 51 patients with non-affective first-episode psychosis. A comprehensive neurocognitive battery was administered 18 and 41 weeks after inclusion. Other patient characteristics, which were expected to independently predict clinical recovery, were assessed at baseline. Several neurocognitive tests, especially tests measuring speed of processing, and among others, Duration of Untreated Psychosis (DUP), were significant predictors of clinical recovery. Poor neuropsychological performance accurately predicted non-recovery, but improved neuropsychological performance did not accurately predict recovery. This study confirms previous findings of an association between neurocognition and outcome, but the results also suggest that in order to accurately predict recovery, the role of other factors needs to be investigated.

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1. Introduction

Schizophrenia is a disabling psychiatric disorder in which neurocognitive defects are common (Heinrichs and Zakzanis, 1998). Negative and positive symptoms are core features of the disorder according to current classification systems such as the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). Although disturbance in neurocognition is not incorporated in these classification systems, cognitive functioning has been found to be related to functional outcome of the disorder in cross-sectional studies in chronic patients (Green et al., 2002) and in longitudinal studies in chronic and first episode patients (Green et al., 2004; Robinson et al., 2004; Milev et al., 2005; Holthausen et al., 2007; Gonzalez-Blanch et al., 2010). However, the relationship between neurocognitive defects and long-term functional outcome is not evident. The data do not clarify whether any, and if so, which cognitive domains predict functional outcome (Nuechterlein et al., 2008). An additional problem is the definition of functional outcome, which is a broad and multifaceted concept. Consequently, there is a need for standardized criteria for functional outcome that can be reliably assessed.

In this study, clinical recovery was defined as the combination of both symptomatic and functional remissions, sustained during a certain time frame, according to the criteria proposed by Wunderink et al.

(2009). In short, the criteria for symptomatic remission were adopted from Andreasen et al. (2005), incorporating a selection of items from the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) with an observational period of the last 9 months of a 2-year follow-up period. Functional remission was assessed with the use of the Groningen Social Disabilities Schedule (GSDS) (Wiersma et al., 1990), with the same time frame.

The predictive value of specific neurocognitive domains and clinical variables for clinical recovery was explored in a group of patients with non-affective first-episode psychosis. First we investigated the extent to which symptomatic remission and functional remission were associated with achieving clinical recovery and the extent to which symptomatic remission was associated with functional remission.

Secondly, we investigated whether clinically recovered and non-recovered patients differed at baseline in general psychopathological and sociodemographic characteristics, and whether they differed in neurocognitive performance 18 weeks and 41 weeks after inclusion (i.e. after achieving remission status). Based on these analyses, we then applied a binary logistic regression analysis to identify factors predicting clinical recovery.

Several studies show that although neurocognitive impairments in patients, relative to controls, seem to be stable after the onset of psychosis, neurocognitive performance improves over time, both in controls and in patients (Hoff et al., 1999; Albus et al., 2006). This may be the result of practice effects (Goldberg et al., 2007), but in patients it may also be related to clinical recovery (either as a facilitator or as a

* Corresponding author. Tel.: +31 653395358; fax: +31 102880785.

E-mail address: g.faber@yulius.nl (G. Faber).

result). We therefore additionally investigated whether a greater improvement in neuropsychological performance from the first to the second test is associated with a greater chance of clinical recovery.

2. Methods

2.1. Patient sample

The study was an add-on to an observational prospective study of a first episode cohort of non-affective psychosis over a period of 2 years with assessments at baseline, after 6, 15 and 24 months (Wunderink et al., 2007, 2009). The patients included in this study were first episode patients, aged 18–45 years, who had never been treated before, showed a sufficient treatment response with reduction of positive symptoms (defined by a maximum of 1 score of 4 on the positive sub-scale of the PANSS) within the first 6 months of treatment and did not relapse during at least 6 months before entering the study. Patients were asked to participate as soon as they were able to understand the consequences of participation. After written informed consent had been obtained, the patients were diagnosed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1992). Only patients with first onset psychosis in the schizophrenia spectrum were included. A total number of 125 patients were included in the parent study.

Due to a delay in the start of this add-on study (the medical ethical committee required additional approval) only the second half of the patients included in the main study could be asked for informed consent for a first neuropsychological assessment after inclusion and a second assessment 10 months after inclusion. Major sociodemographic variables were recorded at baseline. Psychopathology (PANSS) and quality of life (World Health Organization Quality of Life scale-abbreviated version, WHOQOL-BREF) were assessed at baseline and furthermore 6 (T6), 15 (T15) and 24 (T24) months after inclusion and social role functioning (GSDS) at baseline and at 15 and 24 months.

Furthermore, the research nurse gathered information from the clinician (and when deemed necessary also from the patient and family) on medication status (type, dosage and adherence), social functioning and possible relapses on a monthly basis. Clinicians were instructed to directly inform the research nurses of changes in psychopathology or social functioning. Stable remission required sustained improvement of symptoms, reflected by symptom severity levels at or below the level of remission as monitored by the clinician. In case of a possible relapse this was subsequently confirmed with a PANSS assessment carried out by a research nurse.

Patients in this subsample used atypical antipsychotics in more than 95% of cases (mainly risperidone and olanzapine). The average dosage was around 2.5–3 mg haloperidol equivalents per day. Medication adherence (assessed by the clinician on the basis of information provided by the patient) was high, with an estimated average of around 90% of the prescribed medication taken adequately.

Full data on recovery (i.e. baseline predictors and outcome measures) after 24 months were available from 45 patients (from 51 who consented). The diagnoses at inclusion according to DSM-IV for this sample were: schizophrenia ($n=18$), schizophreniform disorder ($n=5$), schizoaffective disorder ($n=1$), brief psychotic disorder ($n=4$), delusional disorder ($n=3$) and psychotic disorder not otherwise specified ($n=14$).

The study was approved by the Medical Ethical Committee of the University Medical Center Groningen.

2.2. Symptomatic remission

Criteria for symptomatic remission were adopted from Andreasen et al. (2005). In accordance with these criteria the PANSS was used to assess the relevant symptoms: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), N1 (blunted affect), N4 (social withdrawal), N6 (lack of spontaneity), G5 (mannerisms/posturing) and G9 (unusual thought content). All relevant item scores have to be 3 (mild) or less, on a scale ranging from 1 (not present) to 7 (severe). During a certain observational period (according to Andreasen et al., 6 months; in this study, 9 months), patients have to be monitored for symptomatic relapse. Symptomatic relapses are then defined as an exacerbation of symptoms during at least 1 week with at least one relevant PANSS item score above 3 (mild). No symptomatic relapses are allowed during the agreed observational period for the patient to be considered in symptomatic remission.

2.3. Functional remission: the assessment of social functioning

Functional remission implies proper social functioning in the main domains of everyday life: personal care, living, working, and relating to others (Liberman and Kopelowicz, 2005).

We used the GSDS to measure social functioning in our patient sample (Wiersma et al., 1990; Wiersma, 2005). Social role functioning in this instrument is measured against normative expectations in a certain cultural context. The reference group consists of people from the same cultural background in a comparable position, and the assessment incorporates expectations of key figures in the individual's inner circle. Social disabilities are assessed by means of a semi-structured investigator-based interview with the patient and when deemed necessary corroborated by information from clinicians, family and other relevant caregivers. The GSDS measures social functioning and adjustment over the last 4 weeks in eight social roles, each of which is

composed of different role dimensions: Self-care, Housekeeping, Family relationships, Partner relationships, Community integration, Relationship with peers, Vocational role and Parental role. For instance when exploring the Vocational role, information is gathered about: daily routine, working performance, contacts with colleagues and goal-directedness of activities. A disability is rated by the investigator on a 4-point scale: no (0), minimal (1), obvious (2) and serious (3) disability. The scores on each role have anchor points, describing the nature and severity of the corresponding problems with criteria for (a) the frequency and duration of the functional deficits; (b) the damage inflicted to the individual or to others; and (c) the need for help.

In this study, the parental role was left out because of limited applicability. A total disability score was calculated by combining seven role scores, ranging from 0 to 21. We decided that a functionally remitted patient should function adequately in all seven social roles with none or only a minimal disability in any of the roles (not allowing a score of 2 or 3 on any GSDS role).

2.4. Operational criteria for clinical recovery

The proposed clinical recovery criteria are based on two dimensions: symptomatic remission and functional remission, which should be sustained during a prolonged period. In this study the last 9 months of a 24-month follow-up period after first treatment response was chosen as the observational window through which social functioning and symptomatology were monitored to establish the occurrence of the clinical recovery status. Patients were considered to have recovered if at both assessments (e.g. 15 and 24 months after inclusion) PANSS criteria for remission according to Andreasen et al. (2005) were fulfilled, and GSDS role functioning scores were ≤ 1 , without a symptomatic relapse or social deterioration during the observation period.

2.5. Predictors of clinical recovery

As possible predictors of clinical recovery we recorded age, gender, living situation (living alone vs. with others), level of education (no or lower education (L), secondary education (S), higher education or university (H)), diagnosis (SCAN interview), use of illicit drugs (SCAN interview), antipsychotic dosage, baseline psychopathology (PANSS-Positive (P), -Negative (N) or -General (G) sub-scales), social functioning (GSDS), quality of life (WHOQOL-BREF), duration of untreated psychosis (DUP) and time to response of positive symptoms (TTR).

DUP was assessed during the SCAN interview and defined as the time between the first manifestation of any positive psychotic symptom and the start of antipsychotic treatment. TTR was defined as the time from the start of antipsychotic treatment to first treatment response. The baseline measurement of the GSDS was related to the 1-month period prior to the first mental health contact. Quality of life was assessed with the WHOQOL-BREF, a 26-item self-report questionnaire, comprising satisfaction with health, psychological functioning, social relationships and environmental opportunities, as experienced over the last 2 weeks. Each item is scored on a five-point scale, higher scores indicating better quality of life. We used the total score, ranging from 26 to 130 (O'Carroll et al., 2009).

The neurocognitive test battery, administered by trained neuropsychologists, consisted of the Stroop color naming and Stroop color-word naming tests (time to complete in seconds; Stroop, 1935), the Continuous Performance Test (CPT-RT, sustained attention version, reaction time in milliseconds; Smid et al., 2006), Trailmaking Test A (connecting letters) and B (connecting alternately digits and letters, time to complete in seconds; Spreen and Strauss, 1998), Verbal Fluency (animal and profession categories, total number of words produced; Benton and Hamsher, 1978), Symbol Substitution, Digit Span Forward and Backward (scaled scores, WAIS-III; Wechsler, 1997), California Verbal Learning Test (CVLT, total recall score; Delis et al., 2000), and Fingertapping (total number of taps; Lezak, 1995).

These tests were chosen because they make it possible to measure performance in different cognitive domains, i.e.: sustained attention (CPT-RT), selective attention (Stroop color-word naming), divided attention (Trailmaking Test B), speed of processing (Verbal Fluency, Trailmaking Test A, Symbol Substitution, Stroop color naming), working memory (Digit Span Forward and Backward), verbal learning and memory (CVLT) and motor speed (Fingertapping) (Nuechterlein et al., 2008).

The first neurocognitive assessment took place on average 18 weeks (T4) after inclusion in the study (i.e. after achieving remission status). Neurocognition was re-assessed on average 23 weeks after the first assessment and thus 41 weeks after inclusion (T10). Complete data from this second testing were available from 39 of the 45 patients.

2.6. Training and reliability

Training and instruction of test psychologists for the neurocognitive battery were conducted on site by the first two authors in order to guarantee uniformity of testing.

Psychiatrists who were trained by the Groningen WHO Training Center administered the SCAN interview. Training of the research nurses for PANSS and GSDS was provided at investigator meetings, supplemented by written training materials. Training for the PANSS and GSDS included rating of a videotaped interview, followed by discussion and review of ratings. Regular booster meetings were organized to maintain interrater reliability. Reliability of the GSDS was established by 12 raters all rating the same 11 subjects. We used another 12 subjects, all rated by 11 raters, to

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