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# Cognition, ethnicity and recovery in early psychosis

Luyken Stouten





**Cognition, ethnicity and recovery in early psychosis**  
Searching for predictors of symptomatic and functional outcome

Luyken Holland Stouten



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VRIJE UNIVERSITEIT

**Cognition, ethnicity and recovery in early psychosis**  
Searching for predictors of symptomatic and functional outcome

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan  
de Vrije Universiteit Amsterdam,  
op gezag van de rector magnificus  
prof.dr. V. Subramaniam,  
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van de Faculteit der Gedrags- en Bewegingswetenschappen  
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door

Luyken Holland Stouten  
geboren te Den Haag

promotoren: prof.dr. M. van der Gaag  
prof.dr. W.A. Veling

*"All we have to decide is what to do with the time that is given to us."*

- J.R.R. Tolkien, *The Fellowship of the Ring*





## Table of contents



## Table of contents

Chapter 1	General introduction	12
Chapter 2	Psychosocial functioning in first-episode psychosis and associations with neurocognition, social cognition, psychotic and affective symptoms	28
Chapter 3	Psychotic symptoms, cognition and affect as predictors of psychosocial problems and functional change in first-episode psychosis	44
Chapter 4	Predicting recovery after a first-episode psychosis	58
Chapter 5	Cognitive deficits and ethnicity: a cohort study of early psychosis patients in The Netherlands	74
Chapter 6	Psychopathology, cognition and functional recovery in Dutch and immigrant first-episode psychosis patients	94
Chapter 7	General discussion	110
References		140
Nederlandse samenvatting		166
Dankwoord		172
Publications		180
Curriculum vitae		184



## **Chapter 1    General introduction**

## The psychosis spectrum

Psychotic disorders, among which schizophrenia, have a lifetime prevalence of around 2-3% (Perälä *et al.* 2007). High heritability estimates indicate a strong genetic component in the overall vulnerability for developing a psychotic disorder (Harrison & Weinberger 2005; Norton *et al.* 2006; Collier 2008; Crow 2008; O'Donovan *et al.* 2008; Sullivan 2008; Ripke *et al.* 2014), especially when coinciding with exposure to environmental risk factors (van Os *et al.* 2010). Although the precise individual and societal burden of psychotic disorders is difficult to estimate, cost-of-illness indications uniformly point to high human and financial costs (Mueser & McGurk 2004). Although current illness prognosis is better than traditionally assumed (Van Os & Kapur 2009), the large variability in illness trajectories and treatment outcome are still poorly understood.

Psychotic disorders are defined by the presence of psychotic symptoms, also referred to as 'positive symptoms', for at least one day for a brief psychotic disorder up to a minimum of one month for schizophrenia (with overall symptoms and/or dysfunctioning present for at least six months). Positive symptoms are defined as a range of experiences that distort reality perception, categorized into delusions (e.g. that behaviour and/or general remarks of others [on the street, radio or TV] are meant especially for them, or holding the belief that one's thoughts are being withdrawn or broadcasted), hallucinations (e.g. hearing voices), disorganized speech (e.g. frequent derailment or incoherence), grossly disorganized or catatonic behaviour (i.e. experiencing an immobile or unresponsive stupor).

In addition, people with a psychotic disorder often experience reduced emotional and volitional responsivity. These so-called 'negative symptoms' manifest in the form of affective flattening, poverty of speech (alogia) or general lack of drive (apathy, avolition), are generally present before the onset of positive symptoms and tend to be unaffected or even worsened by pharmacological treatment.

Aside from these symptom domains and the aspect of symptom duration, the psychosocial functioning of the individual must also be significantly impaired in one or more major areas (e.g. study, work, social relationships) for a set period of time for a diagnosis within the psychosis spectrum to be applicable.

Lastly, there are a number of exclusion criteria that need to be considered, namely whether or not the manifested symptoms can be accounted for by another mental or physical disorder, or as a result of substance use. To summarize, all characteristic symptom domains and diagnostic criteria for psychotic disorders according to the fifth version of the Diagnostic and Statistical Manual (DSM-5) are presented in Table 1.1.

**Table 1.1** Characteristic symptoms and other diagnostic criteria for schizophrenia

<b>A</b>	<p><b>Characteristic symptoms</b></p> <p>Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2) or (3):</p> <ul style="list-style-type: none"> <li>(1) delusions</li> <li>(2) hallucinations</li> <li>(3) disorganized speech (e.g., frequent derailment or incoherence)</li> <li>(4) grossly disorganized or catatonic behaviour</li> <li>(5) negative symptoms (i.e., diminished emotional expression or avolition)</li> </ul>
<b>B</b>	<p><b>Social/occupational dysfunction</b></p> <p>For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic or occupational achievement).</p>
<b>C</b>	<p><b>Duration</b></p> <p>Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).</p>
<b>D</b>	<p><b>Schizoaffective and Mood Disorder exclusion</b></p> <p>Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.</p>
<b>E</b>	<p><b>Substance/general medical condition exclusion</b></p> <p>The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.</p>
<b>F</b>	<p><b>Diagnosis of schizophrenia in addition to an autism spectrum disorder</b></p> <p>If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).</p>

Source: *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, 5<sup>th</sup> edition

When the symptoms (A-criterion; Table 1.1) are severe, they are easy to identify. Symptom expression in the early stages of psychosis, however, is often subtle and covert, and much closer to what might be considered ‘normal’. However, as a result of the current categorical approach used to classify mental disorders, clinicians and researchers need to answer questions, like ‘What *are* normal experiences and behaviours for



adolescents or young adults?', and 'Will the observed (mild) symptoms or dysfunctional behaviours remit spontaneously (i.e. benign or self-limiting states), or are they early markers of underlying chronicity that should be intervened upon as soon as possible?'. This issue is further complicated by the fact that psychotic experiences are quite common in the general population, and are not unequivocal indicator of pathology (Johns & van Os 2001). Overall, it can be difficult to distinguish mental illness from 'normal' (or transitory) changes in experiences, emotions and behaviour, particularly in young people in the early stages of a mental illness like psychosis (McGorry *et al.* 2010).

Moreover, the current categorical diagnostic system lacks therapeutic validity, since it does not reflect the heterogeneity of symptoms, illness severity and course of illness. Subsequently, it does not provide differential treatment guidelines, i.e. ranging from preventive interventions for those that might be at risk for a specific disorder but do not yet have any symptoms, to those who have been chronically ill for decades and are in need of daily or even fulltime care. As the situation is now, clinicians are left to navigate, without any clear guidelines, between doing too much and doing too little for those that might be in the early stages of a serious mental disorder.

In an attempt to advance description of diagnostic categories, McGorry and colleagues (2010) developed a heuristic clinical staging model (McGorry *et al.* 2010) (see also Table 1.2), which defines both the extent of progression of a disorder at a particular time point (i.e. clinical stages), and where an individual currently is along the continuum of the course of an illness (i.e. stage-specific diagnoses). Also, it provides specific guidelines to what interventions might be suitable at various stages. Due to the transitory design (i.e. patients will move up (i.e. moving back to stage 3 after reaching stage 4) or down through the different stages, depending on changes in illness expression and treatment outcome over time), this model might prove particularly useful in differentiating early, milder clinical phenomena from those that accompany illness progression and chronicity (McGorry *et al.* 2010). Structuring the present study within this conceptual framework, all data presented in this thesis was collected from patients in stage 2, first episode of psychosis.

When examining this model, it becomes apparent that major changes in symptom expression and functional problems occur in stages 1 and 2, also known as 'the critical period'. The concept of 'critical period' in psychotic disorders has been formulated to indicate period of rapid progression of symptomatic, cognitive and psychosocial decline that occurs in the early stages of these disorders (i.e. stage 1 and 2), including the period of untreated psychosis (Birchwood *et al.* 1998; Marshall & Rathbone 2006). After these early stages, progression of morbidity is assumed to slow down or stop, and the level of disability remains stable or recovery is attained (Crumlish *et al.* 2009).

**Table 1.2** Clinical staging model framework for psychotic and severe mood disorders

Stage	Definition	Target populations for recruitment	Potential interventions
<b>0</b>	Increased risk of psychotic or severe mood disorder; no symptoms currently	First-degree relatives of probands (especially aged 12 to 25 years)	Improved mental health literacy, family education, drug education, and brief cognitive skills training
<b>1a</b>	Mild or nonspecific symptoms, including mild neurocognitive deficits of psychosis or severe mood disorder; mild functional change or decline	Screening or active case finding within teenage and emerging adult populations; referral by primary care physicians, school counsellors, and self- and family referrals	Formal mental health literacy and first aid; supportive counselling and problem solving; family psycho-education; exercise; active substance abuse reduction
<b>1b</b>	UHR: moderate but subthreshold symptoms, with moderate neurocognitive changes and functional decline to caseness (GAF 70)	Referral by educational agencies, primary care physicians, emergency departments, welfare agencies, drug and alcohol agencies, police and forensic services, and self- and family referrals	Family psycho-education; individual and (or) group CBT; cognitive remediation and social cognition interventions; active substance abuse reduction; neuroprotective agents (for example, omega-3 and other candidates)
<b>2</b>	FEP or severe mood disorder (mania or severe or persistent depression); full threshold disorder with moderate-to-severe symptoms, neurocognitive deficits and functional decline (GAF 30-50)	Referral by primary care physicians, emergency departments, welfare agencies, specialist care agencies, drug and alcohol services, police and forensic services, and self- and family referrals	Family psycho-education; CBT; active substance abuse reduction; atypical antipsychotic agents for psychotic symptoms, if present; antidepressant agents or mood stabilizers for full mood syndrome; vocational rehabilitation
<b>3a</b>	Incomplete remission from first episode of care; could be linked or fast-tracked to Stage 4	Primary and specialist care services	As for 2, with additional emphasis on medical and psychosocial strategies to achieve full remission
<b>3b</b>	Recurrence or relapse of psychotic or mood disorder that stabilizes with treatment at a level of GAF, residual symptoms, or neurocognition below the best level achieved following remission from FEP or mood disorder	Primary and specialist care services	As for 3a, with additional emphasis on relapse prevention and early warning signs strategies
<b>3c</b>	Multiple relapses, when worsening in clinical extent and impact of illness is objectively present	Specialist care services	As for 3b, with emphasis on long-term stabilization
<b>4</b>	Severe, persistent, or unremitting illness as judged on symptoms, neurocognition, and disability criteria	Specialist care services	As for 3c, but with emphasis on clozapine, and augmentation strategies, assertive community treatment

Source: McGorry *et al.* 2010

It seems unlikely that associations between illness dimensions (i.e. psychopathology, affect, psychosocial problems and environmental factors) are comparable across different stages of the illness (clinical staging model: McGorry *et al.* 2010) (see Table 1.2), since all these variables follow different trajectories. Also, samples across illness stages do not contain similar sets of individuals. At-risk or first-episode psychosis patient samples (stage 1b and 2) incorporate the full range of psychopathological profiles, genetic- and environmental parameters, and therefore include both good and poor prognoses. In contrast, chronic patient samples (stage 4) have gone through a selective drift and will, by definition, only contain “poor prognosis patients”.

Taken together, it is clear that findings from one illness stage (e.g. stage 4; chronic psychosis) cannot be generalized to other illness stages (e.g. stage 2; first-episode psychosis). Combined with the fact that most studies to date have been done in patients with a long duration of illness (stage 3 and 4), this constitutes a central problem when attempting to understand psychosocial problems during the critical period that encompasses illness onset.

### **The cognitive dimension**

Although nowadays the psychotic disorders are primarily defined by the presence of positive and/or negative symptoms in the DSM (see Table 1.1), it was not always so. When schizophrenia was first described about one century ago, primary focus was on the general cognitive deterioration that Kraepelin observed in the large number of cases he studied (Kraepelin 1919). Based on his observations, he did not consider delusions and hallucinations ‘core’ symptom dimensions (i.e. necessary for diagnosis) for his *dementia praecox* classification (first described in 1891). Building on this work, it was Eugen Bleuler who shifted the emphasis more towards what we nowadays would call positive and negative symptoms (i.e. ‘deficits in associations’, ‘dysregulated affect’ and ‘ambivalence’), and categorized the cognitive deterioration as ‘secondary symptoms’. Subsequently, he coined the classification term *schizophrenia* to describe this pathological model (first described in 1908).

During the ensuing decades, European and American clinicians proposed changes to this nosological model. The European focus was directed more towards cognitive decline and the Americans approach put more emphasis on positive symptoms. These different perspectives were integrated into a new united model in DSM-II, that included criteria relating both to a substantial period of dysfunctional behaviour (assumed to be a proxy for general intellectual deterioration) and also to the (prolonged) presence of positive symptoms (APA 1968). Although this consensus was an important step in unifying these aspects into a single model, understanding of the development and course

of psychotic disorders at that time was still poor. To quote Ernest Gruenberg on this point, chairman of the Committee on Nomenclature and Statistics of the APA at that time, as he noted in the foreword of the DSM-II in 1968: *"Consider, for example, the mental disorder labelled in this Manual as "schizophrenia," which, in the first edition, was labelled "schizophrenic reaction." The change of label has not changed the nature of the disorder, nor will it discourage continuing debate about its nature or causes. Even if it had tried, the Committee could not establish agreement about what this disorder is; it could only agree on what to call it."* Clearly, some unresolved etiological and nosological issues there. And over four decades later, they are still far from resolved ([www.psychosenet.nl/bestaat-schizofrenie-wel-niet/](http://www.psychosenet.nl/bestaat-schizofrenie-wel-niet/)).

Although both current classification systems (i.e. the American DSM-5 and European International Classification of Diseases, Mental and Behaviour Disorders, ICD-10) do not include cognitive deterioration as a diagnostic criterion, cognitive deficits have attracted a resurgence of scientific and clinical interest. This effort has primarily been driven by the hypothesis that cognitive deficits (Allott *et al.* 2011; Fett *et al.* 2011; Mancuso *et al.* 2011; Fett & Maat 2013) might predict the large secondary impairment associated with psychotic disorders (e.g. psychosocial and psychological dysfunction) more accurately than positive symptoms (Green 1996; Heinrichs & Zakzanis 1998; Green *et al.* 2000a, 2004; Allott *et al.* 2011; Fett *et al.* 2011).

In the study of cognitive performance in psychotic disorders, two interrelated but largely independent constructs are identified, i.e. 'neurocognition' and 'social cognition' (Green *et al.* 2008; van Hooren *et al.* 2008). Neurocognition can generally be defined as a set of 'core' cognitive abilities involved in processing, linking and appraising of stimuli. The current consensus on the comprehensive neurocognitive assessment in psychotic disorders consist of six subdomains: 'speed of processing', 'attention/ vigilance', 'working memory', 'verbal learning', 'visual learning', and 'reasoning/problem solving' (Kern *et al.* 2004; Nuechterlein *et al.* 2008). The measures used in the studies presented in this thesis to assess neurocognitive performance are presented in Table 1.3.

Social cognition generally refers to the cognitive abilities needed to process information within a social context, i.e. to construct mental representations about others, oneself and relationships between people; social cognition enables people to draw inferences about other people's beliefs and intentions and to judge social situational factors in making these inferences (Green *et al.* 2008). There is no consensus on what domains should be included in a comprehensive social cognitive assessment, although 'theory of mind', 'emotion perception', 'social knowledge' and 'attribution bias' are most often studied in this context (Green *et al.* 2008). The measures used in the studies presented in this thesis to assess social cognitive performance are presented in Table 1.4.

**Table 1.3** Neurocognitive measures used in this thesis per cognitive domain

Domain	Measure	Description	Indicator
<i>Attention/ Vigilance</i>	Continuous performance task (3-7 version; Berisoft cooperation n.d.; Nuechterlein & Dawson 1984)	This computer based task presents series of single digits (range 0-9) at a rate of one per second. Participants press a response button whenever a "3" is directly followed by a "7".	Hit rate, discrimination index
	Block design subtest (WAIS-III; Wechsler 1997)	Participants reproduce a number of visual 2D patterns (between 4 and 14, depending on performance) with 3D blocks as fast as possible.	Score index (based on correct completion, difficulty of completed trials and completion speed)
<i>Problem solving</i>	Tower of London (Shallice 1982)	Participants are presented with a computer screen and a wooden puzzle made up out of a frame with three pegs in different lengths and three balls in different colours in a pre-set position (start state). In consecutive order, goal positions (between 3 and 12, depending on performance) are presented on the screen, and participants were instructed to transform the start state into the goal state in a minimum number of moves.	Score index (based on correct completion and difficulty of the completed trials).
	Digit-Symbol coding subtest (WAIS III; Wechsler 1997)	Participants copy symbols that are paired with numbers. Using a key, participants draw the matching symbol under the corresponding number.	Total correct responses in 120 seconds.
<i>Speed of processing</i>	Trailmaking task, part A (Reitan 1958)	Participants connect numbers 1 to 25 in consecutive order as fast as possible.	Total time needed to complete task correctly.
	Category fluency task, animal naming (Lezak et al. 2004)	Participants name as many different animals as possible within 60 seconds.	Total unique correct responses in 60 seconds.
<i>Verbal fluency</i>	Rey Auditory Verbal Learning Task (RAVLT; Kalverboer & Deelman 1986)	Participants memorize and reproduce a list of 15 verbally presented words over a series of five trials. After a 15 minute delay, participants attempt to recall the words (free recall). After the free recall, 30 words are verbally presented sequentially and participants must determine for each word whether or not it was presented to them during the learning trials.	Number of words correctly recalled in the five learning trials and recall trial. Number of correct recognitions.

<i>Visual learning</i>	Brief Visuospatial Memory Task - Revised (BVMT; Benedict 2007)	Participants are presented with an A4 sized paper with 6 abstract figures for 10 seconds and memorize and reproduce as much figures in three consecutive learning trials. After a 15 minute delay, participants attempt to recall and draw the figures (free recall). After the free recall, 12 figures are presented sequentially and participants must determine for each figure whether or not it was presented to them during the learning trials.	Total points scored for the three learning trials and for the one recall trial, based on the accuracy and location of the drawn figures. Number of correct recognitions.
<i>Working memory</i>	Letter-Number Sequencing subtest (WAIS III; Wechsler 1997)	Participants are verbally presented with a number of strings (between 3 and 21, depending on performance) of letters and numbers and must repeat them in a re-ordered sequence: first the numbers in numerical order and then the letters in alphabetical order.	Number of correctly reproduced letter-number strings.
<i>General cognition</i>	Information subtest (WAIS III; Wechsler 1997)	Participants are verbally presented with a number of "common knowledge" questions (between 5 and 28, depending on performance).	Number of correct responses.
	Calculations subtest (WAIS III; Wechsler 1997)	Participants are verbally presented with a number of arithmetic problems (between 4 and 20, depending on performance). Participants must solve the problems (without paper/pencil) and present the correct answer.	Number of correct responses.

Both neurocognitive (Hoff *et al.* 2005; Bozikas & Andreou 2011; Barder *et al.* 2013) and social cognitive deficits (Green *et al.* 2011; Thompson *et al.* 2011; Horan *et al.* 2012) occur early in the course of psychotic disorders (or even before onset of psychotic symptoms) and generally tend to improve marginally or remain stable over time (Szöke *et al.* 2008). In chronic schizophrenia, cognitive deficits are strongly related to worse functional outcome (Green 1996; Heinrichs & Zakzanis 1998; Green *et al.* 2000a, 2004; Fett *et al.* 2011). Although this association is evident in the end-stage of the illness (McGorry *et al.* 2006, 2010), it is likely that this association is different in the earlier stages of these disorders (Allott *et al.* 2011; Fett *et al.* 2011).

**Table 1.4** Social cognitive measures used in this thesis per cognitive domain

Domain	Measure	Description	Indicator
<i>Facial emotion perception</i>	Amsterdam Neuropsychological Tasks (ANT; Sonnevile 2005)	Participants are presented with a photo of a face displaying the target emotion (i.e. "happy") on a screen. Subsequently, 40 faces (including 20 targets) are sequentially displayed on the screen and participants must determine for each face whether or not it displays the target emotion or a different emotion through pressing the appropriate button. This process was performed for a total of eight emotions (Happy, Sad, Angry, Fearful, Surprised, Disgusted, Shameful, and Contempt).	Hits, false alarms, discrimination index (based on the hits/false alarm ratio) and reaction time.
<i>Theory of mind</i>	Hinting task (Corcoran <i>et al.</i> 1995)	Participants are verbally presented with ten short stories, in which person A makes an implicit request of person B. Participants are first asked what person A really meant to say (meaning the explicit request). If answered incorrectly, participants are asked a follow-up question (hint) "What does person A want person B to do?". A total score was computed based on the number of correct responses.	Score index (based on correct responses before and after hint were provided).
<i>Social knowledge</i>	Picture Arrangement subtest (WAIS III; Wechsler 1997)	Participants are presented with a set of shuffled picture cards. Participants rearrange the pictures into a logical sequence.	Score index
<i>Social cognitive biases</i>	Davos Assessment for Cognitive Biases Scale (DACOBS; van der Gaag <i>et al.</i> 2013)	Participants completed the DACOBS questionnaire. Three subscales were selected to assess social cognitive biases: (1) Attention for Threat subscale (AFT) assesses the preoccupation with possible (social) threats from the environment, (2) External Attribution bias subscale (EA) assesses the tendency to attribute the cause of personal hardships to (the harmful intent of) others, and (3) Social Cognitive Problems subscale (SCP) assesses general problems with interpreting other people's thoughts, feelings and behaviours. Higher scores reflect greater cognitive bias.	Score index per subscale (based on selected answers).

### Functional problems in people with a psychotic disorder

The peak incidence of psychosis onset occurs during late adolescence and early adulthood (Jablensky 2000). Since this period is generally characterized by pivotal academic, vocational and social development, the onset of psychosis frequently contributes to

pronounced social (e.g. disrupted academic development; unemployment; downwards social drift; institutionalization; diminished social network; family discord; social stigma associated with mental illness) and psychological difficulties (e.g. loss of confidence and achievement motivation; social and community survival skills impaired or fall into disuse; dependent or semi-independent on family or institutions; distress due to poor coping with persisting symptoms) during and after this critical period. This, together with the often chronic nature of these disorders, means that their psychosocial impact often continues for several decades (Lin *et al.* 2013a). But even though psychosocial problems in people with psychosis have been studied extensively, mechanisms that account for these problems are still poorly understood. Why is comprehending these deficits so difficult?

In first part, this may be due to the fact that it took science several decades to disprove the basic assumption that the core of problems observed in people with psychotic disorders were caused by positive symptoms, as is still strongly reflected in their primary position among the diagnostic criteria for schizophrenia (APA 2013b). But even though this hypothesis maintains a high face-validity, it has been convincingly refuted (Green 1996; Heinrichs & Zakzanis 1998; Green *et al.* 2000a, 2004; Allott *et al.* 2011; Fett *et al.* 2011).

Researchers to date are working to verify and extend two basic paradigms on the nature of these functional deficits. The first basic paradigm states that psychosocial functioning may be an early marker of a chronic developmental illness that has already begun before the onset of psychotic symptoms (Lin *et al.* 2013a). The second basic paradigm states that psychosocial problems are the result of a wide range of illness-related factors, such as positive and negative symptoms, but also depression, anxiety, demoralization, social stigma and substance use (Killackey & Yung 2007). Obviously, these paradigms are not mutually exclusive and are likely to reflect parallel processes. However, considering the sizeable implications for interventions aiming to improve functional outcome in people with psychotic disorders that both these paradigms have, further study of these causative models remains crucial. This is especially true considering the early stages of psychotic disorders, in which young people are less far removed from their psychosocial trajectories; that is to say, the impact of the secondary consequences of having a mental illness (like unemployment or a diminished social network) has been relatively short (compared to chronic patients), and distinction between paradigms and effective intervention might therefore be more achievable.

### **Psychotic disorders and the environment: ethnic minority position**

In work aimed to understand the underpinnings of psychotic disorders, genetic predisposition has often been emphasized (Harrison & Weinberger 2005; Ripke *et al.*



2014). However, epidemiological data indicate that there are also environmental risk factors that increase vulnerability for psychotic disorders (van Os *et al.* 2010). As a result, the current etiological perspective tends more toward the idea that the onset of psychosis is not a direct result of this genetic predisposition, but rather of the way this vulnerability is enkindled by environmental factors such as early life trauma (Varese *et al.* 2012), growing up in an urban environment (Krabbendam & van Os 2005), minority group position (Mustanski *et al.* 2010; Bourque *et al.* 2011; Veling 2013) and cannabis use (Moore *et al.* 2007).

To better understand these environmental mechanisms, many studies attempted to study populations with elevated exposure to many (or all) of these environmental risk factors. Not surprisingly therefore, ethnic minority populations have often been studied in this context (Veling 2013). Since psychosis incidence rates are frequently elevated in ethnic minority populations compared to native populations (Bourque *et al.* 2011), comparison of symptom expression and illness trajectories between immigrant and non-immigrant patients might yield valuable insight into these environmental risk factors (van Os *et al.* 2010).

The epidemiological study of psychotic disorders, meta-analytic data shows a two-fold increase (or higher) in the incidence of these disorders in immigrants compared to non-immigrants across studies performed in America, Europe, the Middle East and Australia (Selten *et al.* 2007a; Bourque *et al.* 2011).

A key issue that must be mentioned here is misdiagnosis / diagnostic bias, i.e. the systemic tendency to over-diagnose psychotic disorders in immigrants compared to non-immigrants. Diagnostic bias is defined as clinicians missing or misinterpreting crucial diagnostic information because of insufficient attention to social, cultural and contextual factors that shape symptom expression and illness behaviour (Veling 2013). The literature on this issue illustrates three points, (1) 'general' diagnostic procedures leave much to be desired (Gara *et al.* 2012); (2). 'Culturally sensitive' diagnostic procedures tend to have better overall quality than 'general' diagnostic procedures, by including more comprehensive individual assessment and standard incorporation of information from key informants (Zandi *et al.* 2010; Adeponle *et al.* 2012); (3). Most common effects of diagnostic bias are (a) overvaluing of positive symptoms and (b) overlooking or undervaluing affective symptoms (Gara *et al.* 2012).

Aside from diagnostic bias, initial study of mechanisms that might account for the differences in incidence between groups from various ethnic backgrounds predominantly focussed on factors that might predispose immigrants to an increased risk for psychosis; i.e. people at risk for psychosis are less likely to be well integrated and generally 'at ease' in their country of origin and are therefore more likely to emigrate, resulting in an

artificially increased overall risk for psychosis in immigrants. However, the hypothesis of selective migration to account for the increased incidence of psychotic disorders in immigrants has been refuted (van der Ven *et al.* 2014).

Subsequently, recent scientific effort tends to focus more on the personal experiences that result from being part of a minority group with a disadvantageous socio-environmental position ('social defeat hypothesis', Selten *et al.* 2007a: e.g. *non-heterosexual orientation*, Gevonden *et al.* 2013; *hearing impairment*, van der Werf *et al.* 2011; *childhood adversity*, van Dam *et al.* 2012; Kraan *et al.* 2015a; *discrimination*, Veling *et al.* 2008a; *social marginalization*; van der Ven *et al.* 2016) as is in line with the socio-environmental paradigm that is currently dominant is the study of psychosis (van Os *et al.* 2010).

Notwithstanding our increased comprehension of the increased incidence of psychosis in ethnic minority groups that this paradigm shift has yielded, we still know little of possible differences in symptom expression, illness trajectories and functional outcome between these groups. Due to variation in the aforementioned socio-environmental aetiology components between these groups, it seems plausible that symptom expression and illness course are present, might be affected by these same components, and may subsequently yield clinically relevant insight into differences between these groups. In the present study, the following groups definitions will be used to study some of these issues: 'Dutch', i.e. patients who were born in The Netherlands with two Dutch-born parents); 'first generation immigrants', i.e. patients who were born abroad; 'second generation immigrants', i.e. patients who were born in The Netherlands and had at least one parent born abroad.

### **Outline and scope of this thesis**

This thesis aims to advance our understanding of the impact that neurocognitive- and social cognitive deficits, biases and problems have on illness trajectory and psychosocial performance early in the course of psychosis. To this end, the impact of these cognitive factors on psychosocial and psychopathological outcome will be studied in the first year after baseline contact in a large cohort sample of first-episode psychosis (FEP) patients, both as a single group and also between subgroups from different migration backgrounds.

Specifically the following research questions will be addressed:

### **Part I: symptom profiles, cognitive performance and psychosocial functioning in early psychosis patients**

## Chapter 2

Which neurocognitive and social cognitive problems can be identified in patients with first episode psychosis? How are these cognitive factors related to (other) psychopathology dimensions in FEP? Do these cognitive factors contribute to understanding current psychosocial problems, in addition to current psychotic- and affective problems?

## Chapter 3

To what extent are current and short-term future psychosocial functioning in FEP patients influenced by baseline psychotic symptoms, affective problems and deficits in specific neurocognitive- and social cognitive subdomains?

## Chapter 4

What symptomatic and cognitive variables distinguish between individuals with and without recovery in the first 12 months after baseline? And what factors discriminate between those who keep experiencing symptoms but function well from those who are largely free of symptoms but function poorly?

## **Part II: ethnic differences in cognitive performance, illness expressions and recovery in early psychosis patients**

## Chapter 5

Do immigrant patients have cognitive deficits similar to non-immigrant patients? Do cognitive differences and/or similarities between immigrant and non-immigrants patients give any clues to whether or not misdiagnosis explains increased incidence rates in immigrants?

## Chapter 6

What are notable differences in symptom expression between Dutch, first-generation immigrant and second-generation immigrant first-episode psychosis patients? How does this impact psychosocial functioning differently across ethnic groups in the first year after baseline?

### **Part III: summary and discussion**

#### **Chapter 7**

The main findings are summarized and integrated with the available literature, considering important strengths and limitations. Furthermore, key implications for early psychosis diagnostic procedures, treatment programs, and future research are discussed.



## **Chapter 2   Psychosocial functioning in first-episode psychosis and associations with neurocognition, social cognition, psychotic and affective symptoms**

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## Abstract

**Aim** Most studies on the determinants of psychosocial functioning in first-episode psychosis used few predictors. This study examines the effects of multiple cognitive domains and multiple symptoms on psychosocial functioning.

**Methods** A total of 162 patients with a first-episode psychosis were assessed within three months after referral to an early-psychosis treatment department. Four psychopathological subdomains (positive and negative symptoms, depression and anxiety) and five subdomains of psychosocial functioning (work/study, relationships, self-care, disturbing behaviour and general psychosocial functioning) were measured. Neurocognitive and social cognitive factors were identified through principal component analyses (PCA) of a 15-measure cognitive battery. Stepwise backward regression models were computed to identify determinants of psychosocial functioning.

**Results** The three neurocognitive and four social cognitive factors identified through PCA were largely independent of psychopathology. The strongest associations were between cognitive factors and anxiety. Higher levels of negative symptoms, poor general neurocognition and poor general social cognition showed strongest associations with impaired psychosocial functioning, followed by low verbal processing speed and low emotion processing speed. Together, these factors accounted for 39.4% of the variance in psychosocial functioning.

**Conclusions** Results suggest that negative symptoms, impaired neurocognition and poor social cognition are related to psychosocial problems in patients with first-episode psychosis. None of the affective or positive symptoms had a marked impact on psychosocial functioning.

## Keywords

Early psychosis; first-episode psychosis; psychosocial functioning; psychopathology; neurocognition; social cognition

## Introduction

Neurocognitive deficits, such as deficits in attention, working memory and processing speed, have been extensively studied in schizophrenia patients and are limiting factors in psychosocial functioning (Green 1996; Heinrichs & Zakzanis 1998; Green *et al.* 2000a, 2004; Fett *et al.* 2011). More recent studies have shown the importance of social cognition for psychosocial functioning (Couture *et al.* 2006; Fett *et al.* 2011; Mancuso *et al.* 2011). Social cognition generally refers to the ability to construct mental representations about others, oneself and relationships between people; it enables to draw inferences about other people's beliefs and intentions and to judge social situational factors in making these inferences. People with schizophrenia often perform poorly on tasks such as facial emotion processing, theory of mind, social knowledge, and social perception (Couture *et al.* 2006; Yager & Ehmann 2006; Fett *et al.* 2011; Mancuso *et al.* 2011). A recent meta-analysis showed that neurocognitive deficits are still studied more frequently than social cognition, but that overall associations with psychosocial functioning appear to be stronger for social cognition domains (Fett *et al.* 2011). Because neurocognitive and social cognition deficits have a common and unique variance, entering both into one analysis can confirm the contribution of each to the domain of psychosocial functioning (Couture *et al.* 2006; van Hooren *et al.* 2008; Pijnenborg *et al.* 2009). Neurocognitive and social cognitive deficits are often evident early in the course of psychosis (Galderisi *et al.* 2009; Mesholam-gately *et al.* 2009; Thompson *et al.* 2012) and appear to be relatively stable over the first years of psychotic illness (Bozikas & Andreou 2011; Green *et al.* 2011; Horan *et al.* 2012; Barder *et al.* 2013). However, although interest has increased, the impact of cognition on functional changes in the early stages of psychosis remains poorly understood (Menezes *et al.* 2006; Lin *et al.* 2011, 2013a).

The main limitation of previous studies on the relationship between cognition and psychosocial functioning is that they included mainly chronic schizophrenia patients and often had limited clinical scope (Fett *et al.* 2011). A systematic review of 22 longitudinal studies on cognitive problems at illness onset as predictors of psychosocial outcome, found strong cognitive predictors but more null associations (Allott *et al.* 2011). However, most of these latter studies lacked statistical power (<0.80 to detect a medium effect size). Based on the eight studies with adequate power (Johnstone *et al.* 1990; Bilder *et al.* 2000; Keshavan *et al.* 2003; Addington *et al.* 2005; Milev *et al.* 2005; Carlsson *et al.* 2006; Holthausen *et al.* 2007; González-Blanch *et al.* 2010), 'processing speed' (Milev *et al.* 2005), 'sustained attention' (González-Blanch *et al.* 2010), 'verbal learning' (Keshavan *et al.* 2003; Milev *et al.* 2005), and 'general cognition' (Keshavan *et al.* 2003; Addington *et al.* 2005; Carlsson *et al.* 2006) were identified as significant indicators of functional outcome



over time in patients with a psychotic disorder. Three studies found no significant cognitive predictor of functional outcome (Johnstone *et al.* 1990; Bilder *et al.* 2000; Holthausen *et al.* 2007). Although social cognition was not examined in any studies in that review, social cognition as a predictor of psychosocial functioning social cognition has yielded promising results (e.g. Green *et al.* 2011; Horan *et al.* 2012b).

Similar issues remain concerning the association between cognition and other symptoms in first-episode psychosis (FEP), where most studies found cognition to be largely independent of psychopathology (Bilder *et al.* 2000; Lucas *et al.* 2004; Galderisi *et al.* 2009). A review of 58 studies investigating both chronic and FEP samples, concluded that neurocognitive deficits are related to negative symptoms, but not to positive and affective symptoms (Dominguez *et al.* 2009). Again, most studies in that latter review concerned chronic samples and social cognition was not included in the analyses. In FEP patients, several studies found significant associations between neurocognitive deficits and negative symptoms (e.g. Williams *et al.* 2008; Kravariti *et al.* 2012). Also, associations have been reported between positive symptoms and social cognitive domains (e.g. Janssen *et al.* 2006; An *et al.* 2010).

The present cross-sectional study has two aims. First, to examine how neurocognitive and social cognitive deficits are associated with (other) domains of psychopathology in FEP. Second, to examine how psychosocial functioning is associated with deficits in both neurocognition and social cognition, as well as with psychopathology (positive and negative symptoms, depression and anxiety), in the early stage of psychosis.

## Methods

### *Participants*

The study included 162 patients who made first contact with our Outpatient Department for early intervention for psychosis (The Hague) between 1 December 2009 and 31 December 2011, who had completed the diagnostic procedure and were diagnosed with a non-affective psychotic disorder (Table 2.1). Patients were referred to our department for a (suspected) psychotic disorder by their general practitioner (11 patients), emergency health services (25 patients), other mental healthcare departments (96 patients) or after hospitalisation (30 patients). All baseline data presented here were collected within 3 months (average 1.8, SD 0.6 months) after the first contact with our department. The study was approved by the local Medical Ethical committee (reference: NL31561.098.10). Informed written consent was obtained from all participants.

### *Diagnostic procedure*

The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing *et al.* 1990) were administered and used to make a DSM-IV diagnosis. The Retrospective Assessment of the Onset of Schizophrenia (IRAOS) (Häfner *et al.* 1992) was used to exclude any patients with a psychotic episode in their history.

### *Measures*

The measures for cognitive performance, psychopathology and psychosocial functioning obtained during this study are described below. Higher scores reflect better performance or functioning, unless otherwise specified.

### *Cognition*

A psychological test battery was compiled with 15 cognitive measures to assess eight neurocognitive domains (see Neurocognition and Appendix I) and four social cognitive domains (see Social cognition and Appendix II). The test battery was administered within 3 months after referral in two separate 75-min sessions. Short descriptions and indicator variables per measure are shown in Appendix I (neurocognitive deficits) and Appendix II (social cognitive). Standardised scores were computed for all cognitive scores based on normative data.

### *Neurocognition*

The neurocognitive measures were selected to include all six neurocognitive domains as identified by the MATRICS consortium (Nuechterlein *et al.* 2008), plus verbal fluency and general neurocognition (Appendix I). Neurocognitive assessment included the subdomains attention (Continuous Performance Task, 3-7 version) (Nuechterlein & Dawson 1984), problem solving (Wechsler Adult Intelligence Scale, WAIS III, Block design; Tower of London) (Shallice 1982; Wechsler 1997) speed of processing (WAIS III, Digit-symbol coding; Trail making task, part A) (Reitan 1958; Wechsler 1997), verbal fluency (Category fluency, animal naming) (Lezak *et al.* 2004), verbal learning (Rey Auditory Verbal learning Task, RAVLT) (Rey 1964; Kalverboer & Deelman 1986), visual learning (Brief Visuospatial Memory Task Revised, BVMT-R) (Benedict 2007), working memory (WAIS III, Letter-number sequencing) (Wechsler 1997) and general cognition (WAIS III, Information and Calculations) (Wechsler 1997).

### *Social cognition*

The social cognitive measures (Appendix II) included assessment of the subdomains emotion perception (Amsterdam Neuropsychological Tasks) (Sonneville 2005), theory of

mind (Hinting Task) (Corcoran *et al.* 1995), social knowledge (WAIS III, picture arrangement) (Wechsler 1997) and social cognitive biases (Davos Assessment of Cognitive Biases Scale) (Bastiaens *et al.* 2013; van der Gaag *et al.* 2013).

### *Psychopathology*

The Positive and Negative Symptom Scale (PANSS) (Kay *et al.* 1987) is a semi-structured interview that was used to assess positive and negative symptoms. Depression was assessed using the Beck Depression Inventory (BDI-II) (Beck *et al.* 1996a) and anxiety using the Beck Anxiety Inventory (BAI) (Beck *et al.* 1988). Higher scores reflect more severe symptoms.

### *Psychosocial functioning*

The Personal and Social Performance scale (PSP) (Morosini *et al.* 2000) was used to assess overall psychosocial functioning in the last month. The PSP is a clinician-rated 100-point single-item rating scale, subdivided into 10 equal intervals. Scores  $\leq 30$  indicate that the person's functioning is so poor that intensive support is needed to perform basic tasks. Scores from 31-70 indicate manifest problems in various degrees, while scores  $\geq 70$  indicate mild difficulties only. The scale also enables the scoring of above average functioning (91-100; excellent functioning). The four main areas of functioning on which the 10-point rating intervals and total PSP scores are based are: a) socially useful activities, including work and study (occupational and/or academic performance), b) personal and social relationships, c) self-care and care for personal environment, and d) disturbing and/or aggressive behaviour (range 0-5; problems absent to very severe problems). Higher subscale scores reflect larger deficits in that area.

### *Statistical analysis*

Analyses were performed with SPSS version 20. Preliminary analyses of the raw cognitive data showed that Continuous Performance Task and Amsterdam Neuropsychological Tasks (false alarm rate) scores were significantly skewed, which was normalised with logarithmic transformation. Scores per cognitive task were standardised (z-scores) using normative data. Standardised cognitive deficits (z-scores) are discussed as 'small' ( $\leq -1$  SD), 'moderate' ( $-1$  to  $-2$  SD) and 'large' ( $\geq -2$  SD). Spearman's correlations were subsequently investigated between cognitive variables. For data reduction purposes, neurocognitive and social cognitive data were subjected to two separate principal components analyses (PCA) followed by varimax rotations (Nuechterlein & Barch 2004). In both analyses, the number of factors was determined by examination of scree plots and the size of eigenvalues ( $> 1.00$ ). Further, bivariate correlations between cognitive factors

and the assessed psychopathology domains were investigated. Finally, we used stepwise regression analyses with backward elimination (p-value to remove was set at 0.10) to explore neurocognitive and social cognitive factors and psychopathological subdomains as cross-sectional predictors of psychosocial functioning. Standardised regression weights ( $\beta$ ) are discussed as ‘small’ (< 0.250), ‘moderate’ (0.251 to 0.500) and ‘large’ (> 0.501).

## Results

### *Sample characteristics*

Table 2.1 presents the demographic and psychopathology variables for the study sample.

**Table 2.1** Demographics and psychopathology scores for the study sample

	Mean / N	SD / %
<i>Demographics</i>		
N	162	-
Male sex	116	71.6%
Age	27.61	6.30
Years of education	11.91	2.31
<i>DSM-IV diagnoses</i>		
Schizophrenia	81	50.0%
Schizo-affective disorder	9	5.6%
Brief psychotic disorder	9	5.6%
Delusional disorder	5	3.1%
Shared psychotic disorder	2	1.2%
Psychotic disorder NOS	56	34.6%
<i>Psychopathology</i>		
Positive symptoms (PANSS)	13.82	5.16
Negative symptoms (PANSS)	13.11	5.63
Anxiety (BAI)	19.60	15.22
Depression (BDI)	19.21	12.45

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition; NOS = Not Otherwise Specified; PANSS = Positive and Negative Syndrome Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory.

### *Psychosocial functioning*

Based on the PSP operational criteria (Morosini *et al.* 2000) (added in italics) general psychosocial functioning was considerably impaired (PSP;  $m = 52.10$ ,  $sd = 14.19$ ; ‘*Marked problems in one of the specific areas a-c, or manifest difficulties in area d*’) and functional problems in four specific areas of psychosocial functioning were manifest: occupational/academic performance (PSP SUA;  $m = 2.65$ ,  $sd = 1.02$ ; ‘*manifest to marked*’),

personal and social relationships (PSP PSR;  $m = 2.31$ ,  $sd = 1.01$ ; '*manifest to marked*'), self-care and care for personal environment (PSP SC;  $m = 0.59$ ,  $sd = 0.88$ ; '*absent to mild*') and disturbing and/or aggressive behaviour (PSP DAB;  $m = 0.56$ ,  $sd = 0.95$ ; '*absent to mild*').

### Cognitive deficits

Zero-order correlates between all cognitive variables are presented in Appendix III. Raw cognitive scores were standardised (Z-scores) to enable comparison between performances on different cognitive measures. Raw and standardised neurocognitive and social cognitive scores are presented in Tables 2.2 and 2.3, respectively. Neurocognitive deficits ranged from 0.34 SDs below the norm on the WAIS III Information subtask to 2.91 on the Trail making task (part A). Social cognitive deficits ranged from 0.79 SDs below the norm for the number of hits on the ANT task to 1.77 on the Hinting task.

**Table 2.2** Raw and standardized neurocognitive scores and factor loadings

Domain	Task	M	SD	Z-score	Neurocognitive components		
					VPS	GNC	M&P
PSp	TMT, part A (seconds)	47.63	32.66	-2.91	<b>-.760</b>	-.142	-.052
VeL	RAVLT, recognition (N correct)	26.93	4.68	-1.97	<b>.743</b>	.067	.108
AT	CPT, hit rate	0.81	0.19	-2.39	<b>.721</b>	.350	.175
VeL	RAVLT, delayed recall (N correct)	8.95	3.71	-0.45	<b>.690</b>	.213	.339
PSp	WAIS III, digit-symbol coding (score)	58.75	21.53	-0.77	<b>.608</b>	.395	.267
VF	Category fluency task (N correct)	19.90	4.44	-0.83	<b>.502</b>	.231	.280
GC	WAIS III, calculations (score)	9.93	5.90	-0.97	.132	<b>.829</b>	.191
GC	WAIS III, information (score)	13.57	5.72	-0.34	.235	<b>.802</b>	.124
PSo	WAIS III, block design (score)	31.44	18.55	-1.03	.275	<b>.782</b>	.257
WM	WAIS III, letter-number (score)	9.19	3.10	-0.61	<b>.411</b>	<b>.708</b>	.237
ViL	BVMT, immediate recall (score)	22.40	7.76	-1.37	.188	.318	<b>.819</b>
ViL	BVMT, delayed recall (score)	8.96	3.22	-1.26	.290	.322	<b>.766</b>
PSo	Tower of London (score)	17.05	9.25	-1.23	.002	.341	<b>.594</b>
VeL	RAVLT, immediate recall (N correct)	41.03	12.19	-0.76	<b>.468</b>	.196	<b>.519</b>
ViL	BVMT, recognition (N correct)	10.96	2.82	-0.41	.292	-.240	<b>.484</b>
Eigenvalue					3.49	3.26	2.60
% of variance					23.3	21.8	17.3

PSp = Processing Speed; VeL = Verbal Learning; AT = Attention; VF = Verbal Fluency; GC = General Cognition; PSO = Problem Solving; WM = Working Memory; ViL = Visual Learning; TMT = trailmaking task; RAVLT = Rey Auditory Verbal Learning Task; CPT = Continuous Performance Task; WAIS III = Wechsler Adult Intelligence Scale, third edition; BVMT = Brief Visuospatial Memory Task; VPS = Verbal processing speed; GNC = general neurocognition; M&P = memory and planning. Factors loadings greater than .400 are marked in bold.

### Neurocognitive components

Guided by the scree plot and eigenvalues, the PCA of the neurocognitive variables was forced into a three-component solution that explained 62.34% of the variance. After

varimax rotation, these three factors were identified as ‘verbal processing speed’, ‘general neurocognition’ and ‘memory and planning’. Factor loadings are presented in Table 2.2.

### *Social cognitive components*

After examining the scree plot and eigenvalues from the PCA of the social cognitive variables, four components were retained that explained 71.93% of the variance. These four factors were identified as ‘social cognitive biases’, ‘emotion processing speed’, ‘general social cognition’ and ‘attribution and inference bias’. Factor loadings are presented in Table 2.3.

**Table 2.3** Raw and standardised social cognitive scores and factor loadings

Domain	Task / scale	M	SD	Z-score	Social cognitive components			
					SCB	EPS	GSC	AIB
CB	DACOBS, Safety behaviors	17.02	8.02	-1.06	<b>.958</b>	-.023	.026	-.071
CB	DACOBS, Subj. cognitive problems	23.89	7.61	-1.17	<b>.932</b>	.007	.037	-.095
CB	DACOBS, Belief inflexibility bias	21.76	6.93	-1.05	<b>.912</b>	.059	-.031	.093
CB	DACOBS, Social cognitive problems	23.67	8.40	-0.79	<b>.859</b>	-.087	.005	.169
CB	DACOBS, Attention for threat	26.00	6.47	-0.93	<b>.663</b>	.058	-.017	.225
EP	ANT, reaction time, false alarms (ms)	1553	805	-	.001	<b>.951</b>	.029	.013
EP	ANT, reaction time, hits (ms)	1058	336	-	.017	<b>.936</b>	-.149	.066
ToM	Hinting Task, score	11.87	4.95	-1.77	.028	-.137	<b>.767</b>	-.029
SK	WAIS III, picture arrangement, score	10.85	4.71	-1.13	.051	-.031	<b>.762</b>	.168
EP	ANT, false alarm rate	0.13	0.14	-	.049	-.171	<b>-.598</b>	.151
EP	ANT, hit rate	0.85	0.14	-	-.009	-.092	<b>.562</b>	-.067
CB	DACOBS, External attribution bias	23.31	7.50	-0.91	.066	-.058	-.080	<b>.902</b>
CB	DACOBS, Jumping to conclusions	25.11	5.44	-0.02	.131	.140	-.013	<b>.894</b>
Eigenvalue					3.82	1.88	1.88	1.78
% of variance					29.4	14.4	14.4	13.7

CB = Cognitive Biases; EP = Emotion Processing; ToM = Theory of Mind; SK = Social Knowledge; DACOBS = Davos Assessment of Cognitive Biases Scale; ANT = Amsterdam Neuropsychological Task; IFE = Identifying Facial Emotions; WAIS III = Wechsler Adult Intelligence Scale, third edition; SCB = social cognitive biases; EPS = emotion processing speed; GSC = general social cognition; AIB = attribution and inference bias. No standardized scores could be computed for the ANT IFE since normative data was not available for the full set of facial emotions assessed with this measure. Factors loadings greater than .400 are marked in bold.

### *Relationships between cognitive components and psychopathology*

Spearman’s correlations between cognitive components and psychopathological subdomains are presented in Table 2.4. Neurocognitive and social cognitive domains are ordered based on their average association with the four symptom domains, large to small. Verbal processing speed was related to all areas of psychopathology, except for positive symptoms. Attribution and inference bias and general social cognition were related to anxiety and to positive symptoms.

**Table 2.4** Spearman correlations between cognitive factors and symptom domains

	<i>Psychopathology domains</i>			
	POS	NEG	ANX	DEP
<i>Neurocognitive factors</i>				
Verbal processing speed	-.013	-.353***	-.354***	-.348***
Memory and planning	-.091	-.029	-.184	.120
General neurocognition	-.057	-.110	-.107	-.011
<i>Social cognitive factors</i>				
Attribution and inference bias	.286**	.071	.352***	.160
General social cognition	-.243*	-.179	-.269*	-.013
Social cognitive bias	.044	.130	.190	.170
Emotion processing speed	-.006	.097	-.022	.026

POS = positive symptoms (PANSS); NEG = negative symptoms (PANSS); ANX = anxiety (BAI); DEP = depression (BDI). Asterisks denote significant correlations (marked in bold).

\*  $p \leq .05$ , \*\*  $p \leq .01$ , \*\*\*  $p \leq .001$

### *Predicting psychosocial functioning*

We constructed five regression models, including all psychopathological subdomains and cognitive factors, to explore cross-sectional predictors of psychosocial functioning in FEP patients. Table 2.5 presents the regression models. General functioning was predicted by general social cognition, negative symptoms and general neurocognition. On the psychosocial functioning subdomains, problems in work and/or study were predicted by verbal processing speed, negative symptoms and emotion processing speed. Problems in social relationships were associated with negative symptoms only. Problems with self-care and care for the personal environment were most strongly predicted by general neurocognition and to a lesser extent by negative symptoms, general social cognition and verbal processing speed. Disturbing and/or aggressive behaviour was not predicted by any of the psychopathological domains or cognitive factors. Depression and anxiety did not contribute to any of the cross-sectional regression models predicting psychosocial functioning.

## **Discussion**

### *Main findings*

Our findings demonstrate moderate neurocognitive and social cognitive deficits in patients with FEP psychosis, which appear to be largely independent from (other) domains of psychopathology. Negative symptoms, neurocognition and social cognition were moderately associated with psychosocial problems, whereas affective and positive symptoms had no marked impact on psychosocial functioning in this early stage of psychotic disorder.

**Table 2.5** Regression models predicting psychosocial functioning

	Predictors	$\beta$	$r^2$	F	p (F)
General functioning	General social cognition	.436***	.394	9.11	< .001
	Negative symptoms	-.394***			
	General neurocognition	-.364**			
Work and study	Verbal processing speed	-.343**	.263	6.30	< .001
	Negative symptoms	.322**			
	Emotion processing speed	-.310*			
Relationships	Negative symptoms	.498***	.278	10.39	< .001
Self-care	General neurocognition	.474***	.428	7.62	< .001
	Negative symptoms	.348**			
	General social cognition	-.318*			
	Verbal processing speed	-.239*			
Disturbing behaviour	Positive symptoms	.254	.064	3.79	.057

Positive betas indicate that better cognitive functioning is associated with higher levels of psychosocial functioning; negative betas indicate that more symptoms are associated with lower levels of psychosocial functioning. Asterisks denote significant regression weights ( $\beta$ ).

\*  $p \leq .05$ , \*\*  $p \leq .01$ , \*\*\*  $p \leq .001$

### *Comparison with previous studies*

In line with the available literature, we found neurocognitive (Townsend & Norman 2004; Bozikas & Andreou 2011) and social cognitive (Green *et al.* 2011; Thompson *et al.* 2011) deficits of moderate size in our FEP sample, on average about one SD below the norm. Neurocognitive deficits were largely unrelated to psychopathology. The single exception was the neurocognitive factor ‘verbal processing speed’, which was related to negative symptoms, anxiety and depression. Overall the large majority of null associations between neurocognition and psychopathology concurs with recent meta-analytic data from prodromal and FEP (Bora & Murray 2014) as well as from chronic psychosis samples (Dominguez *et al.* 2009). Bora and Murray concluded that neither psychotic symptoms nor non-specific symptoms (e.g. depression or anxiety) appear to impact on neurocognitive function in first-episode (and prodromal) patients, suggesting that neurocognitive deficits are already established before the early stages of psychosis (Bora & Murray 2014).

The available literature on social cognitive deficits and clinical correlates in FEP is limited (Green *et al.* 2011; Thompson *et al.* 2012). Consistent with our findings, previous studies showed that social cognitive impairment is present early in the course of psychotic illness, and that these deficits remain stable across different stages of psychosis. The present findings and several related studies indicate that social cognitive deficits are, unlike neurocognitive deficits, associated with positive symptoms in FEP, especially the



Theory of Mind (Bora & Pantelis 2013), attribution bias (An *et al.* 2010) and emotion recognition problems (Amminger *et al.* 2012). This may suggest that misinterpretation of intentions and emotions of others, as well as cognitive tendencies to blame negative outcomes on others or to make decisions based on limited information, might contribute to the development of (rather than be the result of) positive symptoms. Such a cognitive psychological pathway has been hypothesised for persecutory delusions (Freeman *et al.* 2002).

Reviews on predictors of functional outcome in FEP patients indicate that poor neurocognitive functioning (Allott *et al.* 2011) and negative symptoms (Malla & Payne 2005) during prodromal and early stages are associated with poor psychosocial functioning, especially in the areas of self-care (Bratlien *et al.* 2013), interpersonal functioning and academic/vocational performance (Tsang *et al.* 2010; Allott *et al.* 2013; Torgalsbøen *et al.* 2014); these findings are replicated in the present sample. Our findings also suggest that positive and affective symptoms have no marked impact on psychosocial functioning in the early stages of psychosis. Although psychopathology scores in our sample were marginally different from those observed in other samples, i.e. slightly higher affective symptoms (Jackson *et al.* 2005; Mueser *et al.* 2010) and lower positive symptoms (Lucas *et al.* 2008; Chang *et al.* 2011; Barder *et al.* 2013; Lin *et al.* 2013b; Torgalsbøen *et al.* 2014), we believe that our methods and the scope of psychopathology measures obtained were adequate to address our study aims. These findings notwithstanding, the overall lower levels of positive symptoms might partially explain their marginal impact on psychosocial functioning.

In addition, our data add to findings of other studies showing that social cognitive deficits predict psychosocial problems in FEP (e.g. Horan *et al.* 2012b). However, in our study, social cognitive deficits did not account for problems in the area of social relationships (as might be expected), but in the areas of vocational/academic functioning and self-care. Based on the findings of our regression analyses, we hypothesise that even if FEP patients have the ability to initiate and maintain personal relationships (i.e. social cognition and social skills), this ability will not help to maintain or improve their role performance in the acute stage of the disorder when they also experience marked negative symptoms. Also, a review of the role of social cognition in FEP indicated social cognition as a potential mediator between neurocognition and psychosocial functioning, implying that a substantial part of the negative influence of neurocognitive deficits on psychosocial functioning is caused by their adverse effect on social cognitive performance (Schmidt *et al.* 2011).

It should be noted that overall levels of explained variance in all regression models were moderate to low, with the best regression model explaining little over 40% of the variance in social functioning. Although these levels of explained variance using psychopathological and cognitive predictors are relatively common in FEP samples (Allott *et al.* 2011), they show that the greater part of the variance in psychosocial functioning in these patients is not accounted for by clinical measures of psychopathology or cognition. Notwithstanding that a recent study indicates that self-report measures might provide more accurate predictions of functional outcome than clinical measures (Kiwanuka *et al.* 2014), the issue of general low levels of explained variance still raises an obvious question, i.e. are we measuring “the right stuff” to understand functional problems in FEP? Research to date has provided several environmental and personal contributing factors, such as duration of untreated psychosis (Perkins *et al.* 2005), levels of premorbid adjustment (MacBeth & Gumley 2008), personality traits (Boyette *et al.* 2014) and attachment styles (Berry *et al.* 2007b), that might expand our understanding of functional problems in FEP; all these factors clearly warrant further study.

Finally, depressive symptoms in the present study were only associated with one cognitive factor (1/7) and did not contribute to the regression models predicting psychosocial functioning. However, previous research did find a relationship between depression and cognitive deficits (Lee *et al.* 2012), and also indicated that depression is likely to be a predictor of poor outcome in FEP (Upthegrove *et al.* 2010, 2014). Our findings suggest that the impact of depression on functioning might be small in the acute phase of psychosis; however, recent studies showed that depressive symptoms in the early stages of psychosis may be determinants of other important outcomes. Upthegrove *et al.* stress that it is prodromal depression, and not the severity of positive or negative symptoms, that is predictive of depression (and related suicidality and functional problems) in the early stages of psychosis (Upthegrove *et al.* 2010, 2014). Therefore, prodromal depressive symptoms should be explicitly targeted to improve future outcome and reduce the risk for future depression, self-harm and suicidality in FEP patients.

### *Strengths*

A strength of the current study is that the present sample is highly representative for early psychosis, since it includes all consecutive patients with a first-episode of psychosis who made first contact with specialised mental health services in an urban area during the study period. Since all data were collected within the first 3 months after referral, possible impact of confounding variables associated with chronic psychosis and long-term treatment (particularly, long-term use of antipsychotic medication) is considered

negligible. Another strength is that we used a wide clinical scope (including positive and negative symptoms, anxiety and depression, and 15 separate psychometric tools to assess neurocognition and social cognition) and, finally, assessed one general plus four specific domains of psychosocial functioning.

### *Limitations*

The study also has some limitations. First, the cross-sectional design limits its clinical value and applicability. Because longitudinal data needed, we are currently following-up this study sample. Second, because no medication records were available at the time of this study, possible effects of medication use on cognitive performance, symptoms and outcome could not be taken into account. However, besides the short period of time that patients could have used antipsychotic medication, meta-analytic data suggest that the impact of anti-psychotic medication on cognition is likely to be absent or small (Mishara & Goldberg 2004; Woodward *et al.* 2007). Third, no data on cannabis (or other substance) use were available at the time of the study. Based on previous work from our department the lifetime prevalence of cannabis use in FEP patients can be as high as 60% (Veling *et al.* 2008b). However, we propose that any effect of cannabis use in our data is likely to be small, since cannabis appears to have both modest positive and negative effects on cognitive performance (Yücel *et al.* 2010) and on the level of psychotic symptoms (Schubart *et al.* 2011). Fourth, data on the duration of untreated psychosis (DUP) were not structurally acquired in the present sample. Finally, the quality of available normative data varied between the cognitive instruments. However, we note that this is an intrinsic and inevitable limitation of using such a wide scope of cognitive measures. In addition, the standardised cognitive scores were not used in any of the regression analyses and were only provided to enable comparison of the scores between the cognitive measures.

### *Implications for early psychosis care*

Our findings show that negative symptoms, neurocognition and social cognition are indicators for difficulties in psychosocial functioning in the early stage of psychosis. Both neurocognitive and social cognitive deficits are largely independent of the psychopathology. Because the predictors of functioning differ in the various stages of psychotic illness, findings in multi-episode psychosis cohorts cannot be generalised to first-episode psychosis patients.





## **Chapter 3**

# **Psychotic symptoms, cognition and affect as predictors of psychosocial problems and functional change in first-episode psychosis**

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## Abstract

**Aim** To enable further understanding of how cognitive deficits and psychopathology impact psychosocial functioning in first-episode psychosis patients, we investigated how psychopathology and cognitive deficits are associated with psychosocial problems at baseline, and how they predict psychosocial functioning at 12-months follow-up. Also, we tested whether baseline cognitive deficits are a stronger predictor of change in psychosocial functioning in the first 12 months after baseline than baseline psychotic symptoms.

**Methods** Eight neurocognitive and four social cognitive subdomains, psychopathology (positive and negative symptoms, depression and anxiety) were assessed at baseline in 153 non-affective first-episode psychosis (FEP) patients. Psychosocial functioning (work/study, relationships, self-care, disturbing behavior and general psychosocial functioning) was assessed at baseline and 12 months. Spearman correlations were examined and backward regression models were computed to test our hypotheses.

**Results** At baseline, psychosocial functioning was associated strongest with positive and negative symptoms of all assessed clinical domains, followed by neurocognition and social cognition. In contrast, psychosocial functioning at 12 months was not predicted by psychotic symptoms, but rather by neurocognition, social cognition and depression. Change in social functioning in the first 12 months after baseline was predicted by positive and negative symptoms, but to a similar degree by neurocognition and social cognition.

**Conclusions** Whereas psychotic symptoms show marked impact on psychosocial functioning at illness onset, cognitive deficits appear to be more accurate longitudinal predictors of psychosocial problems and functional recovery in the early course of psychosis.

## Keywords

First-episode psychosis; Social cognition; Neurocognition; Affect; Psychosocial functioning

## Introduction

Cognitive deficits occur early in the course of psychosis and generally tend to improve marginally or remain stable over time (Szöke *et al.* 2008). In chronic schizophrenia, cognitive deficits are strongly related to poorer functional outcome (Green 1996; Heinrichs & Zakzanis 1998; Green *et al.* 2000a, 2004; Fett *et al.* 2011). Although this association is evident in the end-stage of the illness (McGorry *et al.* 2006, 2010), our understanding of how cognitive deficits contribute to functional problems in earlier stages of psychosis is still limited. The assumption that findings on cognition-outcome relations cannot be generalized across different illness stages seems evident, since first-episode psychosis patient samples incorporate the full range of psychopathological profiles, genetic- and environmental parameters, including both good and poor prognoses, whereas chronic patients samples have gone through a selective drift towards the “poor prognosis first episode patients”. As chronic and first-episode samples thus vary both in illness stage as well as sample characteristics and prognoses, the study of cognition-outcome interrelations in first-episode psychosis may help to advance ideas about cognition and psychosis in general, and may also have implications for selecting effective interventions at various stages of these disorders (Bora *et al.* 2010; McGorry *et al.* 2010).

A recent review of 22 longitudinal first-episode psychosis (FEP) studies on cognition as predictor of functioning concluded that many different cognitive domains showed marked impact on psychosocial functioning over time, but also that the extensive variability and the methodological limitations of the studies precluded any firm conclusions (Allott *et al.* 2011). In most studies, sample size was small, only a limited number of neurocognitive domains were included, and measures of functional outcome were quite global. Not a single study in the review investigated social cognition, although recent studies on this topic have yielded promising results (e.g. Horan *et al.*, 2012b). The review further showed that there is a much higher frequency of null findings than significant predictive relationships across every cognitive domain. However, the ratio of significant predictors appears to increase with the length of the follow-up period, indicating that long-term impact of cognitive deficits on psychosocial functioning might be more pronounced than short-term impact.

Besides the various methodological limitations, the current cognition-outcome FEP literature is also lacking explicit investigations on cognitive predictors of the degree of functional change between different points in time, rather than absolute levels at these different points (for example, predicting a GAF-change score of +10 points or +20 percent, rather than just predicting the related absolute GAF scores, i.e. a baseline score of 50 and a follow-up score of 60). Although identifying predictors of absolute level of psychosocial



functioning is relevant, it is also important to investigate specific predictors of improvement and deterioration of functioning. This may be particularly relevant in when studying the early stages of these disorders.

The aim of the present study is to investigate predictors of psychosocial problems in a first-episode psychosis patient sample, including comprehensive baseline assessment of neurocognition and social cognition as well as psychotic and affective symptoms. Several domains of psychosocial functioning were included and assessed both at baseline and at 12-months follow-up. Absolute levels of psychosocial functioning as well as the degree of change in psychosocial functioning between illness onset and 12-months follow-up will be used as outcome measures.

In this prospective study, we will test the following three hypotheses: first, (1a) baseline psychotic symptoms and (1b) baseline cognitive deficits, are associated with psychosocial functioning at baseline. Second, (2a) baseline psychotic symptoms and (2b) baseline cognitive deficits predict psychosocial functioning at 12-months follow-up. Third, baseline cognitive deficits are a stronger predictor of change in psychosocial functioning in the first 12 months after baseline than baseline psychotic symptoms.

## **Method**

### *Subjects*

For the present study, a comprehensive set of cognitive, symptomatic and functional measures was collected in a large sample of consecutive first-episode psychosis patients from one urban area (The Hague, The Netherlands). In the present study a 'first-episode psychosis' (FEP) patient was defined as an individual who presents at a clinical setting with psychosis, who has never previously presented at a clinical setting with psychosis (Breitborde *et al.* 2009); i.e. first time 'stage 2', McGorry *et al.* 2010). During the study period (December 1, 2009 and December 31, 2011), 153 individuals were diagnosed with a non-affective first-episode psychotic disorder (DSM-IV diagnoses: 81 schizophrenia, 9 brief psychotic disorder, 5 delusional disorder, 2 shared psychotic disorder, and 56 psychotic disorder NOS) after making contact with a specialized outpatient department for first episode psychosis in The Hague, the Netherlands. Baseline measures and follow-up assessment for psychosocial functioning 12 months after baseline assessment were obtained for all patients. All baseline data presented in this study were gathered within three months after first contact with our department (average of 1,8 months, SD 0.6) and follow-up measures for psychosocial functioning were completed exactly 12 months after baseline functioning measures. The study was approved by the local ethics committee

(reference number: NL31561.098.10). Informed written consent was obtained from all participants.

### *Diagnostic protocol*

The diagnostic protocol used to obtain a DSM-IV diagnosis, included the following measures: the Schedules for Clinical Assessment in Neuropsychiatry interview (SCAN) (Wing *et al.* 1990), standard psychiatric assessment, the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987) (see 2.4.), and cognitive assessment (see 2.3.). Hetero-anamnestic data was collected from family members using the Instrument for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) (Häfner *et al.* 1992).

### *Cognitive assessment*

Clinical psychologist performed the cognitive assessment, assessing eight neurocognitive (see section ‘neurocognition’) and four social cognitive (see section ‘social cognition’) subdomains.

### *Neurocognition*

Neurocognitive assessment included assessment of the subdomains *attention* (Continuous Performance Task, CPT 3-7 version) (Nuechterlein & Dawson 1984), *problem solving* (Wechsler Adult Intelligence Scale, WAIS III, Block design; Tower of London) (Shallice 1982; Wechsler 1997) *speed of processing* (WAIS III, Digit-symbol coding; Trail making task, part A) (Reitan 1958; Wechsler 1997), *verbal fluency* (Category fluency, animal naming) (Lezak *et al.* 2004), *verbal learning* (Rey Auditory Verbal learning Task, RAVLT) (Rey 1964; Kalverboer & Deelman 1986), *visual learning* (Brief Visuospatial Memory Task Revised, BVM-T-R) (Benedict 2007), *working memory* (WAIS III, Letter-number sequencing) (Wechsler 1997) and *general cognition* (WAIS III, Information and Calculations) (Wechsler 1997).

### *Social cognition*

The social cognitive measures included assessment of the subdomains *emotion perception* (Amsterdam Neuropsychological Tasks, ANT) (Sonneville 2005), *theory of mind* (Hinting Task) (Corcoran *et al.* 1995), *social knowledge* (WAIS III, picture arrangement) (Wechsler 1997) and *social cognitive biases* (Davos Assessment of Cognitive Biases Scale) (Bastiaens *et al.* 2013; van der Gaag *et al.* 2013).

### *Psychopathology*

We used three separate measures to assess psychotic symptoms, anxiety and depression. The Positive and Negative Symptom Scale (PANSS) (Kay *et al.* 1987) was used to assess positive, negative and general symptoms. Anxiety and depression were assessed using the Beck Anxiety Inventory (BAI) (Beck *et al.* 1988) and Beck Depression Inventory (BDI-II) (Beck *et al.* 1996a) respectively. For all three measures, higher scores reflect more severe symptoms.

### *Psychosocial functioning*

The Personal and Social Performance scale (PSP) (Morosini *et al.* 2000) was used to assess psychosocial functioning (range 0 to 100; very poor to excellent), including the following subdomains (range 0 to 4; absent to severe): (a) socially useful activities, including work and study, (b) personal and social relationships, (c) self-care and care for personal environment, and (d) disturbing and/or aggressive behavior. Higher scores on overall personal functioning reflect better functioning, where higher scores on the four subscales reflect larger deficits in that area.

### *Data analysis*

The analyses were performed in SPSS version 20. Descriptives and frequencies for the demographic variables were computed. Cognitive scores were standardized (z-scores) based on normative data. Mean z-scores per cognitive subdomain were computed by averaging all cognitive test z-scores per domain. Functional change was computed by dividing psychosocial functioning scores at 12-months follow-up by baseline scores per domain. Homogeneity of overall functional change was explored for the study sample.

Backward regression models were computed used to identify most potent predictive models for psychosocial functioning at baseline, at 12-months follow-up, and for the amount of functional change in the first 12 months. Given the significant interrelations between psychopathology and both neurocognitive and social cognitive deficits found in this sample, all psychotic-, affective- and cognitive subdomains were initially included in all models.

And finally, post-hoc analyses (Holm-Bonferroni correction) were completed in the case of significant baseline-, 12-months follow-up- and functional change regression models.

## Results

### *Demographic and psychopathology variables*

A total of 153 participants, mean age of 27.8 years (111 males, 42 females), completed assessment of positive symptoms (PANSS POS;  $m = 13.86$ ,  $sd = 5.20$ ), negative symptoms (PANSS NEG;  $m = 13.01$ ,  $sd = 5.59$ ), anxiety (BAI;  $m = 19.81$ ,  $sd = 15.06$ ) and depression (BDI;  $m = 19.26$ ,  $sd = 12.54$ ). The average number of completed years of education was 11.96 ( $sd = 2.37$ ).

### *Cognitive deficits*

Standardized cognitive scores for the neurocognitive and social cognitive subdomains assessed in this study are presented in Table 3.1.

**Table 3.1** Standardized cognitive deficits, ordered large to small, for neurocognition and social cognition

	Mean z-score	SD
<i>Neurocognition</i>		
Attention	-2.39	3.21
Processing speed	-1.84	3.02
Problem solving	-1.13	1.19
Verbal learning	-1.06	1.75
Visual learning	-1.01	1.40
Verbal fluency	-0.83	1.13
Working memory	-0.61	1.10
General neurocognition	-0.66	1.17
<i>Social cognition</i>		
Theory of mind	-1.77	0.33
Social knowledge	-1.13	1.15
Social cognitive biases	-0.86	1.92
Facial affect perception	-0.82	1.71

### *Psychosocial functioning and functional change*

Scores for baseline and 12-months follow-up psychosocial functioning, and the degree of functional change in the first 12 months after baseline, are presented in Table 3.2. Exploring the overall levels of functional change, we identified three “functional change” subgroups in our sample. The first group ( $N=68$ ) showed marked functional improvement (+20% or more), where the second ( $N=52$ ) showed marked functional decline (-20% or more). The rest of the sample ( $N=42$ ) showed more or less stable functioning in the first 12 months after baseline (between -20% and +20% functional change).

**Table 3.2** Psychosocial functioning at baseline and 12-months follow-up for the study sample

		Baseline		12 months		Functional change
		Mean	SD	Mean	SD	
<i>Functioning</i>						
General psychosocial functioning		51.30	14.24	54.98	15.28	+ 7.17%
Work and study problems		2.65	1.05	2.37	1.09	+ 10.61%
Problems in relationships		2.31	0.95	2.01	1.12	+ 12.99%
Self-care problems		0.60	0.90	0.67	0.95	- 11.67%
Disturbing/aggressive behavior		0.59	0.99	0.43	0.89	+ 27.12%

Note: the '+' and '-' signs have been added to the last column and reflect that the following percentage is either an improvement (+) or a decline (-) compared to baseline psychosocial functioning.

### *Psychopathology, cognition and psychosocial functioning: associations at baseline*

Higher positive and negative symptom scores at baseline were related to lower scores in general psychosocial functioning and problems in social relationships (Table 3.3; first column). Positive symptoms were further associated to disturbing behavior (regression model no longer significant after Holm-Bonferroni correction) and negative symptoms were associated to vocational/academic- and self-care problems. The results also showed that of all cognitive domains, visual learning and general cognition were the only cognitive domains related to psychosocial functioning at baseline, i.e. self-care. Furthermore, depression was associated to vocational/academic problems, where anxiety was not associated at all to psychosocial functioning at baseline.

### *Predicting future psychosocial functioning in first-episode psychosis*

Baseline positive symptoms were not associated to psychosocial functioning at 12-months follow-up (Table 3.3; second column). In fact, the only clinical domains that significantly predicted psychosocial functioning at one 12-months follow-up (after correction) were Theory of Mind predicting problems in social relationships, and both depression and negative symptoms predicting vocational/academic problems.

### *Predicting functional change*

Our analysis of predictors of functional change yielded a number of results (Table 3.3; third column). First, positive symptoms, and not cognitive deficits, were the only significant predictors of general functional change in the first 12 months after baseline. Second, visual learning was the strongest predictor for changes in vocational/academic performance and social relationship problems, supplemented by positive symptoms in the latter model. Third, all assessed clinical domains (psychosis, affect, social cognition, neurocognition) significantly contributed to changes in self-care in the first 12 months, although this model was no longer significant after correction.

**Table 3.3** Optimal regression models predicting functioning at baseline, at 12-months follow-up, and the amount of functional change in the first 12 months, using baseline psychopathology, neurocognition and social cognition as predictors

Domain	Baseline					12-months follow-up					Functional change in first 12 months				
	Predictors	$\beta$	$r^2$	F	p (F)	Predictors	$\beta$	$r^2$	F	p (F)	Predictors	$\beta$	$r^2$	F	p (F)
General functioning	Negative symptoms	-.346*	.262	7.64	.001	Visual learning	-.225	.051	1.92	.175	Positive symptoms	.373*	.236	6.02	.005
	Positive symptoms	-.312*									Processing speed	-.250			
Work and study problems	Negative symptoms	.374**	.246	7.01	.002	Depression	.272*	.162	4.56	.015	Visual learning	.402**	.257	6.74	.003
	Depression	.288*				Negative symptoms	.254*				Positive symptoms	-.257			
Problems in relationships	Negative symptoms	.335*	.229	6.38	.004	Theory of Mind	.351*	.123	6.74	.012	Visual learning	.371*	.265	4.58	.008
	Positive symptoms	.278*									Positive symptoms	-.296*			
Self-care problems	Negative symptoms	.452***	.372	8.29	.000	Visual learning	.271*	.152	4.21	.021†	Social knowledge	-.517**	.272	3.46	.017†
	Visual learning	-.326*				Negative symptoms	.249				Depression	.472**			
Disturbing behavior	General cognition	.266*									Visual learning	.451*			
											Negative symptoms	-.413*			
	Positive symptoms	.353*	.155	3.94	.027†	Problem solving	-.273*	.097	2.52	.091	Theory of Mind	.300	.090	3.96	.053
	General cognition	.248				Attention	.238								

Regression models that were no longer significant after post-hoc Holm-Bonferroni correction are marked with a dagger (†). Significant regression weights ( $\beta$ ) are marked with an asterisk (\*). \*  $\leq .05$ , \*\*  $\leq .01$ , \*\*\*  $\leq .001$

## Discussion

### *Main findings*

The aim of the present study was to investigate cross-sectional and longitudinal associations between cognitive deficits psychotic symptoms, and psychosocial problems in first-episode psychosis patients.

Our findings confirmed that psychotic symptoms (positive and negative) (hypothesis 1a) as well as cognitive deficits (hypothesis 1b) are related to psychosocial functioning at baseline, where psychotic symptoms showed stronger overall cross-sectional associations with psychosocial functioning than cognitive deficits.

However the present findings refute that positive symptoms are a valid predictor of psychosocial functioning at 12-months follow-up (hypothesis 2a). Furthermore, they show that, even though cognitive deficits predicted psychosocial functioning at 12-months follow-up (hypothesis 2b), they only did one single area of psychosocial functioning: Theory of Mind deficits predicted problems with social relationships.

Lastly, the hypothesis that baseline cognitive deficits are a stronger predictor of change in psychosocial functioning than baseline psychotic symptoms (hypothesis 3) was both only partially confirmed. The results showed that for change in general psychosocial functioning, positive symptoms were the only significant predictor. In contrast however, cognitive deficits were stronger predictors for all the four functional subdomains. This was most evident in the areas of vocational/academic performance and social relationships, for both of which visual learning was the strongest predictor.

### *Comparison with earlier studies*

The predictive models analyzed in this study illustrate a number of points. First, the present findings show that psychotic symptoms are markedly related to concurrent psychosocial functioning, but that they are not accurate predictors of future functioning in young people with psychosis. This is especially true for positive symptoms. In concordance with the literature, the present analyses show that negative symptoms are more consistently related to both current (Chang *et al.* 2011; Bourdeau *et al.* 2012; Evensen *et al.* 2012a, 2012b) and future levels (Albert *et al.* 2011; Álvarez-Jiménez *et al.* 2012; Vesterager *et al.* 2012; González-Ortega *et al.* 2013) of psychosocial functioning than positive symptoms (Albert *et al.* 2011; Faber *et al.* 2011; Ventura *et al.* 2011; Chang *et al.* 2012). Also, that severity levels of both positive and negative symptoms do not appear to be strong predictors of psychosocial functioning after 12 months (Albert *et al.* 2011; Faber *et al.* 2011; Chang *et al.* 2012).

Second, in line with most first-episode psychosis studies to date, cognitive deficits appeared to be of modest importance in explaining problems in psychosocial functioning, since the majority of optimal regression models in this study (8/15; 53.3%) did not retain any cognitive predictor (Allott *et al.* 2011). However the data also indicate that *if* functional problems were in some degree predicted by cognitive deficits, that *then* cognitive deficits were likely to be important in explaining problems in that specific domain, i.e. in all but one of the models where cognitive deficits made a significant contribution, they were the strongest predictor (6/7; 85.7%). This was especially true for the models predicting functioning at 12-months follow-up (3/3) and functional change (3/3). In line with the available literature (Allott *et al.* 2011), these findings indicate multiple neurocognitive (van Winkel *et al.* 2007; Dickerson *et al.* 2008; Leeson *et al.* 2009; Nuechterlein *et al.* 2011) and social cognitive subdomains (Horan *et al.* 2012) as valid longitudinal predictors of psychosocial functioning and/or functional change in FEP patients.

Thirdly, the data illustrate that depression and anxiety play a small to negligible roles in explaining functional problems in the early stages of psychosis. Although this finding could be considered counter-intuitive based on marked levels of depression and anxiety in the present and other FEP samples, this finding is supported by the available literature (Lin *et al.* 2011; Cornblatt *et al.* 2012; Salokangas *et al.* 2013).

Fourthly, the overall moderate to low rates of explained variance for absolute levels of psychosocial functioning by psychotic symptoms and cognitive deficits in this study are on par with various other FEP studies (Addington *et al.* 2005; Milev *et al.* 2005; Allott *et al.* 2011; Ayesa-Arriola *et al.* 2013), but not with the higher rates generally found in chronic studies (e.g. (Green 1996; Harvey *et al.* 1998; Green *et al.* 2000b, 2004), further underlining that the impact of specific illness components (and related mechanisms) on psychosocial problems is likely to differ across patient populations in different illness stages (van Os *et al.* 2009, 2010; McGorry *et al.* 2010).

And lastly, although the present study does indicate cognition as a modest but significant predictor of functional outcome, several previously identified cognitive predictors of functional outcome were not observed in the present study, illustrating the marked methodological issues involved in the study of the cognition-outcome relationship. For example, a recent systematic review (Allott *et al.* 2011) indicated general cognition (e.g. (Jarbin *et al.* 2003; Robinson 2004; Addington *et al.* 2005; Carlsson *et al.* 2006; Leeson *et al.* 2009) and verbal learning (e.g. (Fujii & Wylie 2003; Addington *et al.* 2005; Milev *et al.* 2005) among the strongest predictors of functional outcome in FEP, where visual learning was identified as one of the weakest predictors (e.g. (Malla *et al.* 2002; Verdoux *et al.* 2002; Keshavan *et al.* 2003; Stirling 2003; Addington *et al.* 2005;



Lucas *et al.* 2008; Leeson *et al.* 2009). In the present sample however, the latter rather than the former was identified as the most potent cognitive predictor of longitudinal psychosocial functioning in various domains. In contrast, the former did not appear to have a marked impact in any of the models predicting psychosocial functioning. Obviously, used methodology and sample characteristics differ on many aspects between previous work and the present study, and therefore it is unclear why these associations were not observed here. Nevertheless, we do argue that the present study has adequate statistical power to investigate this issue, where fourteen out of the 22 studies (64%) in the aforementioned review were underpowered (Allott *et al.* 2011), raising some questions concerning the presented consensus on cognitive predictors of outcome in first-episode psychosis patients.

#### *Functional outcome heterogeneity in FEP: illness stage and sample characteristics*

An important finding is that the current sample overall showed little functional change in the first 12 months after baseline. However, this does not mean that most patients were functionally stable during the first 12 months after baseline, as our exploratory analysis showed three subsets of patients (stable, improved or declined social functioning) who negated each others effect on the overall mean. This exploration indicates that illness trajectories in FEP are clearly heterogeneous (Menezes *et al.* 2006). It also illustrates that the present first-episode psychosis patient sample contains patients with prognoses ranging from full functional recovery to progressive functional decline, as presumably most FEP samples do. This in contrast with chronic samples, which unequivocally contain patients with a smaller range of (on average) poorer prognoses. As a result, genetic- and environmental sample characteristics, other than those directly related to illness stage and chronicity, are likely to be evident between these samples and account for marked differences between predictors of outcome in different illness stages. This also suggests that symptomatic- and cognitive predictors of functional outcome that have been identified in chronic samples are likely to be predictors of functional decline (Green 1996; Green *et al.* 2000b, 2004), whereas study of functional outcome predictors in first-episode psychosis samples are just as likely to yield predictors of functional recovery and resilience, as well as predictors for decline (Menezes *et al.* 2006). Identification and analysis of differential predictors of improvement and decline in psychosocial functioning is beyond the scope of this paper, but unexplained heterogeneity in FEP clearly warrants further study, where these factors should be taken into account.

### *Strengths and limitations*

The most prominent strengths of this study are, first, the prospective design, which assessed not only baseline and short-term follow-up (12 months) psychosocial functioning, but also the amount of functional change between these points. Second, the wide range of psychopathological, affective, neurocognitive and social cognitive measures, that was assessed within three months after first contact for all patients, providing a broad clinical perspective as well as ruling out confounding variables associated with chronicity and long-term treatment. And third, the highly representative FEP sample, containing all consecutive FEP patients from one large urban area during the study period.

The absence of medication records and data on cannabis use at the time of the study should be considered as limitations. Short-term impact of anti-psychotic medication on the observed factors is likely to be absent or small, especially concerning cognitive performance (Mishara & Goldberg 2004; Woodward *et al.* 2007). Also, the effect of cannabis use in our data is likely to be small as well as heterogeneous, since cannabis appears to have both modest augmentative and degenerative effects on cognitive performance (Yücel *et al.* 2010) as well as psychotic symptoms (Schubart *et al.* 2011).

### *General conclusions*

The present study shows that psychotic symptoms, cognitive deficits and affective problems all contribute to psychosocial difficulties in the early course of psychosis. The findings show that the magnitude of this influence not only varies substantially between different areas of psychosocial functioning, but also changes considerably over time. These changes were most notable for psychotic symptoms and cognitive deficits, as impact of baseline psychotic symptoms on psychosocial functioning was initially strong but decreased over time, where the opposite was true for the impact of baseline cognitive deficits.

The present findings further indicate that valid predictors of general levels of psychosocial functioning are not necessarily valid predictors of functional changes in that domain (and vice versa), emphasizing the need to differentiate between these interrelated paradigms in the exploration of mechanisms underlying psychosocial problems in the early stages of psychotic disorders.



## Chapter 4 Predicting recovery after a first-episode psychosis

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*Under review*

## Abstract

**Aim** To identify what proportion of patients with a first-episode psychosis (FEP) reaches symptomatic, functional and full recovery within 12 months after first contact and identify which clusters of baseline characteristics predict symptomatic, functional and full recovery.

**Methods** In total, 167 FEP patients completed baseline measures for positive symptoms, negative symptoms, neurocognition, social cognition, mania and emotional distress, and provided demographic characteristics. Psychosocial functioning was assessed at baseline and at 12 months. Canonical discriminant analysis was used to identify clusters of characteristics that discriminated best between outcome groups ('full recovery', 'symptomatic recovery only', 'functional recovery only' and 'no recovery').

**Results** Of all patients, 53 reached full recovery in 12 months, 56 reached partial recovery (25 symptomatic, 31 functional) and 58 reached neither symptomatic nor functional recovery. Outcome groups differed on psychosocial functioning ( $F(3)=13.60$ ,  $p<.001$ ), positive symptoms ( $F(3)=9.40$ ,  $p<.001$ ), negative symptoms ( $F(3)=7.41$ ,  $p<.001$ ), mania ( $F(3)=4.25$ ,  $p=.007$ ) and social cognition ( $F(3)=3.18$ ,  $p=.040$ ). The 'no recovery' group also contained a higher percentage of males than the other three outcome groups. Discriminant analysis allocated 58.8% of cases (cross-validated 52.2%) correctly across outcome groups and indicated that baseline functioning, positive symptoms, negative symptoms, mania, gender and social cognition together discriminate best between the 'full recovery' and 'no recovery' groups, whereas duration untreated psychosis (DUP) and age discriminated between the 'functional recovery' and 'symptomatic recovery' groups.

**Conclusions** Low levels of positive symptoms, negative symptoms, mania, and good social cognition at baseline characterize patients that attain full recovery within 12 months after first contact. Surprisingly, established predictors of recovery (e.g. good neurocognition, lower emotional distress, higher levels of education/income and age at baseline) had no impact on early recovery.

## Keywords

First-episode psychosis; schizophrenia; outcome; recovery; functioning; symptoms

## Introduction

Illness trajectories in the early stages of psychotic disorder are heterogeneous. Some individuals recover quickly and fully, whereas others recover slowly or partially, remain stable, or even deteriorate in the early stages (Menezes *et al.* 2006). This is apparent for both symptom expression and the functional deficits that characterize these disorders. However, although this issue has been well investigated, the question remains as to what (combination of) factors distinguish between those who will improve and those who will not.

Studies aiming to identify potential baseline predictors of functional recovery found that better premorbid psychosocial functioning (Álvarez-Jiménez *et al.* 2012), milder positive symptoms (Heinrichs *et al.* 2009), milder negative symptoms (Milev *et al.* 2005), better neurocognitive performance (Allott *et al.* 2011), better social cognitive performance (Fett *et al.* 2011), shorter duration of untreated psychosis (Emsley *et al.* 2007), less use of substances (Kerfoot *et al.* 2011) and milder affective symptoms like depression (Upthegrove *et al.* 2014) and mania (Dumais *et al.* 2011), were associated with better functional outcome.

In studies on symptomatic recovery (review: AlAqeel & Margolese 2012), the variables most frequently associated with improved symptomatic outcome are better premorbid function (e.g. Rabinowitz *et al.* 2006), milder symptoms at baseline (specifically negative symptoms) (e.g. Addington & Addington 2008), adherence to medicinal treatment (e.g. Üçok *et al.* 2011), early response to treatment (e.g. de Haan *et al.* 2008), shorter duration of untreated psychosis (e.g. Petersen *et al.* 2008), less use of substances (e.g. Boter *et al.* 2009) and both better neurocognitive (e.g. Buckley *et al.* 2007) and social cognitive performance (e.g. Ciudad *et al.* 2009).

Most research to date has examined only a few of these potential predictors at the same time. This presents a problem, because these independent effects of specific predictors are unlikely to account for the bulk of the variance in outcome, since recovery is most likely predicted by clusters of interrelated (rather than isolated) variables. Also, studies examining both functional and symptomatic recovery indicate that they are likely to have both overlapping (Álvarez-Jiménez *et al.* 2012) as well as unique predictors (Chang *et al.* 2012).

Therefore, the present study investigates the integrated impact of a wide range of previously identified baseline predictors of both functional and symptomatic recovery (i.e. age, education, social economic status, DUP, psychosocial functioning, positive symptoms, negative symptoms, neurocognition, social cognition, mania symptoms and emotional distress) within the one-year course of first-episode psychosis (FEP). The

specific questions are: (1) what proportion of FEP patients reaches symptomatic, functional and full recovery? and (2) which (clusters of) characteristics present at the start of treatment for FEP predict symptomatic, functional and full recovery?

## Method

### *Subjects*

Inclusion for this study took place between December 1, 2009 and January 31, 2012, with the last follow-up measures collected before February 2, 2013. All patients referred to the specialized early psychosis department in The Hague (the Netherlands) who completed the diagnostic protocol (described in detail in: (Stouten *et al.* 2014, 2017) and were diagnosed with a psychotic disorder were included. During the study period 167 individuals were diagnosed with a FEP disorder (DSM-IV diagnoses: 82 schizophrenia, 9 brief psychotic disorder, 6 delusional disorder, 2 shared psychotic disorder, 9 schizoaffective disorder, and 59 psychotic disorder NOS). Follow-up measures for psychosocial functioning were completed exactly 12 months after baseline assessment. The study was approved by the local ethics committee (reference number: NL31561.098.10). Informed written consent was obtained from all participants.

### *Demographic variables*

Years of education were calculated by adding the completed years of education in primary, secondary and tertiary or higher education. Annual income was estimated based on the average level of income per area code for each participant, as provided by the Central Institute of Statistics (CBS) in the Netherlands (*Central Bureau of Statistics* n.d.). The duration of untreated psychosis (DUP) was calculated by taking the date of first contact with our department and subtracting the approximated onset date of the first positive symptoms based on the anamnestic and file information (presented in number of weeks).

### *Neurocognition*

Neurocognitive assessment included assessment of the subdomains *attention* (Continuous Performance Task, CPT 3-7 version) (Nuechterlein & Dawson 1984), *problem solving* (Wechsler Adult Intelligence Scale, WAIS-III, Block design; Tower of London) (Shallice 1982; Wechsler 1997) *speed of processing* (WAIS-III, Digit-symbol coding; Trail making task, part A) (Reitan 1958; Wechsler 1997), *verbal fluency* (Category fluency, animal naming) (Lezak *et al.* 2004), *verbal learning* (Rey Auditory Verbal learning Task, RAVLT) (Rey 1964; Kalverboer & Deelman 1986), *visual learning* (Brief Visuospatial Memory Task

Revised, BVMT-R) (Benedict 2007), *working memory* (WAIS-III, Letter-number sequencing) (Wechsler 1997) and *general cognition* (WAIS-III, Information and Calculations) (Wechsler 1997).

### *Social cognition*

The social cognitive measures included assessment of the subdomains *emotion perception* (Amsterdam Neuropsychological Tasks, ANT) (Sonneville 2005), *theory of mind* (Hinting Task) (Corcoran *et al.* 1995), *social knowledge* (WAIS-III, picture arrangement) (Wechsler 1997), and *social cognitive biases* (Davos Assessment of Cognitive Biases Scale) (van der Gaag *et al.* 2013).

### *Psychopathology*

The Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987) was used to assess positive symptoms, negative symptoms and general psychopathology. Symptomatic recovery was assessed using the eight-item remission tool from the original PANSS (Opler *et al.* 2007), where a score of  $\leq 3$  (mild symptoms) across these eight items was defined as symptomatic recovery.

### *Psychosocial functioning*

The Personal and Social Performance scale (PSP) (Morosini *et al.* 2000) was used to assess psychosocial functioning (range 0-100; higher scores reflect better functioning). The PSP also uses four subscales to assess specific social functioning domains: (a) Socially useful activities including study and work (SUA), (b) Personal and social relationships (PSR), (c) Self-care and care for personal environment (S-C), and (d) Disturbing and/or aggressive behavior (DAB). Higher subscale scores reflect more problems. Functional recovery was operationalized as having a PSP score of  $\geq 61$ . Using the PSP operational criteria, a score of 61 implies manifest (i.e. difficulties clearly noticeable by everyone, but not interfering substantially with the person's ability to perform his/her role in that area) in one functional domain (a-d), with mild (i.e. difficulties only known to someone who is very familiar with the person) or absent problems in the other domains.

### *Data analysis*

The analyses were performed in SPSS (version 22). To examine symptomatic change during the study period, psychopathology subscale scores were computed by adding the related items from the PANSS for baseline and follow-up assessment. Symptomatic recovery was operationalized as having no more than mild symptoms (score  $\leq 3$ ) on any of the eight items from the PANSS remission tool at 12 months. Based on these scores, a



single binary symptomatic remission (SR) variable was computed (remission = 1; no remission = 0). A binary variable for functional remission (FR) was computed based on the total PSP score (61 or higher = 1; 60 or lower = 0). Based on these cut-offs, patients were allocated to one of four outcome groups, 'full recovery' (SR=1; FR=1), 'symptomatic recovery' (SR=1; FR=0), 'functional recovery' (SR=0; FR=1), and 'no recovery' (SR=0; FR=0).

The symptom dimensions neurocognition and social cognition were computed using two single-solution confirmatory factor analyses including all neurocognitive and social cognitive subscale scores, respectively (see Appendix I for factor loadings).

For descriptive purposes, symptom subscale scores were computed by adding the related items of the three subscales from the PANSS into positive symptoms (7 items), negative symptoms (7 items) and general symptoms (16 items). However, for analytic purposes we followed the factor model to restructure the related items from the PANSS as described by Van der Gaag and colleagues (van der Gaag *et al.* 2006) (see Appendix I for factor loadings): symptom scales were computed using four single-solution confirmatory factor analyses, for *positive symptoms* (items P1, P3, G9, P6 and P5), *negative symptoms* (items N6, N1, N2, N4, G7, N3, G16 and G8), *excitement* (G14, P4, P7, and G8) and *emotional distress* (items G2, G6, G3, and G4). Independent sample T-tests were used to assess differences on for the demographic variables and the loadings on the six factors between outcome groups.

Finally, we used a canonical discriminant analysis to investigate the power of the six symptom dimensions, and demographic variables to discriminate between the four 12-month outcome groups.

## Results

### *Demographic variables*

Of the total sample of 167 patients, 53 reached full recovery in 12 months, whereas 56 reached partial recovery (25 symptomatic recovery, 31 functional recovery) and 58 reached neither symptomatic nor functional recovery. Demographic variables and dimensional factor scores for the four outcome groups and the total study sample (see Data analysis) are presented in Table 4.1. Between-group comparison indicated significant baseline differences on psychosocial functioning ( $F(3)=13.60$ ,  $p<.001$ ), positive symptoms ( $F(3)=9.40$ ,  $p<.001$ ), negative symptoms ( $F(3)=7.41$ ,  $p<.001$ ), social cognition ( $F(3)=3.18$ ,  $p=.040$ ), mania ( $F(3)=4.25$ ,  $p=.007$ ) and gender (Mann-Whitney non-parametric test.  $FR>NO$ :  $Z = -3.40$ ,  $p < .001$ ;  $FU>NO$ :  $Z = -3.40$ ,  $p < .001$ ) between the outcome groups. These differences were most evident between the Full recovery and No recovery outcome groups.

**Table 4.1** Baseline descriptive variables per outcome group

	Between-group comparison					
	Full recovery	Symptomatic recovery only	Functional recovery only	No recovery	Total	Significant post-hoc
N	53	25	31	58	167	
Age (years)	26.55 (6.73)	26.92 (6.13)	27.77 (6.30)	26.70 (5.81)	26.89 (6.21)	1.11 .346
Gender (% male)*	56%	72%	59%	86%	71%	-
Education (years)	12.50 (2.37)	12.40 (2.58)	11.35 (2.60)	11.76 (1.84)	12.04 (2.31)	1.52 .213
Annual income (x1000)	20.80 (7.73)	20.92 (8.41)	18.68 (5.90)	19.17 (5.12)	19.86 (6.72)	1.50 .218
Functioning (PSP)	58.04 (13.52)	47.00 (14.54)	56.59 (12.35)	44.05 (11.79)	51.26 (12.85)	13.6 .000
DUP (weeks)	46.02 (63.07)	45.28 (56.74)	90.40 (99.67)	60.88 (72.99)	57.97 (73.03)	2.20 .090
Positive symptoms	-0.48 (0.88)	-0.33 (1.07)	0.31 (0.95)	0.42 (1.10)	0.00 (1.00)	9.40 .000
Negative symptoms	-0.34 (0.87)	-0.16 (0.89)	0.07 (1.03)	0.34 (1.14)	0.00 (1.00)	7.41 .000
Neurocognition	0.30 (0.89)	0.01 (1.09)	-0.09 (1.01)	-0.23 (1.05)	0.00 (1.00)	1.62 .187
Social cognition	0.29 (0.96)	0.14 (0.81)	-0.08 (1.02)	-0.27 (1.11)	0.00 (1.00)	3.18 .040
Mania	-0.39 (0.71)	-0.12 (0.62)	0.18 (1.30)	0.32 (1.28)	0.00 (1.00)	4.25 .007
Emotional distress	-0.16 (0.89)	-0.25 (1.02)	0.09 (1.04)	0.22 (1.07)	0.00 (1.00)	1.37 .253

PSP = Personal and Social Performance scale; FR = Full recovery; SY = Symptomatic recovery only; FU = Functional recovery only; NO = No recovery; DUP = Duration untreated psychosis, i.e. the time between the onset of the first positive symptom and the date of first contact with the Centre for Early Psychosis; \*non-parametric test (Mann-Whitney; two-tailed) used to assess differences in distribution.

1: Z = -3.40, p < .001

2: Z = -2.63, p = .009

### *Symptomatic and functional change*

Psychopathology and psychosocial functioning scores at baseline and 12-month follow-up are presented in Table 4.2. All three symptom subscales decreased and all functional domains (except self-care) improved significantly during the follow-up period for the study sample.

### *Canonical discriminant analysis*

To identify determinants of outcome category at 12 months, discriminant analysis was used (Table 4.3). This analysis yielded three discriminant functions (functions 1-3: Wilks  $\lambda$  = .53;  $\chi^2$  = 80,07; df = 36;  $p$  < .001) with eigenvalues of 0.50 (% of variance: 68.3%; canonical correlation 0.58), 17.3 (23.3%; 0.38), and 0.06 (8.4%; 0.24). The analysis of baseline variables clustered baseline functioning, positive symptoms, negative symptoms, mania, gender and social cognition into the first factor, whereas DUP and years of education were clustered in the second factor. Education, neurocognition, emotional distress and annual income were clustered into the third factor. Table 4.3 shows the correlations of all baseline variables with the discriminant functions,

### *Sample distribution*

Figure 4.1 is a scatterplot (individual scores and group centroids) of the study sample by scores on functions one and two (see Table 4.3), which together accounted for 91.6% of the variance. Visual inspection of Figure 4.1 (group centroids) suggests that function one (i.e. baseline functioning, positive symptoms, negative symptoms, mania, gender and social cognition) discriminates between Full recovery and No recovery, whereas function two (i.e. DUP and years of education) discriminates between Functional recovery and Symptomatic recovery.

### *Classification accuracy*

On the basis of the three discriminant functions 58.8% of the cases (cross-validated: 52.2%) could be classified correctly in one of four outcome groups (Table 4.4). Sensitivity (i.e. outcome group membership correctly classified) was high for the full recovery (79,3%) and no recovery (70,7%) groups, and low for the symptomatic recovery (24.0%) and functional recovery (35,5%) groups. Specificity (i.e. outcome group non-membership correctly classified) was 77.2% for full recovery, 94.6% for symptomatic recovery, 96.9% for functional recovery and 73.9% for no recovery.

**Table 4.2** Symptomatic and functional change

	Symptoms (PANSS)			Psychosocial functioning (PSP)				
	POS	NEG	GEN	SUA	PSR	S-C	DAB	General
<i>Study sample</i>								
Baseline	11.05 (3.78)	12.95 (5.04)	29.02 (6.95)	2.59 (0.97)	2.28 (0.90)	0.64 (0.91)	0.63 (1.03)	51.26 (12.85)
12 months	10.09 (2.90)***	12.42 (4.38)*	26.80 (6.55)***	2.23 (0.75)***	1.93 (0.86)***	0.61 (1.11)	0.38 (1.02)***	56.52 (8.61)***
<i>Full recovery</i>								
Baseline	9.02 (3.23)	10.44 (3.45)	25.11 (5.90)	2.23 (1.09)	1.91 (0.94)	0.47 (0.83)	0.38 (0.90)	58.04 (13.52)
12 months	7.49 (1.99)***	9.03 (2.14)**	21.13 (4.39)***	1.29 (0.82)***	1.09 (0.81)***	0.24 (0.52)*	0.07 (0.25)**	69.83 (8.06)***
<i>Symptomatic recovery</i>								
Baseline	10.24 (3.95)	11.84 (4.67)	27.22 (6.74)	2.75 (1.00)	2.52 (0.90)	0.77 (0.97)	0.94 (1.39)	47.00 (14.54)
12 months	8.58 (2.50)*	10.54 (3.01)*	24.10 (6.13)**	2.96 (0.81)	2.67 (0.83)	0.98 (1.07)	0.86 (1.28)	43.37 (9.29)
<i>Functional recovery</i>								
Baseline	11.69 (3.49)	12.85 (5.57)	30.00 (6.86)	2.23 (0.96)	1.92 (0.96)	0.36 (0.71)	0.36 (0.71)	56.59 (12.35)
12 months	11.15 (3.20)	13.03 (5.25)	28.85 (6.55)	1.49 (0.64)***	1.36 (0.58)***	0.18 (0.39)	0.10 (0.38)*	67.64 (6.14)***
<i>No recovery</i>								
Baseline	12.90 (4.35)	15.78 (6.37)	32.84 (8.04)	3.05 (0.86)	2.70 (0.84)	0.90 (1.06)	0.88 (1.16)	44.05 (11.79)
12 months	12.54 (3.75)	16.00 (6.54)	32.06 (8.65)	3.16 (0.71)	2.68 (0.86)	1.01 (1.11)	0.61 (1.02)	44.09 (10.14)

PANSS = Positive and Negative Syndrome Scale; POS = Positive symptoms; NEG = Negative symptoms; GEN = General symptoms; SUA = Socially useful activities (work and study); PSR = Personal and social relationships; S-C = Self-care and care for personal environment; DAB = Disturbing and/or aggressive behaviour; PSP = Personal and Social Performance. Asterisks denote significant change within the 12-month follow-up period.

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$

**Table 4.3** Structure matrix

	Function		
	1	2	3
Baseline functioning (PSP)	<b>-.671*</b>	.357	.150
Baseline positive symptoms (factor)	<b>.500*</b>	.432	.066
Baseline negative symptoms (factor)	<b>.433*</b>	.057	.429
Baseline mania (factor)	<b>.384*</b>	.181	-.119
Gender	<b>.378*</b>	-.241	-.152
Baseline social cognition (factor)	<b>-.269*</b>	-.181	-.001
DUP (weeks)	.190	<b>.613*</b>	-.035
Years of education	-.157	<b>-.393*</b>	.076
Annual income (x1000)	-.033	-.250	<b>.436*</b>
Age (years)	.077	.228	<b>-.430*</b>
Baseline neurocognition (factor)	-.169	-.200	<b>.242*</b>
Baseline emotional distress (factor)	.173	.037	<b>.239*</b>

Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions. Variables are ordered by absolute size of correlation within function. Asterisks denote the largest absolute correlation between each variable and any discriminant function.

## Discussion

### *Main findings*

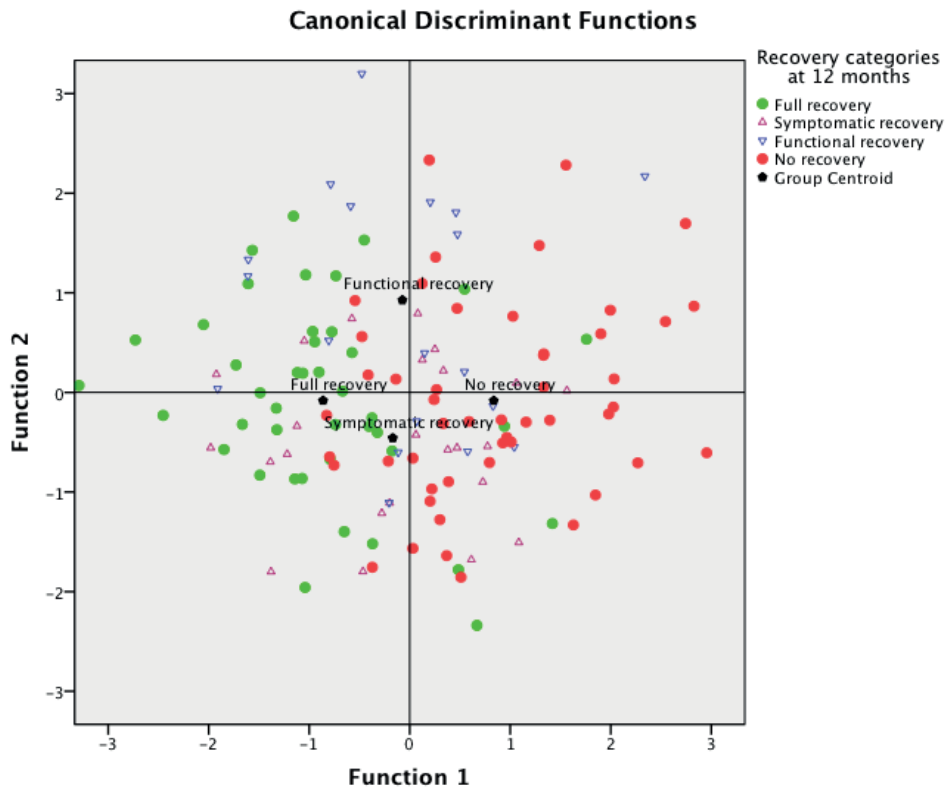
This study found that one third of these patients with FEP was fully recovered after one year, one third was not recovered, and one third partially recovered. Overall, patients showed a significant improvement with regard to positive, negative, and general symptoms. Also, they improved in vocational/academic performance, social and general functioning, and had less disturbing behaviour.

Better baseline functioning, lower levels of positive-, negative- and mania symptoms, and better social cognitive functioning at baseline, discriminated between patients with full recovery and those who were not recovered in the first 12 months after baseline. Also, female patients were more likely to recover fully than male patients. Within the subset of patients that showed partial recovery (i.e. symptomatic only or functional only), shorter DUP and more years of education discriminated between those who primarily showed improved symptomatic outcome and those who primarily showed improved functioning outcome at 12-month follow-up.

### *Comparison with previous studies*

In line with previous work, our study confirmed that functioning and both positive and negative symptoms are baseline predictors of functional outcome (Álvarez-Jiménez *et al.* 2012) as well as symptomatic outcome (AlAqeel & Margolese 2012).

Figure 4.1 Scatterplot of canonical discriminant functions



In addition to positive and negative symptoms, model accuracy was improved by mania symptoms, gender and social cognition (Table 4.3). These findings are consistent with previous findings of better short-term outcome in patients with an affective psychotic disorder compared to non-affective acute psychosis, schizoaffective disorder or schizophrenia (Tohen *et al.* 2000), and also with recent longitudinal work (Horan *et al.* 2012) and meta-analytic data (Fett *et al.* 2011) that indicated social cognition as a predictor of functional outcome, exceeding neurocognition.

Although sub-threshold mania symptoms are not frequently studied in FEP patients, our data illustrate that they do have a direct impact on outcome, even in the early stages of psychotic disorders (Demjaha *et al.* 2009). In addition there may be other relevant indirect effects; for example, a recent study on interrelations between symptom

dimensions and cognitive domains indicated that mania relates to cognitive performance by an inverted-U-shaped relationship, implying that moderate levels of mania are related to better cognitive function (Kravariti *et al.* 2012).

**Table 4.4** Classification results

			Predicted Group Membership				Total
			Full	SR	FR	None	
Original	Count	Full recovery	42	0	3	9	53
		Symptomatic recovery only	8	6	0	11	25
		Functional recovery only	8	3	11	9	31
		No recovery	10	5	2	41	58
	%	Full recovery	79.25	0.00	4.76	16.67	100.00
		Symptomatic recovery only	32.00	24.00	0.00	44.00	100.00
		Functional recovery only	25.81	9.68	35.48	29.03	100.00
		No recovery	17.24	8.62	3.45	70.69	100.00
Cross-validated <sup>b</sup>	Count	Full recovery	39	0	3	11	53
		Symptomatic recovery only	8	3	1	13	25
		Functional recovery only	9	3	8	11	31
		No recovery	12	5	4	37	58
	%	Full recovery	73.58	0.00	5.66	20.75	100.00
		Symptomatic recovery only	32.00	12.00	4.00	52.00	100.00
		Functional recovery only	29.03	9.68	25.81	35.48	100.00
		No recovery	20.69	8.62	6.90	63.79	100.00

a. 58.8% of original grouped cases correctly classified.

b. Cross validation is done only for those cases in the analysis. In cross validation, each case is classified by the functions derived from all cases other than that case.

c. 52.2% of cross-validated grouped cases correctly classified.

Also, our findings underline the hypothesis that longer DUP is associated with poorer outcome (Marshall *et al.* 2005; Perkins *et al.* 2005; White *et al.* 2009). However the present study suggests that receiving treatment for psychosis sooner rather than later is a *specific* protective factor that improves chances of symptomatic recovery (as might be expected), but does not appear to be related to impaired chances of functional recovery in the present sample.

The results of this study are not consistent with the literature on several points. First, meta-analytic data indicate that neurocognition is a predictor of outcome (Mohamed *et al.* 2008; Allott *et al.* 2011). However, in the present study the overlap with social cognition may have taken away the variance that they have in common and, subsequently, have left neurocognition with limited statistical contribution (see

‘Methodological considerations’). Another consideration is that, in the present sample, neurocognition and social cognition were only mildly affected (for details: Stouten et al., 2015), which may have led to a smaller impact of these factors on outcome in the present data compared to previous studies.

Second, depression is a frequent co-morbid disorder that occurs in many patients during the course of psychotic disorders (Uptegrove *et al.* 2010, 2014). However, despite marked emotional distress in the present sample, there was no significant relation between this factor and outcome.

Third, factors associated with socio-economic status (education and income) did not impact outcome. Although previous findings are inconsistent, it is feasible that a higher level of education and/or more financial means may positively impact outcome. However, studies on the impact of these socio-economic factors suggest that it may not be the *absolute* levels for such variables, but rather the *relative* levels (i.e. having more or less education/money/social status compared to those in your social context) that determine outcome (Veling 2013).

In summary, both functional and symptomatic outcome in FEP patients generally improve within 12 months after first contact. In line with previous work, less functional problems, low positive, negative and mania symptoms, and good social cognition at baseline are associated with early recovery. Also, female patients were more likely to achieve full recovery compared to males. However, in contrast with previous findings, higher income, good neurocognition, lower emotional distress and a lower age at baseline did not appear to be related to either functional- or symptomatic outcome.

### *Methodological considerations*

As part of the discriminant analysis method, the first function was built to optimize group differences (x-axis; Figure 4.1), as the second function was built to be orthogonal to the first and still optimize group differences (y-axis; Figure 4.1). Subsequently, the third function was built to be orthogonal to both previous functions and, again, to optimize group differences (z-axis; not displayed). Due to this procedure, the variance accounted for by predictors in the first function was maximized at the expense of predictors in the second and third functions. Therefore, this method is likely to underestimate the impact of those predictors in the second and third functions that were highly correlated to predictors in the first function (*multicollinearity*). Subsequently, in our analysis, the impact of neurocognition on outcome is likely to be underestimated due to the strong correlation with social cognition ( $r = 0.617$ ; see Appendix I). This finding supports the hypothesis that



social cognition mediates the effect of neurocognition on outcome in FEP patients (Addington 2010; Schmidt *et al.* 2011).

### *Limitations*

The key limitation of the presented study is that records on use of anti-psychotic medication were not available to the researchers. However, previous data indicate that the short-term impact of anti-psychotic medication on the predictors used in this study is likely to be absent or small, especially concerning cognition (Mishara & Goldberg 2004; Woodward *et al.* 2007). Previous work also indicates that the use of anti-psychotic medication in the early stages of the disorder is not strongly related to better functional outcome (Menezes *et al.* 2006), but may even be associated with poorer long-term functional recovery (McGorry *et al.* 2013; Wunderink *et al.* 2013). Although our follow-up period is probably too short to study these effects, this issue clearly warrants further study. Another limitation is that the quality of the data on the duration of untreated psychosis (DUP) was rather poor in a number of cases. In retrospect, we consider the used method to acquire this data (i.e. anamnestic interview and medical file study) adequate in the majority of cases, there were a substantial number of patients that did not have a medical file that was available to the researcher (due to recent migration or other factors), and/or where patients did not remember when they experienced their first positive symptom. In these cases, a best estimate was made together with the patients, based on the data that was available.

### *Strengths*

The present study has several strengths. First, it offers an integrated longitudinal investigation of psychopathology, functioning and demographic values as predictors of symptomatic and functional outcome in FEP, identifying a cluster of interrelated factors at baseline (i.e. baseline functioning, positive symptoms, negative symptoms, mania symptoms, gender and social cognition) that enables (at illness onset) to discriminate between those who are likely (or not) to recover in the early stages of psychosis. Second, for all patients, all psychopathological, affective, neurocognitive and social cognitive baseline measures were completed within three months after the first contact, thereby ruling out confounding variables associated with chronicity and long-term treatment. Third, the present patient sample was highly representative, including all consecutive FEP patients that entered the psychiatric services in The Hague during the study period.

### *Implications*

Prediction of recovery after a FEP with clinical, social and socioeconomic characteristics at first presentation is limited. Although a wide range of previously identified predictors was used, only a relatively small part of the variation in symptomatic and functional outcome was explained. These findings suggest that other contextual, (epi-)genetic, biological and psychosocial factors should be included in prediction models, in order to be of clinical significance.

Subsequently, it seems clear that multifactorial approaches should be applied not only to predictor variables but also to outcome domains in patients with FEP (Menezes *et al.* 2006; Lin *et al.* 2013a), incorporating clinical factors (e.g. relapse, remission, symptom reduction, hospitalization, treatment compliance, suicidal behaviour and mortality) as well as dimensions of recovery (e.g. employment status, academic performance, social functioning, role functioning, self-care, independent living, cultural and identity development, sexual functioning and overall quality of life).

Despite these methodological issues, our data show that more severe symptoms and lower levels of personal functioning at the start of treatment are the strongest indicators of poorer symptomatic and functional outcome at 12-month follow-up. This implies that the best outcome in FEP will result from intensive treatment programs that integrate treatment to reduce clinical symptoms together with interventions that explicitly and directly aim to improve social role functioning. The fact that social cognition was identified as a predictor of recovery in the present sample also emphasizes the need to differentiate between neurocognition and social cognition (van Hooren *et al.* 2008), and to allocate resources to routinely assess (and possibly to improve (Choi & Kwon 2006) the latter in the early stages of psychosis.



## **Chapter 5 Cognitive deficits and ethnicity: a cohort study of early psychosis patients in The Netherlands**

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## Abstract

**Aim** Incidence rates of psychotic disorders are higher in immigrant groups compared to native populations. This increased risk may partly be explained by misdiagnosis. Neurocognitive deficits are a core feature of psychotic disorders, but little is known about the relationship between migration and cognition in psychotic disorders. We examined whether immigrant patients have cognitive deficits similar to non-immigrant patients, in order to investigate the plausibility of misdiagnosis as explanation for increased incidence rates.

**Methods** Patients who made first contact for non-affective psychotic disorder were assessed in the cognitive domains sustained attention, immediate recall and delayed recall. Immigrant patients were compared to Dutch patients on cognitive performance.

**Results** 407 Patients diagnosed with a non-affective psychotic disorder completed cognitive assessment (157 Dutch, 250 immigrants). Both Dutch and immigrant patients showed large cognitive deficits. Between-subgroup comparisons revealed large cognitive deficits for immigrants compared to Dutch, especially for immigrants from Morocco, Turkey and other non-Western countries.

**Conclusions** These results indicate that immigrant status is associated with poorer cognitive functioning in early psychosis. The findings argue against diagnostic bias as an explanation for the increased incidence of psychotic disorders in immigrants.

## Keywords

Schizophrenia, psychosis, migration, ethnicity, cognition

## Introduction

Various studies demonstrated increased incidence rates of schizophrenia and other psychotic disorders in immigrant groups (Selten *et al.* 2001; McGrath *et al.* 2004; Cantor-Graae & Selten 2005; Kirkbride *et al.* 2006; Veling *et al.* 2006, 2007b; Bourque *et al.* 2011; Jarvis *et al.* 2011). It has been argued that these high rates were the result of diagnostic bias: experiences and behavior of ethnic minorities may be misinterpreted as positive or negative symptoms of schizophrenia by clinicians who are not familiar with the immigrants' culture (Selten & Hoek 2008; Zandi *et al.* 2010). If this kind of diagnostic bias does in fact lead to a larger number of incorrect psychotic diagnoses in immigrant groups compared to non-immigrants, it is likely that average severity of symptoms in clusters other than positive or negative symptoms would be lower in immigrant groups. Studies of ethnic differences in symptom profiles reported contradictory findings (Sharpley *et al.* 2001; Arnold *et al.* 2004; Veling *et al.* 2007a), but were limited to positive, negative and affective symptoms. With regard to the latter, Veling and colleagues found higher levels of depressive or manic symptoms in some, but not all, immigrant groups (Veling *et al.* 2007a).

Neurocognitive functioning is another main symptom category in psychotic disorders (Green 1996; Braff *et al.* 2008; Mesholam-gately *et al.* 2009; Van Os & Kapur 2009). Three of the most impaired neurocognitive functions in psychotic disorders are sustained attention, immediate recall and delayed recall (Heinrichs & Zakzanis 1998; Aleman *et al.* 1999; Niemi *et al.* 2003). Cognitive deficits in these areas tend to precede psychotic symptoms (Cornblatt *et al.* 1999; Niendam *et al.* 2006), to persist after psychotic episodes (Seidman *et al.* 1992) and are more prominent than in other psychiatric disorders (Krabbendam *et al.* 2005; Stefanopoulou *et al.* 2009). If the high rates of psychotic disorders in immigrants are an artifact of misdiagnoses, it is unlikely that we would find large cognitive deficits in immigrant patients, whereas similar or larger cognitive impairments in immigrants compared to non-immigrants would argue against diagnostic bias (Zandi *et al.* 2010).

Cognitive measures are likely to have ethnic bias in themselves, since cultural and linguistic differences may impact measurement scores considerably (Boone *et al.* 2007). A review showed that immigrants and non-immigrants in the general population of The Netherlands tend to differ on average one standard deviation in cognitive performance tests (Te Nijenhuis & Van Der Flier 2001). This difference was substantially smaller in second generation immigrants than in first generation immigrants.

This study examines cognitive differences between immigrants and non-immigrants and between first- and second generation immigrants with three cognitive measures in a multi-ethnic clinical sample of first episode schizophrenia spectrum patients. We hypothesized that (1) both immigrant patients and non-immigrant patients have cognitive test scores more than one SD below the general Dutch population norm scores, (2) differences in cognitive deficits between immigrant- and non-immigrant patients are smaller than one SD, and (3) differences between second generation immigrants and non-immigrants will be smaller than those between first generation immigrants and non-immigrants.

## **Method**

### *Subjects*

All patients who made first contact with mental health services in The Hague between September 1, 2000 until September 1, 2009, who completed our diagnostic protocol, were diagnosed with a non-affective psychotic disorder (APA 2013a) (DSM IV: schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, delusional disorder and psychotic disorder NOS) and who also completed neuropsychological assessment were included in this study. The study was approved by the Dutch ethics committee for mental health care. No informed consents were obtained, since all data were collected as part of routine outpatient diagnostic procedures and care over an extended period of time, without premeditation of subsequent data analyses.

### *Classification of ethnicity*

Ethnicity was classified as follows: those patients who are Dutch-born with two Dutch-born parents were categorized as Dutch (DP), those who are Dutch-born and have at least one foreign-born parent were categorized as second generation immigrant (IP2), and those who are foreign-born were categorized as first generation immigrant (IP1). The seven ethnic subcategories were: (1) Dutch, (2) Morocco, (5) the Netherlands Antilles, (3) Surinam, (4) Turkey, (6) western(ized) countries (northern, southern or western Europe, the former Yugoslavia, the USA, Canada, Australia, New Zealand, Japan or former Netherlands East Indies), and (7) all other (non-western) countries.

### *Diagnostic protocol*

The patients were interviewed by Dutch residents in psychiatry using two different semi-structured diagnostic interviews: Comprehensive Assessment of Symptoms and History (CASH) (Andreasen *et al.* 1992) (from start study until 30-09-2008) and Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO 1992) (from 01-10-2008 until end study). Cognitive assessment was performed by clinical psychologists. Relatives were interviewed by trained nurses using the Instrument for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) (Häfner *et al.* 1992). Using information derived for CASH/SCAN, IRAOS, cognitive assessment and the medical file, the residents compiled a narrative history of the patient's illness. For the patients who refused the interviews and/or the cognitive assessment, they constructed a history using information from the responsible physician. On the basis of the narrative history two psychiatrists made a consensus DSM-IV diagnosis during a diagnostic meeting.

### *Cognitive assessment*

The assessment was structured as follows: firstly, date of birth, completed years of education and some other personal characteristics were obtained through a short structured interview. Secondly, the five learning trails of the RAVLT (immediate recall) were conducted (see section 'verbal memory'). Thirdly, the patients completed the CPT task (see section 'sustained attention') and finally, the RAVLT delayed recall trail (15 min delay) was administered (see section 'verbal memory'). Based on demographics-corrected normative data contained within the test manuals (Berisoft cooperation n.d.; Nuechterlein & Dawson 1984), raw scores were converted to Z scores for all cognitive measures to allow for clinical interpretation. Scores were adjusted so that higher Z scores reflected better performance.

### *Verbal memory*

Verbal short-term memory (immediate recall) and verbal declarative memory (delayed recall) were both assessed in all subgroups with the Dutch version of the Rey's Auditory Verbal Learning task (RAVLT) (Rey 1964; Kalverboer & Deelman 1986). This task consist of spoken single-syllable words, presented in five identical trials of fifteen words with immediate reproduction after every trial and one delayed recall trial after a 15-minute delay.



### *Sustained attention*

Sustained attention was assessed in all subgroups with the Continuous Performance Task (CPT, 3-7 version) (Berissoft cooperation n.d.; Nuechterlein & Dawson 1984). During this 10-minute test, A string of 600 single digits is sequentially shown on a computer screen. A “hit” is counted when a mouse-click is registered directly after the presentation of first the number three, directly followed by the number seven; 90 targets in total.

### *Education*

Completed years of education was ascertained through adding the total number of years completed in primary-, secondary- and tertiary- or higher education.

### *Global functioning*

Global functioning was assessed with the modified Global Assessment of Functioning (GAF) score (APA 2013a).

### *Cannabis use*

The treating physicians gathered information on current (five times use or more in the last month) and lifetime (five times use or more ever) cannabis use during the psychiatric interview.

### *Data analysis*

The analyses were performed with SPSS version 18 for Windows (IBM n.d.). Descriptive statistics of all variables involved were first computed. Immediate recall scores (RAVLT) were calculated by adding the scores of the five learning trails. Pearson chi-squares were calculated to identify group differences in gender- and cannabis use distributions. Between-group differences on all other variables were assessed using Student’s t-tests. Correlations between dependent variables and independent variables were examined to identify covariates. Hierarchical regression models (method enter) were used to assess the predictive quality of cognitive performance on education per ethnic subgroups. The relationship between cognitive performance and education was compared between ethnic groups (ANCOVA) to examine homogeneity of regression slopes and interaction effects. An alpha level of .05 was regarded as acceptable for all analyses.

Additional analysis explored the potential cross-cultural measurement bias (CCMB) for the used psychometric tools. A measure may demonstrate CCMB if the

regression models that relate the predictor (here: cognitive functioning) to a predicted outcome (e.g. years of education) differ between ethnic groups (Cleary 1968; Pedraza & Mungas 2008). Bias is likely if (a) ethnic groups differ in cognitive functioning (regression intercepts) and (b) ethnic groups differ in the associations between cognitive functioning and completed years of education. Education is a useful outcome for this analysis, because it is associated to both immigrant status and cognitive functioning.

## Results

### *Subjects*

854 subjects made first contact during this nine-year period, of which 496 completed cognitive assessment (58.1%). Of the total of 496, 407 subjects (82.1%; 307 male, 100 female) were diagnosed with a non-affective psychotic disorder (schizophrenia spectrum disorder: N=319, brief psychotic disorder: N=13, and psychotic disorder NOS: N=75). The group of subjects that did not complete cognitive assessment (N=358) contained higher percentages of females ( $p \leq .05$ ) and immigrants ( $p \leq .01$ ) and a lower percentage of lifetime cannabis users ( $p \leq .05$ ) compared to the group that did. No differences were observed on any of the other available variables.

### *Demographic variables and cognition*

Table 5.1 shows descriptive statistics and frequencies for the study sample, DP, total immigrant subgroup (IPT), IP1, and IP2: sex, age, GAF, education, cannabis use (current and lifetime), immediate recall (RAVLT immediate recall), delayed recall (RAVLT delayed recall) and sustained attention (CPT hit rate). Performance by Dutch patients was -0.45 SD for memory (average over two recall tasks) and -1.14 SD for attention below the norm of the test manuals. Performance by immigrant patients was -0.89 SD and -2.96 SD respectively below these norms. Although first generation immigrants showed poorer performance compared to second generation immigrants on all measures, only the difference on sustained attention was significant ( $p \leq .001$ ). Figure 5.1 shows the standardized cognitive scores for the three cognitive variables per subgroup.

**Table 5.1** Descriptive statistics and frequencies for the study sample: sex, age, global functioning (GAF), education, cannabis use (current and lifetime), immediate recall (RAVLT immediate recall), delayed recall (RAVLT delayed recall) and sustained attention (CPT hit rate)

	Sample total	Dutch total	Immigrants		
			total	2nd generation	1st generation
N	407	157	250	112	138
Sex <sup>a</sup> (male/female)	307/100	115/42	192/58	86/26	106/32
Age	26.90 (7.21)	27.56 (7.66)	26.47 (6.89)	25.11 (7.23)*	27.59 (6.41)
GAF	46.89 (12.63)	48.40 (13.24)	46.00 (12.20)	45.62 (10.89)	46.32 (13.27)
Years of Education	11.34 (2.45)	12.06 (2.26)	10.89 (2.46)***	11.34 (2.30)*	10.52 (2.54)***
Cannabis, current <sup>b</sup>	128 (31.4%)	53 (33.8%)	75 (30.0%)	42 (37.5%)	33 (23.9%)
Cannabis, lifetime <sup>c</sup>	263 (64.6%)	112 (71.3%)	151 (60.4%)	78 (69.6%)	73 (52.9%)
RAVLT IM recall <sup>1</sup>	39.95 (11.36)	43.42 (10.44)	37.61 (11.44)***	38.88 (10.78)**	36.57 (11.91)***
RAVLT DE recall <sup>1</sup>	8.45 (3.26)	8.94 (2.94)	8.14 (3.42)	8.43 (3.22)	7.89 (3.57)
CPT hitrate <sup>1</sup>	.808 (.180)	.870 (.126)	.769 (.197)***	.820 (.161)*	.729 (.213)***

RAVLT = Rey Auditory Verbal Learning Task; IM = immediate; DE = delayed; CPT = Continuous Performance Task.

Asterisks denote significant differences in comparison with the Dutch subgroup.

\*  $p \leq .05$ , \*\*  $p \leq .01$ , \*\*\*  $p \leq .001$

<sup>1</sup> Differences adjusted for education and cannabis use.

<sup>a</sup>  $\chi^2 (2) = .608$ ,  $p = .738$

<sup>b</sup>  $\chi^2 (2) = 5.09$ ,  $p = .078$

<sup>c</sup>  $\chi^2 (2) = 12.82$ ,  $p = .002$

### *Cannabis use*

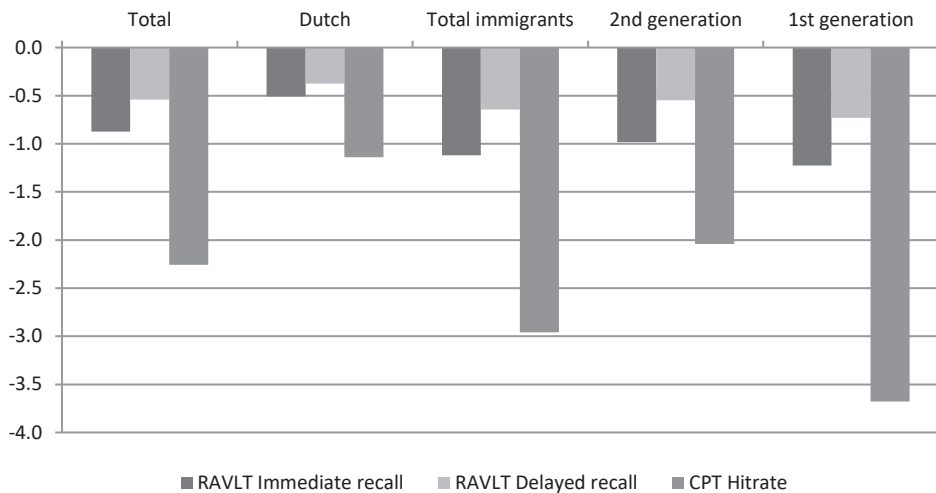
Post-hoc analysis revealed a lower percentage of lifetime cannabis users in IPT ( $p \leq .01$ ) and lower percentages of both current ( $p \leq .05$ ) and lifetime ( $p \leq .001$ ) cannabis users in IP1 compared to DP. No differences in cannabis use were observed between DP and IP2. Cannabis use was unrelated to education and global functioning in all subgroups, except for lifetime use in DP, where those with lifetime cannabis use had slightly higher GAF scores ( $T(154) = 1.49$ ,  $p = .14$ , ns).

### *Cognition, education and cannabis*

Table 5.1 and Figure 5.1 further show the cognitive measures scores for these groups. All immigrant groups (IP1, IP2 and IPT) had significantly lower scores on all three cognitive measures compared to DP. In addition, current cannabis use was related to smaller deficits on delayed recall ( $d = 0.41$ ) and sustained attention ( $d = 0.46$ ) in IP1 and lifetime cannabis was related to smaller attention deficits in DP ( $d = 0.24$ ). Post-hoc tests revealed significant differences between IP1 and IP2 on all cognitive measures ( $p \leq .01$

for all). Differences between all groups on delayed recall were no longer significant, when controlled for education and cannabis use.

**Figure 5.1** Standardized cognitive scores for immediate recall (RAVLT IR), delayed recall (RAVLT DR) and sustained attention (CPT) for the study sample and the following subgroups: Dutch, total immigrants, second generation immigrants and first generation immigrants



RAVLT IR = Rey Auditory Verbal Learning Task, immediate recall; RAVLT DR = Rey Auditory Verbal Learning Task, delayed recall; CPT = Continuous Performance Task

#### *Descriptive statistics: immigrant subgroups*

To examine within-ethnic group differences, the IPT subgroup was split into six subgroups based on ethnicity (see section ‘classification of ethnicity’). Table 5.2 shows the same means and frequencies for these subgroups as Table 5.1, adding the distribution of first- and second generation subjects per subgroup. After controlling for education and cannabis use, immigrants from Morocco ( $p \leq .001$ ), Turkey ( $p \leq .01$ ) and other non-Western countries ( $p \leq .01$ ), showed poorer immediate recall compared to DP. Furthermore, the Moroccan ( $p \leq .001$ ), Turkish ( $p \leq .001$ ), other non-Western countries ( $p \leq .001$ ), Surinam ( $p \leq .05$ ) and the Netherlands Antillean ( $p \leq .05$ ) subgroups demonstrated larger attentional deficits compared to DP.

**Table 5.2** Descriptive statistics and frequencies per ethnic subgroup

	Surinam	Antilles	Turkey	Morocco	Non-Western	Western
N	65	16	34	58	58	19
Generation (1st/2nd) <sup>a</sup>	31/34	9/7	15/19	38/20	37/21	8/11
Sex <sup>b</sup> (male/female)	45/20	11/5	23/11	50/8	47/11	16/3
Age	27.25 (7.15)	25.63 (5.54)	26.61 (10.30)	26.50 (5.54)	25.93 (6.28)	25.81 (5.01)
GAF	45.03 (12.47)	43.88 (10.91)	44.42 (10.00)	45.18 (12.18)	49.56 (13.25)	45.59 (12.13)
Years of Education	10.74 (2.36) <sup>***</sup>	11.75 (2.17)	10.80 (2.58) <sup>**</sup>	10.34 (2.19) <sup>***</sup>	11.04 (2.78) <sup>**</sup>	12.11 (2.16)
Cannabis use, current <sup>c</sup>	23 (35.4%)	4 (25.0%)	5 (14.7%)	19 (32.8%)	19 (32.2%)	6 (31.6%)
Cannabis use, lifetime <sup>d</sup>	42 (64.6%)	9 (56.3%)	16 (47.1%)	32 (55.2%)	38 (64.4%)	15 (78.9%)
RAVLT immediate recall <sup>1</sup>	38.91 (10.77)	43.06 (13.25)	34.97 (9.44) <sup>**</sup>	34.41 (10.69) <sup>***</sup>	37.09 (12.84) <sup>**</sup>	44.94 (8.57)
RAVLT delayed recall <sup>1</sup>	8.44 (3.33)	9.67 (3.36)	7.55 (3.26)	7.55 (3.49)	7.89 (3.58)	9.50 (2.90)
CPT hitrate <sup>1</sup>	.805 (.178) <sup>*</sup>	.779 (.203) <sup>*</sup>	.754 (.151) <sup>***</sup>	.720 (.235) <sup>***</sup>	.757 (.207) <sup>***</sup>	.852 (.130)

RAVLT = Rey Auditory Verbal Learning Task; CPT = Continuous Performance Task; GAF = Global Assessment of Functioning. Chi-squares were calculated including the Dutch subgroup, except for the generation distribution for the ethnic subgroups (a). Asterisks denote significant differences in comparison with the Dutch subgroup.

\*  $p \leq .05$ , \*\*  $p \leq .01$ , \*\*\*  $p \leq .001$

<sup>1</sup> Differences adjusted for education and cannabis use.

<sup>a</sup>  $\chi^2(12) = 317.81$ ,  $p = .000$

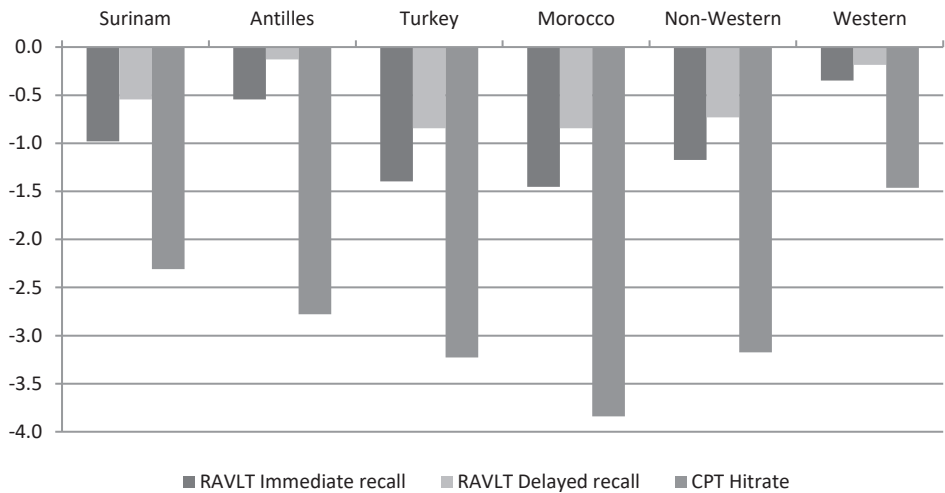
<sup>b</sup>  $\chi^2(6) = 8.50$ ,  $p = .204$

<sup>c</sup>  $\chi^2(6) = 7.16$ ,  $p = .307$

<sup>d</sup>  $\chi^2(6) = 14.93$ ,  $p = .021$

Figure 5.2 shows the standardized cognitive scores for the three cognitive variables for the six immigrant subgroups.

**Figure 5.2** Standardized cognitive scores for all ethnic subgroups for immediate recall (RAVLT IR), delayed recall (RAVLT DR) and sustained attention (CPT)



RAVLT IR = Rey Auditory Verbal Learning Task, immediate recall; RAVLT DR = Rey Auditory Verbal Learning Task, delayed recall; CPT = Continuous Performance Task.

*Cross-cultural measurement bias: regression weights*

The regression models for predicting education with cognitive predictors for DP, IP1 and IP2 with gender and age as covariates are displayed in Table 5.3. In Figure 5.3, the regression models from Table 5.3 are plotted. As was indicated by Table 5.1 and 5.3, different intercept and slopes are demonstrated between the three subgroups on all three measures (for statistical testing, see section ‘cross-cultural measurement bias: regression slopes’).

*Cross-cultural measurement bias: regression slopes*

To investigate CCMB for the cognitive measures that were used in this study, the homogeneity of the regression slopes was assessed with ANCOVA analysis. Results are displayed in Table 5.4, indicating that the ethnicity x cognition interaction (CCMB) was significant only in the DP vs. IP2 group comparison. Overall, CCMB explained between

0.0% and 2.2% of the variance in education in these between-group comparisons, where ethnicity accounted for between 0.1% and 3.5% of this variance and cognition for 3.0% to 13.6%.

**Table 5.3** Hierarchical regression models (method enter) for cognitive predictors of education per ethnic subgroup, adjusted for gender and age

		Model	$\beta$	$r^2$	$\Delta r^2$	p-value (F)
Dutch	Box 1	Gender	-.004	.004	-	.746
		+ Age	.061			
	Box 2a	Box 1 + RAVLT immediate recall	.225**	.054	.050	.042
	Box 2b	Box 1 + RAVLT delayed recall	.105	.015	.011	.531
	Box 2c	Box 1 + CPT hitrate	.176*	.037	.030	.135
2nd generation	Box 1	Gender	-.074	.010	-	.601
		+ Age	-.069			
	Box 2a	Box 1 + RAVLT immediate recall	.485***	.233	.223	.000
	Box 2b	Box 1 + RAVLT delayed recall	.421***	.180	.170	.000
	Box 2c	Box 1 + CPT hitrate	.316***	.105	.095	.010
1st generation	Box 1	Gender	.001	.012	-	.463
		+ Age	-.110			
	Box 2a	Box 1 + RAVLT immediate recall	.365***	.140	.128	.000
	Box 2b	Box 1 + RAVLT delayed recall	.316***	.109	.097	.002
	Box 2c	Box 1 + CPT hitrate	.200*	.050	.038	.085

RAVLT = Rey Auditory Verbal Learning Task; CPT = Continuous Performance Task.

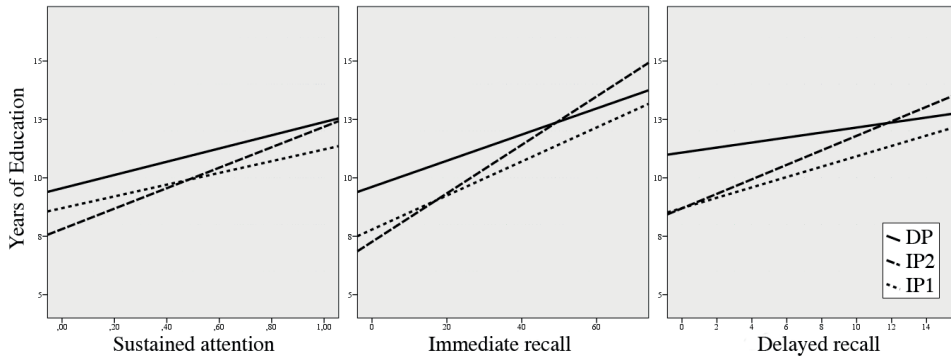
Asterisks denote significant betas ( $\beta$ ).

\*  $p \leq .05$ , \*\*  $p \leq .01$ , \*\*\*  $p \leq .001$

## Discussion

This study in a sample of first-episode schizophrenia spectrum patients showed substantial cognitive impairment on immediate recall (range: -0.55 SD to -1.45 SD), delayed recall (range: -0.13 SD to -0.85 SD) and sustained attention (range: -1.14 SD to -3.84 SD) in both Dutch and immigrant patients groups. The deficits observed on immediate recall were larger than those observed on delayed recall, even though the latter is generally considered a more strenuous cognitive task. The results revealed significantly larger cognitive deficits in immigrant patients compared to Dutch patients and in first generation immigrant patients compared to second generation immigrant patients, controlling for education and use of cannabis. Overall, the Moroccan, Turkish and other Non-Western subgroups demonstrated the largest cognitive deficits.

**Figure 5.3** Plotted regression lines for the education x cognition (sustained attention, immediate recall and delayed recall) interaction per ethnic subgroup



DP = Dutch patients; IP2 = second generation immigrant patients; IP1 = first generation immigrant patients.

Reviewing the differences between immigrants and non-immigrants on immediate- and delayed recall we conclude that none of the immigrant subgroups scored one SD or more below the Dutch patients (range: 0.19  $\Delta$ SD to -0.95  $\Delta$ SD), although the Turkish (-0.89  $\Delta$ SD) and Moroccan (-0.96  $\Delta$ SD) subgroups approached this mark. However, all immigrant subgroups, except the Western subgroup (-0.32  $\Delta$ SD), scored more than one SD below the Dutch patients on sustained attention (range: -1.17  $\Delta$ SD to -2.70  $\Delta$ SD).

Based on these findings we conclude that (1) both immigrants and non-immigrants with psychotic disorders show marked cognitive deficits in immediate recall, delayed recall and attention, (2) there are marked differences in cognitive deficits between immigrant- and non-immigrant patients, where no clear differences in psychotic symptom profiles were evident in our subsample analysis (Selten *et al.* 2001; Sharpley *et al.* 2001; Arnold *et al.* 2004; McGrath *et al.* 2004; Cantor-graae *et al.* 2005; Selten 2005; Veling *et al.* 2007a, 2007b; Kirkbride *et al.* 2006; Veling *et al.* 2006; Bourque *et al.* 2011; Jarvis *et al.* 2011), and (3) second generation immigrant show better performance than first generation immigrants, especially for sustained attention.

Examining these results further, we assessed if cross-cultural measurement bias accounts for ethnic differences in cognitive performance. Figure 5.3 illustrates that the Dutch subgroup and first generation immigrant subgroup mainly differ in intercept, while the second generation immigrant subgroup primarily differs from both groups in



slope in these plotted regression models. Subsequently, we did find a significant ethnicity x cognition interaction in the Dutch patients vs. second generation immigrant patients comparison (Figure 5.3, Table 5.4), but this interaction explained between 0.0% and 2.2% only of the variance in education in all ethnic groups (Table 5.4, partial  $\eta^2$ ). Compared to the overall explained variance for the cognitive models of education (between 7.5% and 18.6%) the impact of cross-cultural measurement bias on the between-group differences in cognitive performance is found to be modest. Therefore, we conclude that cross-cultural measurement bias is no valid explanation for ethnic differences in cognitive performance. In addition, smaller rather than larger cognitive deficits would be expected in ethnic minority patients, if a substantial number of these ethnic minority cases had been incorrectly diagnosed with a psychotic disorder. Since test scores of immigrant patients on sustained attention differed more than 1 SD from non-immigrant patients' scores, it is unlikely that the observed differences can be attributed to measurement bias (Te Nijenhuis & Van Der Flier 2001). These combined findings argue against diagnostic bias as an explanation for the increased incidence rates of psychosis in immigrant groups (Selten & Hoek 2008; Zandi *et al.* 2010).

**Table 5.4** Assessment of homogeneity of regression slopes in DP vs. IP1 and PD vs. IP2 comparisons

	Dutch vs. 1st generation			Dutch vs. 2nd generation		
	F value	p value	Partial $\eta^2$	F value	p value	Partial $\eta^2$
Immediate recall	21.86	.000	.186	17.16	.000	.164
Ethnicity	3.88	.050	.013	6.19	.013	.023
RAVLT immediate recall	26.96	.000	.086	41.12	.000	.136
Ethnicity x RAVLT IR	0.65	.422	.002	4.598	.033	.017
Delayed recall	17.84	.000	.158	11.45	.000	.116
Ethnicity	10.15	.002	.034	9.51	.002	.035
RAVLT delayed recall	14.39	.000	.048	22.35	.000	.079
Ethnicity x RAVLT DR	1.92	.167	.007	5.76	.017	.022
Sustained attention	13.75	.000	.126	6.98	.000	.075
Ethnicity	0.34	.561	.001	1.16	.283	.004
CPT hitrate	8.81	.003	.030	13.77	.000	.050
Ethnicity x CPT	0.04	.841	.000	0.62	.431	.002

RAVLT IR = Rey Auditory Verbal Learning Task, immediate recall; RAVLT DR = Rey Auditory Verbal Learning Task, delayed recall; CPT = Continuous Performance Task.

### *Explanations for the associations*

The association between psychotic illness, cognitive functioning, measures, culture and language are complex and difficult to disentangle. While we do not have a definitive

explanation for the results, several factors are likely to have contributed to the observed differences.

### *Illness severity*

The observed cognitive differences between groups might be due to more severe illness in immigrant patients compared to the Dutch patients. However, subsequent subgroups analysis revealed no differences in global functioning. Also, we previously performed an analysis of a subset (N= 361, with and without cognitive assessment) of this sample described elsewhere (Veling *et al.* 2007a) that revealed no significant differences between the subgroups on positive symptoms and a significantly raised score on negative symptoms only for the Moroccan subgroup ( $p \leq .05$ ). In addition, none of the groups in this subset showed increased rates of comorbid current manic episodes and only the Moroccan ( $p \leq .01$ ) and the Turkish ( $p \leq .05$ ) subgroups showed increased prevalence of comorbid current depressive symptoms. These findings suggest that differences in psychotic symptoms, comorbidity or global functioning between immigrant patients and Dutch patients are unlikely to explain the lower scores of immigrants performed on the cognitive measures. Although cognitive dysfunctioning in itself can obviously be considered an indicator of illness severity, it appears the only severity indicator clearly differing between immigrants and non-immigrants with psychosis, warranting further investigation.

### *Language*

An evident factor that most likely has significantly influenced our findings is familiarity with the Dutch language. Immigrants from Surinam and the Netherlands Antilles (both former Dutch colonies) as well as second generation immigrants from all backgrounds are generally fluent in the Dutch language. Also, second generation immigrant patients most often have lived in The Netherlands all their lives. In most cases, neither is true for first generation immigrant patients. This obviously might account for some of the observed differences in verbal memory performance, even though research on this matter has classified the impact of assessment-language on test scores as small (Ji & Nisbett 2004). Aside from this, the difference in language and cultural familiarity still do not provide means to interpret the large difference between first and second generation immigrant patients on the non-verbal sustained attention task ( $\Delta z$ -score= 1.64).

### *Cannabis use*

Differences in cannabis use may account for some of the observed cognitive differences between immigrant patients and Dutch patients. The findings indicate that cannabis use is not a likely candidate to explain worse cognitive performance for ethnic subgroups. On the opposite, the first generation immigrants, with the poorest cognitive performance, used little cannabis. This is in accordance with a recent meta-analysis where first-episode psychosis patients with a history of cannabis use show smaller cognitive deficits compared with non-using patients (Yücel *et al.* 2010). The authors concluded that this effect may be driven by a subgroup of “neurocognitively less impaired” patients, who developed psychosis only after cannabis use, which would subsequently be more frequent in groups with more cannabis use.

### *Cultural background*

A body of literature has shown that cognitive styles differ substantially across cultures (Markus *et al.* 1991; Knight & Nisbett 2007; Kitayama & Park 2010; Park & Huang 2010; Varnum *et al.* 2010). A well-known example of such a difference is analytic vs. holistic. Western(ized) cultures tend to be more analytic, focusing more on elements and details, whereas non-Western cultures tend to be more holistic, focusing more on context and inter-element relationships (Nisbett *et al.* 2001; Nisbett 2003). An analytic or “western” cognitive style might be better suited for our sustained attention task (Masuda & Nisbett 2001; Kitayama *et al.* 2003; Chua *et al.* 2005), since this task focuses exclusively on the target rather than on context. A similar advantage might be present in our verbal learning task (Ji & Nisbett 2004). However, this remains speculative. Research examining this issue is sparse and has thus far focused on “Western” versus “East Asian” samples and not “Arabic” or “African” samples.

In a more general sense, it is also possible that an underlying stress-factor associated with minority status could result in both the lower cognitive scores and the higher incidence rates in immigrants. Factors like stereotype threat (i.e. being at risk of confirming a negative stereotype about one’s group) have been found to predict worse cognitive performance in immigrants (Steele & Aronson 1995), whereas other social stress factors such as discrimination (Veling *et al.* 2007b, 2008a; Chakraborty *et al.* 2011) and urban ethnic density (Veling *et al.* 2008c) appear to be related to the increased incidence of psychotic disorders in immigrants. Further research is warranted to expand and integrate existing cognitive (Schmader *et al.* 2008) and ecological (Halpern 1993;

Boydell *et al.* 2001; Rutter & Tienda 2005) models linking large cognitive deficits and increased incidence of psychosis in immigrant groups.

### *Strengths and limitations*

A strength of this study is that it, to our knowledge, presents the largest representative first episode schizophrenia spectrum patients sample examining cognitive deficits and migration to date. Another strength is that this study is the first to compare cognitive measures between seven different ethnic subgroups and multiple generations from one urban area. A final strength of this study is that all data were collected from first episode psychosis (FEP) patients within the first three months after they had made contact with psychiatric services, limiting the impact of confounding variables associated with chronic psychoses and long-term treatment.

The study also has a number of limitations. First, although the normative data that was used to standardize and compare cognitive performance scores between groups was corrected for the demographic variables age and gender, the use of either ethnic subgroup specific normative data or descriptive data obtained from healthy control subjects for all various subgroups in this study would have been preferable. Unfortunately, no such data sets were available, so investigations were limited to normative-, between- and within-subgroup comparisons. Second, we have not obtained the completed years of education from those who did not complete cognitive assessment. Therefore, we are unable to investigate the extent of which this selection effect has influenced our results. Third, since psychotic symptoms and comorbid depressive symptoms were only available for a subset of the sample, the exact differences in psychotic symptoms and comorbid depressive episodes between groups cannot be defined. Fourth, information on current antipsychotic medication use was not available. We expect the effect of this confounding variable on our findings to be small, however, since all data were collected within three months after first-contact with mental health services. In addition, meta-analyses indicate that there is only a marginal effect of antipsychotic medication use on cognitive performance (Mishara & Goldberg 2004; Woodward *et al.* 2007). Fifth, duration of untreated psychosis (DUP) was not assessed, and therefore possible effects of (variations in) illness duration prior to first contact cannot be assessed. However we do expect these effects to be very small or absent, since a previous publication on a subset of our sample using identical methodology and performed in the same urban area did not show any differences in DUP between groups (Veling *et al.* 2007a). Sixth, our neuropsychological battery had a

limited span with only three cognitive measures, albeit that these measures assess core domains of neurocognition in psychotic disorders. And finally, cannabis use was assessed in a practical but limited way in our study. Although our findings based on these measures are supported by meta-analytic data (Yücel *et al.* 2010), these counterintuitive findings warrant further studies, preferably with standardized questionnaires and laboratory drug testing.

### *Conclusions and Implications*

In summary, our findings demonstrated (1) substantial cognitive deficits for all subgroups compared to demographics-corrected normative data, (2) markedly poorer cognitive performance on immediate recall for the Moroccan, Turkish and other non-Western subgroups and for all but the Western subgroup on sustained attention compared to Dutch patients, and (3) larger deficits for first generation compared to second generation immigrants. Furthermore, none of these differences were explained by variations education, cannabis use, or cross-cultural measurement bias. The analyses of the subsample (Veling *et al.* 2007a) indicates that these differences are likely to be unrelated to psychotic symptoms and comorbid disorders. Our findings render diagnostic bias implausible as an explanation for increased incidence of psychosis in immigrants.

The results have a number of implications. First, this study clearly shows large differences in cognitive deficits both between and within ethnic subgroups, indicating the necessity and wisdom of integrating a form of cultural assessment in both diagnostic measures and treatment programs for first-episode psychosis patients to expand our knowledge on cross-cultural differences in psychotic disorders and to optimize accuracy and effectiveness of clinical diagnoses and treatment. Second, from a research perspective, these findings further strengthen the need for the development of either truly cultural neutral psychometric tools, or the development of standardized versions for every subgroup, or at least subgroup-specific normative data for every instrument. The obvious drawbacks and complications of these various pursuits will not be discussed here; we just argue the need to find a practical and psychometric sound approach to this issue that will allow future researchers to investigate these cross-cultural between- and within-subgroup effects. And finally, the fact that some part of the observed cognitive deficits appears to be culture- and/or language-related, does not change the fact that these patients live in the Dutch society, an environment where they experience these culture- and or language-related difficulties every day. From a clinical perspective the

observed deficits therefore are likely to accurately reflect cognitive difficulties these patients experience in daily life.



## Chapter 6

# **Psychopathology, cognition and functional recovery in Dutch and immigrant first-episode psychosis patients**

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In press



## Abstract

**Aim** To examine differences in symptom expression and psychosocial functioning between Dutch, second-generation immigrants and first-generation immigrants with first-episode psychosis, and to identify baseline predictors of functional recovery at 12-months follow-up across these groups.

**Methods** 46 Dutch, 56 second-generation- and 60 first-generation immigrant patients completed baseline measures for six symptom dimensions (positive symptoms, negative symptoms, neurocognitive functioning, social cognitive functioning, excitement and emotional distress) and five domains of psychosocial functioning at baseline and 12 months (general functioning, work and study, relationships, self-care and disturbing behavior). Logistic regression with backward elimination was used to identify predictors of functional recovery.

**Results** Groups differed only on neurocognitive and social cognitive functioning. Psychosocial functioning was similar in groups, although immigrant patients showed slightly more functional improvement than Dutch patients. Negative symptoms, social cognitive functioning and excitement predicted functional improvement in Dutch, where social cognition was the only symptom dimension that predicted functional improvement in second-generation immigrants. Positive symptoms, negative symptoms, neurocognitive functioning, and excitement all predicted functional improvement in first-generation immigrants.

**Conclusions** Psychosocial functioning and symptom profiles are comparable between ethnic groups with first-episode psychosis, excluding neurocognitive and social cognitive deficits. Functional recovery at 12-months is predicted by different symptom domains across ethnic groups.

## Keywords

first-episode psychosis; migration; cognitive deficits; psychopathology; functional recovery

## Introduction

The incidence of psychotic disorders in immigrants is about double the rate found in non-immigrant populations (Veling *et al.* 2006; Bourque *et al.* 2011). Patterns of symptom expression and comorbidity may also differ between ethnic groups (Bhugra 2004), as affective dimensions tend to be more salient in some immigrant groups (Veling *et al.* 2007a). Ethnic differences on other core symptom domains, such as neurocognitive and social cognitive functioning, have hardly been studied (Stouten *et al.* 2013). These differences in risk and phenotype of psychosis are most likely determined by psychosocial and environmental mechanisms, such as ethnic density, perceived discrimination and other experiences of social adversity and exclusion (Morgan *et al.* 2010; Veling & Susser 2011).

Less is known about ethnic differences in functional outcome of psychotic disorders, and how these relate to differences in symptom profiles. Early studies suggested better prognosis among ethnic minorities in the UK, perhaps related to a relatively more affective and acute profile of psychosis in these groups (McKenzie *et al.* 1995, 2001), but a recent review of UK studies concluded that there is insufficient evidence of high quality (Chorlton *et al.* 2012). A Dutch study found a comparable functional outcome after two years in Dutch and ethnic minority patients (Selten *et al.* 2007b).

To our knowledge, there are no studies that have investigated ethnic differences across the full range of symptom expression (Van Der Ven *et al.* 2012) and subsequently linked them to functional outcome domains like vocational/academic performance, personal relationships; self-care; and disturbing behavior (Mausbach *et al.* 2009; Lin *et al.* 2013a). To investigate variability in symptom expression in psychosis and the impact of psychopathology on social functioning, a multi-dimensional approach of psychotic disorders as well as social functioning is required (Van Os & Kapur 2009). Five primary symptom dimensions have been proposed within the psychosis spectrum: *psychosis*; *negative symptoms*; *cognitive symptoms* (neurocognition and social cognition); *emotional distress*; and *excitement/mania* (Dominguez *et al.* 2009; Van Os & Kapur 2009). Of these dimensions, severe negative symptoms and impaired cognitive functioning are generally associated to poorer outcome (Toulopoulou *et al.* 2007; Galderisi *et al.* 2013), whereas predominant affective symptoms and excitement are associated to better outcome (Tohen *et al.* 2000; Jarbin *et al.* 2003).

## Method

### *Classification of ethnicity*

Ethnicity was classified according to the criteria of Dutch Bureau of Statistics (*Central Bureau of Statistics*, see also Stouten *et al.* 2013). Patients who were born in The Netherlands with two Dutch-born parents, were classified as *Dutch*. Those who were born in The Netherlands and had at least one parent born abroad, were categorized as *second-generation immigrant*, and those who were born abroad, were categorized as *first-generation immigrant*.

### *Subjects*

The study was conducted in the period December 1, 2009 to December 31, 2012. All patients who were referred to the department for non-affective early psychosis in The Hague, completed the diagnostic protocol, were diagnosed with a psychotic disorder and completed the 12-months follow-up, were included in the study. The diagnostic protocol is described in full details elsewhere (Stouten *et al.* 2014, 2017). The study sample consisted of 162 patients diagnosed with a first episode of a psychotic disorder (81 schizophrenia spectrum disorder, 9 schizoaffective disorder, 9 brief psychotic disorder, 5 delusional disorder, 2 shared psychotic disorder, and 56 psychotic disorder NOS). Forty-six patients had Dutch ethnicity, 56 were second-generation immigrant and 60 first-generation immigrant. The study was approved by the local Medical Ethics Committee (reference number NL31561.098.10). Informed written consent was obtained from all participants.

### *Demographic variables*

Years of education were calculated by adding the completed years of education in primary, secondary and tertiary or higher education.

### *Cognitive performance*

A comprehensive psychological test-battery was construed to assess the symptom dimensions neurocognitive- and social cognitive functioning.

Neurocognitive assessment included assessment of the subdomains *attention* (Continuous Performance Task, CPT 3-7 version) (Nuechterlein & Dawson 1984), *problem solving* (Wechsler Adult Intelligence Scale, WAIS III, Block design; Tower of London) (Shallice 1982; Wechsler 1997) *speed of processing* (WAIS III, Digit-symbol coding; Trail

making task, part A) (Reitan 1958; Wechsler 1997), *verbal fluency* (Category fluency, animal naming) (Lezak *et al.* 2004), *verbal learning* (Rey Auditory Verbal learning Task, RAVLT) (Rey 1964; Kalverboer & Deelman 1986), *visual learning* (Brief Visuospatial Memory Task Revised, BVM-T-R) (Benedict 2007), *working memory* (WAIS III, Letter-number sequencing) (Wechsler 1997) and *general cognition* (WAIS III, Information and Calculations) (Wechsler 1997).

Social cognition measures included assessment of the subdomains *emotion perception* (Amsterdam Neuropsychological Tasks, ANT) (Sonneville 2005), *theory of mind* (Hinting Task) (Corcoran *et al.* 1995), *social knowledge* (WAIS III, picture arrangement) (Wechsler 1997) and *social cognitive biases* (Davos Assessment of Cognitive Biases Scale) (Bastiaens *et al.* 2013; van der Gaag *et al.* 2013).

### *Symptoms dimensions*

We used the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987) to assess positive and negative symptoms as well as general psychopathology. The Beck Depression Inventory (BDI-II) (Beck *et al.* 1996a, 1996b) and the Beck Anxiety Inventory (BAI) (Beck *et al.* 1988) were used to assess depression and anxiety respectively. Six symptom dimensions were computed: positive symptoms; negative symptoms; neurocognitive functioning; social cognitive functioning; excitement; and emotional distress. (see also 'Data analysis' and appendix I).

### *Psychosocial functioning*

The Personal and Social Performance scale (PSP) (Morosini *et al.* 2000) was used to assess dimensions of psychosocial functioning (range 0-100, where higher scores reflect better functioning). The PSP uses four subscales to assess problems in specific social functioning domains: (a) Social useful activities including study and work (SUA), (b) Personal and social relationships (PSR), (c) Self-care and care for personal environment (S-C), and (d) Disturbing and/or aggressive behavior (DAB). Higher subscale scores reflect more problems.

### *Data analysis*

The analyses were performed in SPSS version 20. Psychopathology subscale scores were computed by adding the items from the related measures. Scores per cognitive task were standardized using normative data and then averaged per cognitive subdomain. Independent sample T-tests and non-parametric tests were used to assess differences

between ethnic groups on demographic-, psychopathological-, cognitive- and psychosocial functioning scores. To examine possible language-related assessment bias in our sample, scores on verbal learning and visual learning (which were assessed using identical methodology) were compared within each of the ethnic groups with general linear models.

The symptom dimensions neurocognition and social cognition were computed using two single-solution confirmatory factor analyses including all neurocognitive and social cognitive subscale scores, respectively. To assess the other four symptom dimensions, we followed the five-factor model to restructure the related items from the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987), as described by Van der Gaag and colleagues (van der Gaag *et al.* 2006). Their cross-validation of the PANSS items yielded 25 items that loaded on the same factor in all ten examined datasets. We used these items to present the following symptom dimension through four single-solution confirmatory factor analyses: *positive symptoms* (items P1, P3, G9, P6 and P5), *negative symptoms* (items N6, N1, N2, N4, G7, N3, G16 and G8), *excitement* (G14, P4, P7, and G8) and *emotional distress* (items G2, G6, G3, and G4). Independent sample T-tests were used to assess differences on the loadings for the six factors between ethnic groups.

Change in social functioning within the 12-months follow-up period was calculated by subtracting the scores at baseline from the scores at 12-months follow-up for all five psychosocial functioning variables. Change scores were subsequently recoded into one binary variable per outcome domain, with value '1' for improved functioning (change score > 0) and value '-1' for stable or declined functioning (change score ≤ 0).

And finally, we constructed stepwise logistic regression models predicting functional improvement for general psychosocial functioning and the four subdomains, including demographic variables (age, level of education) and all symptom dimensions as predictors in all models. Predictors were entered in an identical pre-set order in all models, i.e. age, years of education, positive symptoms, negative symptoms, neurocognitive functioning, social cognitive functioning, excitement and lastly emotional distress, controlling significant predictors for baseline functioning. We predicted functional improvement within the 12-months follow-up period for the ethnic groups separately.

**Table 6.1** Demographic variables, psychopathology and standardized cognitive subscale scores for Dutch, second-generation immigrants and first-generation immigrants with a first episode psychosis

	Dutch		GEN2		GEN1		Between-group comparison		
	M	SD	M	SD	M	SD	F	p (F)	Post-hoc
<i>Demographics</i>									
N (% male)	46	(78%)	56	(70%)	60	(65%)			
Age	29.25	7.31	24.76	5.10	29.53	5.78	5.09	.002	G2<ND=G1
Years of education	12.82	2.13	12.19	2.21	11.21	2.46	3.59	.015	ND=G2>G1
<i>Psychopathology</i>									
Positive symptoms (PANSS)	13.63	4.52	14.23	5.38	13.98	5.71	0.04	.991	-
Negative symptoms (PANSS)	11.90	4.64	13.52	6.24	13.67	5.69	1.15	.330	-
General symptoms (PANSS)	27.05	5.01	30.88	8.28	29.52	7.81	1.06	.167	-
Anxiety (BAI)	12.68	11.85	18.89	17.38	19.51	15.05	1.49	.220	-
Depression (BDI)	15.74	9.85	20.00	15.01	19.30	13.37	0.59	.555	-
<i>Cognition</i>									
<i>Neurocognition (average)</i>									
Attention	-1.18	3.10	-2.15	3.09	-2.58	3.24	2.63	.049	ND>G2=G1
Problem solving	-0.43	1.10	-1.20	1.05	-1.51	1.18	9.16	< .001	ND>G2=G1
Processing speed	-0.71	2.37	-1.92	3.14	-2.72	2.97	5.30	.002	ND>G2=G1
Working memory	-0.16	1.15	-0.51	0.92	-1.08	1.03	4.64	.004	G2=ND>G1
Verbal fluency	-0.25	0.95	-0.71	1.20	-1.26	0.98	13.37	< .001	ND>G2>G1
Verbal learning	-0.36	1.44	-0.75	1.54	-1.32	1.97	3.36	.020	G2=ND>G1
Visual learning	-0.42	1.30	-0.74	1.35	-1.30	1.41	6.30	< .001	G2=ND>G1
General neurocognition	-0.13	1.15	-0.55	1.04	-1.10	1.03	11.94	< .001	ND>G2>G1
<i>Social cognition (average)</i>									
Social knowledge	-0.70	1.01	-1.03	1.13	-1.54	1.16	6.47	< .001	G2=ND>G1
Theory of mind	-0.37	0.25	-0.46	0.35	-0.64	0.33	9.00	< .001	G2=ND>G1
Social cognitive biases	-1.56	1.92	-1.19	2.09	-1.17	1.81	0.24	.872	-
Facial affect perception	-1.01	0.87	-1.30	2.05	-1.77	1.73	1.25	.294	-

PANSS = Positive and Negative Syndrome Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory, second edition.

## Results

### *Diagnoses and demographic data*

Distribution of the schizophrenia and psychotic disorder NOS diagnoses were equally distributed across the ethnic groups (Kruskal-Wallis test;  $p = .202$ ). Demographic variables, and mean scores of Dutch, second- and first-generation immigrants on the psychopathological-, neurocognitive- and social cognitive domains and psychosocial functioning are presented in Table 6.1.

### *Cross-ethnic comparisons of symptom dimensions*

Even though individual variables showed slight differences between groups (see Table 6.1), factor loadings on the symptom dimensions positive symptoms, negative symptoms, excitement and emotional distress did not show any significant differences across ethnic groups.

In contrast to the other symptoms dimensions, factor loadings on the dimensions neurocognitive and social cognitive performance significantly differed between the three groups. Dutch had higher loadings on both factors (indicating better overall neurocognitive and social cognitive performance) than second-generation immigrants (NC:  $t = 5.26$ ,  $p < .001$ ; SC:  $t = 4.52$ ,  $p < .001$ ), where the latter had higher loadings than first-generation immigrants (NC:  $t = 2.61$ ,  $p = .010$ ; SC:  $t = 2.76$ ,  $p = .007$ ). These differences all remained significant after adjusting for age and level of education.

### *Cross-ethnic comparisons of psychosocial functioning*

General psychosocial functioning and all subdomains did not differ significantly between the three subgroups at baseline or at 12-months follow-up, with two exceptions: second-generation immigrants showed more disturbing behavior ( $t = 2.16$ ,  $p = .033$ ) and poorer general psychosocial functioning ( $t = 2.41$ ,  $p = .018$ ) at baseline than Dutch patients (see Table 6.2).

Furthermore, overall change in psychosocial functioning was not significant in Dutch patients. In contrast, first-generation immigrants improved in relationships and self-care, where second-generation immigrants improved in general psychosocial functioning, work and study, relationships, disturbing behavior, but not self-care (see Table 6.2).

**Table 6.2** Psychosocial functioning scores at baseline and 12-months follow-up for Dutch, second-generation immigrants and first-generation immigrants with first episode psychosis

	Baseline		12 months		Change		Trajectories		
	M	SD	M	SD	F	p (F)	-	/	+
Dutch									
General psychosocial functioning	56.06	13.19	58.09	14.46	1.02	.316	58%		42%
<i>Problems per subdomain:</i>									
Work and study	2.39	1.19	2.11	1.16	2.60	.113	64%		36%
Relationships	2.15	0.92	2.02	1.02	0.96	.332	67%		33%
Self-care	0.63	0.88	0.54	0.82	0.64	.428	78%		22%
Disturbing behavior	0.39	0.63	0.37	0.73	0.04	.837	84%		16%
Second-generation immigrants									
General psychosocial functioning <sup>(a)</sup>	50.36	15.96	55.66	16.04	10.76	.002	41%		59%
<i>Problems per subdomain:</i>									
Work and study	2.60	1.13	2.34	1.25	4.89	.030	70%		30%
Relationships	2.27	1.06	1.91	1.14	10.69	.002	68%		32%
Self-care	0.56	0.85	0.56	0.86	0.00	1.000	82%		18%
Disturbing behavior <sup>(a)</sup>	0.81	1.21	0.41	0.89	6.29	.014	73%		27%
First-generation immigrants									
General psychosocial functioning	51.67	14.78	54.01	16.50	2.56	.114	53%		47%
<i>Problems per subdomain:</i>									
Work and study	2.63	0.92	2.41	1.03	3.84	.054	67%		33%
Relationships	2.21	1.02	1.93	1.17	7.54	.008	58%		42%
Self-care	0.51	0.88	0.81	1.08	6.52	.013	93%		7%
Disturbing behavior	0.59	1.14	0.50	1.09	0.45	.506	85%		15%

- / 0 = declined or stable psychosocial functioning; + = improved psychosocial functioning

(a) = second-generation immigrants showed poorer baseline performance on general psychosocial functioning and disturbing behavior compared to Dutch ( $p < .05$ )



### *Language-related assessment bias*

To investigate possible language-related assessment bias in our sample, standardized scores on the verbal learning and visual learning tasks (which used uniform methodology) were compared within the ethnic groups (see Table 6.1). These analyses showed that verbal- and visual memory functioning deficits were identical within Dutch ( $F = 0.214$ ;  $p = .645$ ; *ns*), second-generation immigrants ( $F = 0.010$ ;  $p = .920$ ; *ns*) and first-generation immigrants ( $F = 0.003$ ;  $p = .953$ ; *ns*).

### *Predicting functional improvement across ethnic groups*

In Dutch, lower levels of negative symptoms at baseline were associated with improvement after 12 months of general psychosocial functioning, vocational/academic functioning, social functioning and self-care. Improvement in social functioning was also associated with better social cognitive performance. Lastly, lower levels of excitement were associated with decreased disturbing behavior (see Table 6.3).

In second-generation immigrants, better social cognitive performance at baseline was associated with improved general psychosocial functioning, vocational/academic functioning, and self-care after 12 months. Improvement in social functioning was associated with completed years of education. In this subgroup, none of the assessed predictors had a significant impact on disturbing behavior.

In first-generation immigrants, findings were more heterogeneous. Lower levels of positive symptoms and better neurocognitive performance at baseline were associated with improved general psychosocial functioning after 12 months. Better neurocognitive performance was further associated with vocational/academic improvement. Also, lower levels of negative symptoms were associated with improved self-care and social functioning, where the latter was further associated with lower levels of positive symptoms. Lower levels of excitement were associated with decreased disturbing behavior.

All described models in the three ethnic groups predicting functional change remained significant after controlling for baseline functioning.

## **Discussion**

In this sample of patients with first-episode psychosis, levels of positive symptoms, negative symptoms, excitement and emotional distress did not differ significantly between Dutch, first-generation immigrants and second-generation immigrants. On

**Table 6.3** Predictors of functional improvement (versus stable/declined functioning) per ethnic subgroup

Functional outcome domain	Predictors	Wald	OR	95% CI	p
<i>Dutch</i>					
General psychosocial functioning Work and study Relationships	Negative symptoms	4.49	0.18	(0.04-0.88)	.034
	Negative symptoms	5.00	0.22	(0.06-0.83)	.025
	Negative symptoms	4.05	0.33	(0.11-0.97)	.032
	Social cognition	3.21	3.13	(1.31-12.50)	.018
	Negative symptoms	6.50	0.33	(0.04-0.77)	.022
Self-care Disturbing behavior	Excitement	3.84	0.22	(0.04-1.15)	.031
<i>Second-generation immigrants</i>					
General psychosocial functioning Work and study Relationships Self-care Disturbing behavior	Social cognition	3.90	3.70	(1.01-14.29)	.029
	Social cognition	4.05	3.03	(1.03-8.33)	.044
	Years of education	3.25	1.79	(1.13-3.09)	.045
	Social cognition	3.81	5.26	(1.22-25.00)	.011
	ns	-	-	-	-
<i>First-generation immigrants</i>					
General psychosocial functioning Work and study Relationships Self-care Disturbing behavior	Positive symptoms	3.34	0.38	(0.14-0.99)	.014
	Neurocognition	2.86	2.78	(1.01-9.09)	.042
	Neurocognition	3.40	4.76	(1.17-6.67)	.036
	Negative symptoms	3.08	0.38	(0.13-0.91)	.017
	Positive symptoms	2.90	0.46	(0.19-0.98)	.039
Self-care Disturbing behavior	Negative symptoms	7.16	0.24	(0.09-0.68)	.007
	Excitement	7.29	0.34	(0.15-0.74)	.009

OR = Odds ratio; CI = Confidence interval

neurocognition and social cognition, Dutch performed better than second-generation immigrants, who in turn performed better than first-generation immigrants.

The three ethnic groups further showed similar levels of general psychosocial functioning and comparable problems with work/study, relationships, self-care and disturbing/aggressive behavior, both at baseline and at 12-months follow-up. Average psychosocial social functioning in Dutch patients did not improve over the follow-up period. In contrast, relationships and self-care improved in first-generation immigrants, and all functional domains except self-care improved in second-generation immigrants.

Baseline levels of negative symptoms, social cognition and excitement predicted functional improvement in Dutch patients, whereas social cognition was the only symptom dimension that was associated with functional improvement in second-generation immigrants. In contrast, four of six symptoms dimensions (i.e. positive symptoms, negative symptoms, neurocognition, and excitement) predicted functional improvement in first-generation immigrants. These effects all remained significant after controlling for baseline functioning.

Compared to other first-episode studies, overall psychotic symptoms were moderate to low in this sample (e.g. Lucas *et al.* 2008; Chang *et al.* 2011; Barder *et al.* 2013; Lin *et al.* 2013b; Torgalsbøen *et al.* 2014) and levels of depression and anxiety were rather high (Jackson *et al.* 2005; Mueser *et al.* 2010). But even though immigrants might have slightly more affective symptoms (e.g. anxiety; see Table 6.1) than non-immigrants (McKenzie *et al.* 1995, 2001; Veling *et al.* 2007a; Shaw *et al.* 2012), there do not appear to be any clear indicators within the present sample that the core psychopathology of psychosis manifest differently in patients with different ethnic background (Veling *et al.* 2007a).

Second, neurocognitive- and social cognitive functioning differentiate between the Dutch and immigrants, but also between first- and second-generation immigrants. A general pattern was observed of Dutch performing better than second-generation immigrants, who performed better than first-generation immigrants. However, interpretation of these differences is not straightforward. Primarily because cross-cultural assessment of cognitive functioning is a thoroughly complex issue in itself (Pedraza & Mungas 2008), but also because there are no previous multi-ethnic first-episode studies on cognition (Stouten *et al.* 2013). Considering possible assessment bias, the direction of the observed general cognitive differences between groups suggests a prominent role for language bias, i.e. the observed effect follows the same pattern as might be expected based on the (presumed; not assessed) level of mastery of the Dutch language across

groups (high>moderate>low). To investigate this issue, our key verbal learning and visual learning task were compared within each of the ethnic groups. This comparison showed that verbal- and visual memory problems were of identical size in all three groups. These findings suggest that the impact of assessment-language on cognitive scores in the present study is likely to be small (Ji & Nisbett 2004; Stouten *et al.* 2013), although measurement bias (Te Nijenhuis & Van Der Flier 2001; Pedraza & Mungas 2008; Stouten *et al.* 2013) cannot be ruled out with the used study design. A final post-hoc analyses showed that cognitive differences between groups were also not explained by differences in age or level of education or (see Table 6.1).

Third, the ethnic groups had similar levels of psychosocial functioning in the first year after baseline. Since migration is considered a prominent risk factor for psychosis (Selten *et al.* 2007a; van Os *et al.* 2010; Veling & Susser 2011), it is surprising that ethnic differences in functional outcome of psychotic disorders have not been studied more extensively. Early UK studies on general functional outcome in multi-ethnic samples showed marginally better functional outcome in immigrants compared to non-immigrants (McKenzie *et al.* 1995, 2001). More recent Dutch data showed no significant differences in psychosocial functioning between ethnic groups (Veling *et al.* 2007a). The present results illustrate two points: first, short-term functional outcome is not better or worse for immigrant patient compared to non-immigrants, neither in general levels of functioning, but also not in key subdomains like vocational and academic performance, relationships or self-care (Veling *et al.* 2007a). Second, immigrants (especially of the second generation) do appear to show more functional change (i.e. improvement) than Dutch in the first year after baseline (McKenzie *et al.* 1995, 2001), a finding not negated by the limited overall functional improvement across groups (Stouten *et al.* 2014) (see Table 6.2).

In our exploratory analyses of psychopathological and cognitive predictors of psychosocial functioning, several differences between the ethnic groups were found.

First, functional improvement in Dutch and first-generation immigrants was associated with most symptom dimensions (all dimensions except emotional distress). In contrast, functional improvement in second-generation immigrants was associated with just one out of six dimensions, i.e. social cognition (Fett *et al.* 2011).

Second, although previous research indicates a central role for negative symptoms in functional change in FEP patients (Milev *et al.* 2005; Brill *et al.* 2009; Albert *et al.* 2011; Álvarez-Jiménez *et al.* 2012; Galderisi *et al.* 2013; González-Ortega *et al.* 2013), the present data only replicated this association in Dutch, and to a lesser degree in first-generation immigrants. Also, in line with our previous findings (Stouten *et al.* 2014),

positive symptoms were indicative of future functional problems in the early stages of psychosis, but only in first-generation immigrants (Kuipers *et al.* 2006). Even when considering possible underestimation of positive- and negative symptoms as predictors of future functioning due to low levels of psychotic symptoms (positive and negative) in the present sample, the question why these symptoms do not appear to impact functional outcome in second-generation immigrants remains unanswered.

Third, disturbing behaviour of patients with a psychotic disorder (although rare) is a major public health concern, affecting patients and their environment (Serper 2011). Previous research indicated several environmental (e.g. drug use; Foley *et al.* 2005, and clinical dimensions (e.g. neurocognitive performance; Serper *et al.* 2008, and excitement; Huber *et al.* 2012) that contributed to the manifestation of aggressive behaviour. Although our findings did not confirm the predictive value of neurocognitive performance, our data support higher levels of baseline excitement as predictor of more disturbing behaviour in FEP patients, but only in Dutch and first-generation immigrants and not in second-generation immigrants. Higher levels of social cognitive performance were not associated with decreased disturbing behaviour. Impact of neurocognitive (and social cognitive) performance on this outcome domain may become (more) evident in the later stages of psychosis, when psychotic and/or affective symptoms have been reduced or stabilized.

The major strength of this study is that, to our knowledge, it is the first study to assess ethnic differences in psychopathology, neurocognition, social cognition and psychosocial outcome in one large FEP sample. Furthermore, our study is the first to explore the prospective impact of six key symptom dimensions across three ethnic groups. The high representativeness of this early psychosis sample, i.e. including all consecutive patients with a first-episode psychosis from one large urban area who completed baseline measures within three months after first contact, further adds to this strength.

The absence of data on medication- and cannabis use at the time of the study should be considered as limitations when interpreting the findings. However, impact of both short-term anti-psychotic medication (Mishara & Goldberg 2004; Woodward *et al.* 2007; Nielsen *et al.* 2015) and/or cannabis use (Yücel *et al.* 2010; Schubart *et al.* 2011) on the observed associations is likely to be small as well as heterogeneous.

Overall, the present study shows that psychosis appears to manifest similarly across Dutch, first- and second-generation immigrants (Van Der Ven *et al.* 2012), where only neurocognitive and social cognitive performance appear to differentiate between

these groups. Functional limitations over the first year after baseline also appear to be comparable. Nevertheless, the observed differences in functional change over the 12-months follow-up, and the observation that this change appears to have different predictors across ethnic groups, might indicate subtle but important etiological differences underlying functional problems in first-episode psychosis patients from various ethnic backgrounds (van Os *et al.* 2010).



## **Chapter 7    General discussion**



## Summary of key findings

In the first part of this thesis, symptom profiles, cognitive performance and psychosocial functioning in early psychosis patients were examined.

In **chapter 2**, several questions were addressed concerning cognitive deficits in FEP patients, i.e. which neurocognitive and social cognitive factors can be identified that comprehensively reflect cognitive performance in FEP patients? How are these cognitive factors related to (other) psychopathology dimensions in FEP? Do these cognitive factors contribute to understanding current psychosocial problems, in addition to current psychotic- and affective problems? The FEP patients in our sample demonstrated moderate neurocognitive and social cognitive deficits, which were largely independent of (other) domains of psychopathology. Cross-sectional examination showed that negative symptoms, neurocognition and social cognition were moderately associated with psychosocial problems, whereas affective and positive symptoms were not indicative of psychosocial functioning at baseline.

In **chapter 3**, the impact of baseline predictors, i.e. psychotic symptoms, affective problems and deficits in specific neurocognitive- and social cognitive subdomains, on both current and future psychosocial functioning was examined. Psychotic symptoms, cognitive deficits and affective problems all contributed to psychosocial difficulties in the early course of psychosis. The findings also showed that the magnitude of this influence not only varies substantially between different areas of psychosocial functioning, but also changes considerably between baseline and 12-months follow-up. These changes were most notable for psychotic symptoms and cognitive deficits, as impact of baseline psychotic symptoms on psychosocial functioning was initially strong but decreased over time, where the opposite was true for the impact of baseline cognitive deficits. These findings suggest that predictors of general levels of psychosocial functioning are not necessarily predictors of functional changes in that domain (and vice versa), emphasizing the need to differentiate between these interrelated paradigms in the exploration of mechanisms underlying psychosocial problems in the early stages of psychotic disorders.

**Chapter 4** addresses the issue of whether or not is possible to predict which FEP individuals will attain either functional or symptomatic recovery, or both within 12 months based on their baseline characteristics. What symptomatic and cognitive variables distinguish between individuals who showed full recovery from those who did not show any in the first 12 months after baseline? And what factors discriminate between those who keep experiencing symptoms but function well, from those who are largely free of

symptoms but function poorly? Our findings showed that overall one third of FEP patients fully recovered within one year, whereas one third did not recover, and one third recovered partially. Overall, patients experienced significant reductions in positive, negative and general symptoms. Also, they improved in vocational-academic performance, social and general functioning, and had decreased disturbing behaviour. Fully recovered patients exhibit better functioning, lower levels of positive symptoms, negative symptoms and mania symptoms, and better social cognitive functioning at baseline than patients who were not recovered in the first 12 months after baseline. Within the group of patients that showed partial recovery, those who showed improved symptomatic outcome had shorter DUP and more years of education than those who showed improved functional outcome at 12-months follow-up.

In the second part of this thesis, ethnic differences in cognitive performance, illness expressions, and recovery in early psychosis patients were examined.

In **chapter 5** levels of neurocognitive performance were compared between Dutch patients, first-generation immigrant patients and second-generation immigrant patients. All groups showed moderate cognitive impairment on immediate recall, delayed recall and sustained attention. Overall, immigrant patients had larger cognitive deficits compared to Dutch patients, and first-generation immigrant patients had larger cognitive deficits than second-generation immigrant patients (all adjusted for differences in cannabis use and level of education). Overall, the Moroccan, Turkish and other Non-Western subgroups demonstrated the largest cognitive deficits. Post-hoc examination indicates that these differences cannot be accounted for by language effects, i.e. possible differences in test outcome that might have resulted from differences in the level of mastery of the assessment language (i.e. Dutch) between patient groups.

In **Chapter 6** differences in symptom expression, neurocognitive and social cognitive performance were examined between first-episode psychosis patients who are Dutch, first-generation immigrants and second-generation immigrants, and to what extent these factors impacted various domains of psychosocial functioning across these groups in the first 12 months after baseline. Results showed that levels of positive symptoms, negative symptoms, excitement and emotional distress did not differ significantly between Dutch, first-generation immigrants and second-generation immigrants. On neurocognition and social cognition, the Dutch performed better than the second-generation immigrants, who in turn performed better than the first-generation immigrants. The three ethnic groups further overall showed similar levels of functional

problems with work-study, building and maintaining relationships, personal care and care for their personal environment, and engaging in aggressive or otherwise disturbing behaviour. However, they did not show similar functional change within this period. Average psychosocial functioning in Dutch patients did not significantly improve over the follow-up period. In contrast, relationships and self-care improved in first-generation immigrants. Moreover, all functional domains (except self-care) improved in second-generation immigrants.

**Table 7.1** Predictors of functional improvement per outcome domain per ethnic subgroup

Group	Discriminators regarding functional change per outcome domain				
	General	Work/study	Relationships	Self-care	Disturbing behaviour
Dutch	NEG	NEG	NEG + SC	NEG	EXC
Second-generation immigrants	SC	SC	YoE	SC	-
First-generation immigrants	POS + NC	NC	NEG + POS	NEG	EXC

POS = positive symptoms; NEG = negative symptoms; SC = social cognition; NC = neurocognition; EXC = excitement; YoE = years of education

Differential predictors of functional change between ethnic groups were examined. These examinations, as presented in Table 7.1, showed that baseline levels of negative symptoms, social cognition and excitement predicted functional improvement in Dutch patients. In second-generation immigrants, social cognition was the only symptom dimension that predicted functional improvement. In contrast, four of six symptoms dimensions (i.e. positive symptoms, negative symptoms, neurocognition, and excitement) predicted functional improvement in first-generation immigrants. These effects all remained significant after adjusting for baseline functioning.

## Interpretation of findings

### *Functional outcome heterogeneity in first-episode psychosis*

In line with previous work, the results of this thesis showed that functional outcome after a first-episode psychosis is heterogeneous, as we demonstrated that about one third of patients recover fully within 12-months after first contact with mental health care, whereas one third improves partially and the last third did not show any marked improvement or even deterioration within the same period. Although these findings of early recovery in a substantial number of FEP patients are encouraging, in what way

genetic and environmental mechanisms interact to account for this variability is still poorly understood.

Research on this issue tends to conceptualize psychosocial problems (see Figure 7.1) in two manners (that are not mutually exclusive) (Lin *et al.* 2013a):

(1) Functional problems as *an early indicator* of a chronic neurodevelopmental illness. From this perspective, functional problems are considered an early indicator that has already manifested itself before illness onset. Functional problems, psychotic symptoms and cognitive deficits are all epiphenomena of this underlying illness (Lin *et al.* 2013a). If this hypothesis is true, psychosocial problems should be (a) evident before the onset of positive psychotic symptoms, (b) largely independent of positive symptoms during the course of the illness, and (c) relatively stable over time.

There is a substantial body of evidence that supports this hypothesis, underlining a clear association between the amount of general neurological soft signs (NSS) and illness manifestation within patients and their relatives (i.e. familial association) (Dazzan & Murray 2002; Chan *et al.* 2010). Moreover, large national cohorts show a clear link between the delayed development of specific motor-milestones in early childhood (i.e. functional problem) and the development of psychosis in later life (Jones *et al.* 1994; Isohanni *et al.* 2001, 2004; Niemi *et al.* 2003; Sørensen *et al.* 2010). Although it is unclear whether or not the study of NSS (Hui *et al.* 2009) or developmental milestones (Jääskeläinen *et al.* 2008) will yield a specific endophenotype target for psychotic disorders, it seems evident that the neurodevelopmental component underlying psychosis impacts functioning in at-risk individuals from a very early age onward.

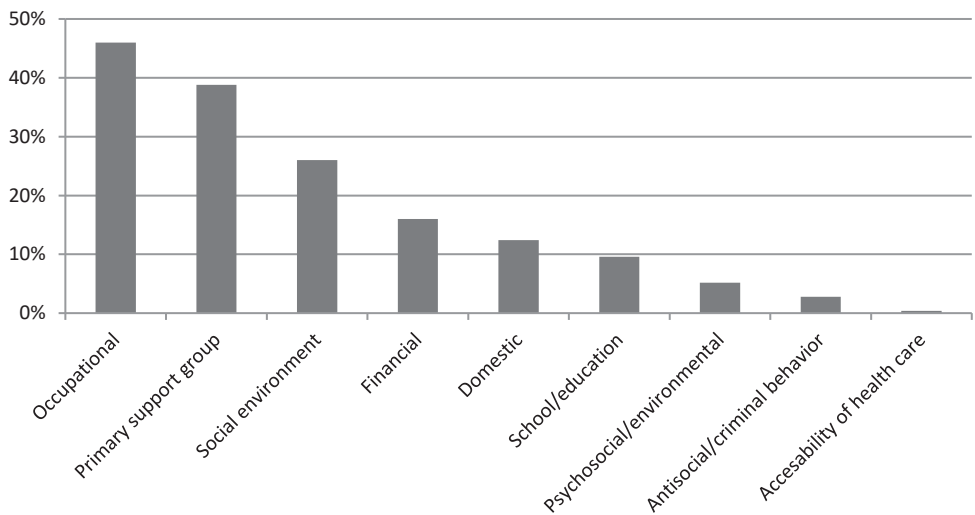
(2) Functional problems as *a result* of illness-related factors. From this perspective, illness-related factors like positive symptoms, depression, demoralization, stigma and self-stigma, discrimination, and substance abuse bring about functional problems. If this hypothesis is true, psychosocial problems should (d) develop around the same time as positive psychotic symptoms, and (e) be related to the factors mentioned above.

Although this field of study is inherently spread across a wide range of topics, there are clear indications that illness-related factors like depression (Coentre *et al.* 2017), demoralization (Tecuta *et al.* 2015), stigma (Corcoran 2016), self-stigma (Belvederi Murri *et al.* 2015), discrimination (Veling 2013) and substance use (Khokhar *et al.* 2017) have a negative impact on the way FEP patients are able to live their daily lives.

Overall, it is considered likely that the heterogeneity in psychosocial functioning across the early stages of psychosis is the result of both neurodevelopmental as well as socio-environmental mechanisms; for some individuals psychosocial problems are primarily the result of longstanding neurological changes, whereas for others it is mainly related to the secondary consequences of depressed mood, demoralization, stigmatization, substance use and increased social withdrawal as a result of the onset of psychosis.

Nevertheless, research showed that psychosocial problems are a characteristic feature in the course of illness of most individuals with psychosis (Tsang *et al.* 2010). For example, as much as two out of three people who make first contact with mental health care for a suspected psychosis are unemployed at that time (Ramsay *et al.* 2012; Tandberg *et al.* 2012). Additionally, in the presented sample, 46% of patients had significant occupational problems (see Figure 7.1).

**Figure 7.1** Percentages of patients with specified DSM-IV axis IV problems per domain, as were diagnosed in the main sample presented in this thesis (chapters 2, 3, 4 and 6)



What does this thesis contribute to our general understanding of this issue? Considering the onset of psychosocial problems, this thesis confirms that (a) psychosocial problems are already evident in multiple areas at first contact in the vast majority of patients, specifically in areas like vocational/academic functioning and personal and social

relationships, and to a lesser degree, and in a smaller number of patients self-care and care for one's personal environment, and disturbing or aggressive behaviour (n.b. multiple functional problems presented in Figure 7.1 tend to coincide in individual patients). Data from Ultra-High Risk (UHR) studies show that social functional is already compromised in UHR patients (general introduction; Table 1.2, 'stage 1b'), but seems to further deteriorate in patients who transition to psychosis ('stage 2') (e.g. Van Der Gaag *et al.* 2012). This thesis confirms that (b) functional problems overall tend to remain evident during the early stages of psychosis, but also that (c) after this initial deterioration, in most patients that receive specialised early-psychosis outpatient treatment functional outcome tends to improve in the first year after transition to psychosis (chapters 2,3,4 and 6).

#### *Symptoms as predictors of psychosocial functioning?*

Although generally studied as a one-way paradigm (i.e. symptoms predict functional outcome; as was done here), in retrospect it seems much more plausible that a two-way or cyclic paradigm (i.e. symptoms predict functional outcome, and, functional outcome predicts symptoms) more accurately reflects the interrelation between symptom expression and everyday functioning. In line with the latter paradigm, previous work indicates that baseline symptoms predict short-term psychosocial recovery, but also that short-term functional recovery predicts long-term functional recovery, as well as symptomatic remission (Álvarez-Jiménez *et al.* 2012). Although testing of this two-way paradigm was beyond the scope of this thesis, it does reflect the current shift in focus towards functional recovery in mental health care in The Netherlands (Haan 2013). Nevertheless, data presented in this thesis underlines the first hypothesis, as both positive symptoms and negative symptoms featured prominently as predictors of various psychosocial outcome domains across the first year after baseline (chapters 2,3,4 and 6).

#### *Neurocognition in the early stages of psychosis*

A wide range of neurocognitive measures was used in the studies presented in this thesis (see 'general introduction', Table 1.3), assessing the following neurocognitive domains: attention, problem solving, speed of processing, verbal fluency, verbal learning, visual learning, working memory, and general neurocognition. In line with the available literature, we found neurocognitive deficits of moderate size in our FEP sample: on average, about 1 SD below the norm (Townsend & Norman 2004; Bozikas & Andreou 2011). Neurocognitive deficits were largely unrelated to psychopathological symptoms. The single exception was the neurocognitive factor 'verbal processing speed', which was

related to negative symptoms, anxiety and depression (chapter 2). Overall, the large majority of null associations between neurocognition and psychopathology concurs with recent meta-analytic data from prodromal and FEP (Bora & Murray 2014) and chronic psychosis samples (Dominguez *et al.* 2009).

Data from this thesis underline the general consensus that neurocognitive deficits are related to functional outcome (chapters 2-6) (Green *et al.* 2000a, 2004; Allott *et al.* 2011). However, we still know very little about *how* these factors relate, although presented findings illustrate that both ‘data driven’ approaches (data reduction; chapter 2) as well as ‘concept driven’ cognitive subdomains (chapters 3-6) yield significant leads on the cognition-functional outcome relationship. Future studies will need to explore the mechanisms and mediators underlying relationships between neurocognition and functional outcome. Recent studies further suggest that social cognition should be taken into account here, since it might mediate the relationship between neuro-cognition and functional outcome (Martínez-Domínguez *et al.* 2015). And yet, the findings of this thesis also illustrate that cognitive deficits account for only a small portion of the variation in short-term illness outcomes in FEP patients. It is also likely that a better understanding of these mechanisms will overall not greatly increase the amount of functional and symptomatic changes that these deficits can explain. Therefore, we should also conclude that it might be more profitable to look for other personal and environmental domains that account for changes in outcome, especially in the early stages of these disorders.

Nevertheless, looking beyond the cognitive scope and the short-term follow-up period of this thesis, the association between neurodevelopmental problems and psychosis becomes more evident: large longitudinal cohort studies indicate that neurodevelopmental deficits are evident before onset of psychopathology, where the magnitude of the deficits appears to be indicative of the psychopathological risk (Sørensen *et al.* 2010; Kim *et al.* 2011). For example, Sørensen and colleagues conducted a 45-year follow-up of the Copenhagen Perinatal Cohort to investigate this issue, where they found that individuals who later developed schizophrenia reached all developmental motor-milestones at a significantly later age than control subjects, where individuals who later developed a non-psychotic psychiatric disorders overall were significantly slower than control subjects but faster than those who later developed schizophrenia.

From the neurodevelopmental paradigm, it appears evident that cognitive deficits can best be viewed as a general early indicator of risk for psychopathology in later life, not just psychosis. As such, studies looking into the aetiology of psychosis should include more general factors that have been found to negatively impact general

neurodevelopment (specifically in the frontal cortical regions and the hippocampus), like childhood adversity (Morgan & Fisher 2007; Varese *et al.* 2012; Teicher & Samson 2013; Kraan *et al.* 2015b). The traumatic experiences in childhood, adolescence and early adulthood can impact neurodevelopment (e.g. smaller frontal- and hippocampal volume; Teicher & Samson 2013) and increase the chances of developing a psychotic disorder (Varese *et al.* 2012). But besides increasing the chances of psychosis, these experiences also tend to have an impact on the illness manifestation and course of these disorders (Mulholland *et al.* 2008). For example, within the group of people that have developed schizophrenia, childhood trauma is associated with higher levels of symptoms (Roy 2005; Kraan *et al.* 2015a), cognitive deficits (Shannon *et al.* 2011; Aas *et al.* 2014) and functional problems (Davidson *et al.* 2009).

### *Social cognition in the early stages of psychosis*

Although no clear consensus exists on what domains should be included in a comprehensive social cognitive assessment (Green *et al.* 2008), work done in recent years has brought us much close to a unified approach to these constructs in clinical practice (Green *et al.* 2015; Henry *et al.* 2016). This thesis presents data on four social cognitive subdomains in a FEP sample, i.e. 'theory of mind', 'emotion perception', 'social knowledge' and 'attribution bias'. In line with previous work, this thesis underlines that deficits across these domains are comparable to those found in neurocognitive functioning (Bora *et al.* 2009; Bora & Pantelis 2013; Ventura *et al.* 2013), about one standard deviation below the norm.

The data presented in this study support the theory that social cognitive deficits are more closely related to positive symptoms, than neurocognitive deficits are to positive symptoms (see chapter 2, Table 2.4) (Frith 1992; Sarfati *et al.* 1997; Fett & Maat 2013). For example, it has been hypothesized that an inability to adequately represent the mental state of another person (Theory of Mind), or the ability to integrate contextual information into this representation (social knowledge), are associated with positive symptoms of disorganization (Hardy-Baylé *et al.* 2003; Sprong *et al.* 2007). Also, it has been suggested that deficits in emotion perception might result in the misattribution of ambiguous negative emotions (e.g. interpreting sadness as anger) or the misreading of another's intentions (Couture *et al.* 2006), stimulating the development of paranoid or delusional thought patterns and related psychosocial difficulties. The research presented in this thesis underlines the association between social cognitive deficits and positive symptoms and therefore these hypotheses, confirming both moderate links between social



cognition and positive symptoms (chapter 2) as well as identifying social cognition as predictor of specific psychosocial problems (e.g. difficulties in relationships and poorer self-care) (chapter 3). These findings are not in line with recent data from a different Dutch FEP cohort (GROUP; Korver *et al.* 2012), which concluded that (a) (social) cognitive functioning does not appear to add much explained variance of functional outcome above negative symptoms, and (b) social cognitive performance does not appear to predict future social functioning (Simons *et al.* 2016). These findings notwithstanding, there are a number of key methodological differences between these studies that make it difficult to integrate these findings. First, *self-report vs. clinician rated*: We used a clinician-rated measure for functional outcome (five functional outcome variables used in the analyses), rather than a self-report measure (one functional outcome variable used in the analyses), that generally are more biased towards the mean (i.e. central tendency or end aversion; Choi & Pak 2005). Second, number of social cognitive tasks: two vs. four. The two tasks used in the GROUP study design assessed the social cognitive subdomains ‘Theory of Mind’ (Hinting task; Corcoran *et al.* 1995) and ‘Emotion perception’ (Degraded Facial Affect Recognition task, DFAR; Van’t Wout *et al.* 2004). In addition to these domains, the present study further assessed social cognitive biases (DACOBS; Bastiaens *et al.* 2013; van der Gaag *et al.* 2013) and social knowledge (WAIS-III picture arrangement; Wechsler 1997). In line with the GROUP findings, the present study also found no predictive effect of the two mutual social cognitive domains (i.e. Theory of Mind and Emotion perception) on *general* functional outcome. However, these two cognitive domains showed to be related to a number of *specific* functional outcome domains, namely work and study (see chapters 2 and 6) and developing and maintaining personal and social relationships (see chapters 3 and 6). Furthermore, presented findings illustrate that social cognition might play a crucial role in understanding functional outcome in FEP patients from different ethnic background (e.g. second-generation immigrants; chapter 6). Taken together, we argue that social cognition is an important predictor of outcome when predicting outcome in specific functional domains or for specific subgroups within the FEP populations.

## *Ethnicity*

### *Symptom expression and differential predictors of recovery*

Previous work on differences in symptom expression has yielded mixed results, overall indicating slightly more positive symptoms (hallucinations, paranoid or religious delusions) and mania symptoms in ethnic minority groups (Barrio *et al.* 2003; Arnold *et al.* 2004;

Veling *et al.* 2007a; Shaw *et al.* 2012). In contrast however, research in this thesis showed that first- and second generation immigrants have similar symptom expression and functional performance compared to Dutch patients, with no significant differences across key symptom domains (chapter 6).

The presented data also showed marked differences between these groups on neurocognitive and social cognitive performance, suggesting that further study of these differences in core neurocognitive and social cognitive information processing might yield new insights into illness trajectories across these groups (chapters 5 and 6). Moreover, this thesis presents preliminary data indicating that understanding the role of cognitive deficits in FEP patients might be especially relevant concerning the study of cross-ethnic differences, since the impact of cognitive deficits (especially social cognitive deficits) on functional outcome appeared to be more prominent in immigrant patients compared to Dutch patients. For example, we consider rather surprising the finding that social cognition was the only significant predictor of functional improvement in general functioning, vocational and academic functioning and self care in second-generation immigrants (Chapter 6). Apparently, whether or not information in social context can be processed effectively is of special significance in this subgroup of patients. This subject clearly warrants further study.

### *Measurement bias*

A diagnostic instrument or assessment tool is considered to demonstrate bias “if it results in different meanings for scores earned by members of different identifiable groups” (AERA *et al.* 1999; Pedraza & Mungas 2008). Considering the comparisons we have made between general ethnic subgroups in this thesis, and the design and cognitive measurements we have used, we consider it inevitable that the linguistic and cultural variability both within and between these groups, will have resulted in some degree of measurement biases (Pedraza & Mungas 2008). We do however consider it unlikely that such biases account for all differences observed between these groups (further argued in the next paragraph). We also argue that exploratory examination and comparison, as we have done here, is essential to improve our understanding of the clear differences that *do* exist between these groups concerning psychosis risk and incidence. Such work will enable us to generate hypothesis and explore plausible theories and mechanisms that might account for these differences. Although further elaboration on this issue is beyond the scope of this thesis, we do offer a number of factors that we argue should be taken into account when examining these issues concerning the presented work.

Considering the observed differences between the groups examined in this thesis, assessment-language bias should be considered; the general tendency of cognitive performance across groups presented in this thesis (Dutch > second-generation immigrants > first-generation immigrants) suggests a prominent role for language bias, i.e. the observed effect follows the same pattern as might be expected based on the (presumed) level of mastery of the Dutch language across groups (high > moderate > low). Our investigation of this issue showed that the key verbal learning task and visual learning task were compared within each of the ethnic groups, demonstrating that verbal- and visual memory problems were of identical size within all three groups (chapter 6). These findings suggest that assessment-language does not explain ethnic differences on cognitive scores in the present study (Ji & Nisbett 2004), although measurement bias (Te Nijenhuis & Van Der Flier 2001; Pedraza & Mungas 2008) can obviously not be ruled out with the used study design, measurements and normative data.

A final post-hoc analysis further showed that cognitive differences between groups were also not explained by differences in age or level of education. Although this thesis does not provide clear explanations that might account for the observed neurocognitive and social differences, our preliminary study of this issue showed that they are not easily accounted for by effects of language, age or level of education, and might therefore be indicative of some differential feature that characterizes illness onset and trajectories across these groups.

A further consideration is that general cognitive styles tend to differ between people from different cultures (Kitayama & Park 2010; Park & Huang 2010; Varnum *et al.* 2010). For example, people from 'Western(ised) cultures' tend to be more focused on elements and details (i.e. 'analytic'), where people from 'Eastern(ised) cultures' tend to be more focussed on context and inter-element relationships (i.e. 'holistic') (Masuda & Nisbett 2001; Nisbett 2003). As our cultural background 'wires' our brain, such differences are likely to have a complex and diffused impact on which specific stimuli elicits which specific response in an individual, and on the speed by which this process is completed. And although this distinction is very rudimentary, even such a crude distinction as 'analytic' vs 'holistic' suggests some possible advantageous effects for specific cognitive tasks. For example, the Brief Visuospatial Memory Task (BVMt) and Continuous Performance Task (CPT) require focus on elements (e.g. the six geometric figures) and on details (e.g. the single digit displayed in the center of the screen). In contrast, the Picture Arrangement task (WAIS-III) and the Digit-Symbol coding task (WAIS-III) require focus on context (e.g. the storyline displayed across the set of presented pictures) and on inter-

element relationships (e.g. the specific digit-symbol pairs). However, these hypotheses, based on these rarely studied differences, all remains highly speculative.

And lastly, a point not previously discussed, but a point that is frequently forwarded by our patients, is that cognitive assessment is generally perceived as stressful. Although it is likely that all patients experienced our cognitive assessment procedure as somewhat stressful, we consider it plausible that this perceived stress level might not have been similar across ethnic groups. Assumed variability in the amount of (received and perceived) discrimination and trauma for these patients might have made the stress response to the stressor 'being assessed by a caucasian male or female' larger in some individuals than in others. Although we did not assess this feature of test experience and can therefore not make such comparison, we argue that the study of factors like discrimination (Berg *et al.* 2011) and minority status (Steele & Aronson 1995) might provide some valuable perspective on the rarely studied cognitive differences between these groups.

#### *Functional outcome*

Since migration is considered a prominent risk factor for psychosis (Selten *et al.* 2007a; van Os *et al.* 2010; Veling & Susser 2011), it is surprising that ethnic differences in functional outcome of psychotic disorders have not been studied more extensively. The data presented in this thesis illustrates that short-term functional outcome is not better or worse for immigrant patients compared to non-immigrants, neither in general levels of functioning, but also not in key subdomains like vocational and academic performance, relationships or self-care (chapter 6). This is consistent with previous work done in The Netherlands (Selten *et al.* 2007b). In line with previous work done in the UK, the presented data also shows that immigrant patients (especially of the second generation) demonstrate more functional change (i.e. improvement) than Dutch patients in the first year after baseline (see chapter 6, Table 6.2) (McKenzie *et al.* 1995, 2001). On top of this, the data presented in this thesis is the first to indicate that different ethnic subgroups of FEP patients might have different predictors of outcome (chapter 6). We argue that extended study of these differences is likely to promote a better understanding of functional deficits in psychosis for at least two reasons: (1) *Differences in outcome variability*. Outcome variability is high in FEP samples, but the mechanisms accounting for this variability are still poorly understood. The body of research on the role of minority position and the increased risk for psychosis has yielded a number of factors that clearly impact illness onset, but most likely will also impact illness trajectories and outcome.

Routinely assessing these factors across the early stages of psychosis will improve our understanding of the role that these mechanisms play beyond the development and onset of psychosis. (2) *Differences in predictors of outcome*. The present data underlines that psychotic symptoms overall manifest similarly across subgroups from various ethnic backgrounds. Small differences are generally found on affective symptoms and DUP, where immigrants tend to have slightly more affective symptoms (Veling *et al.* 2007a) and first-generation immigrants tend to have a longer DUP (Sterk *et al.* 2010; Apeldoorn *et al.* 2014). So, symptom expression is largely similar across these groups. But does this mean that the same illness dimensions will predict outcome across these groups? Our data suggests it does not. To make sure we do not end up with a one-size-fits-nobody 'specialised' FEP treatment methodology, routine assessment and study of the mechanisms that account for such differential predictors of outcome will help us to identify specific risk factors and treatment opportunities.

### *Illness trajectories*

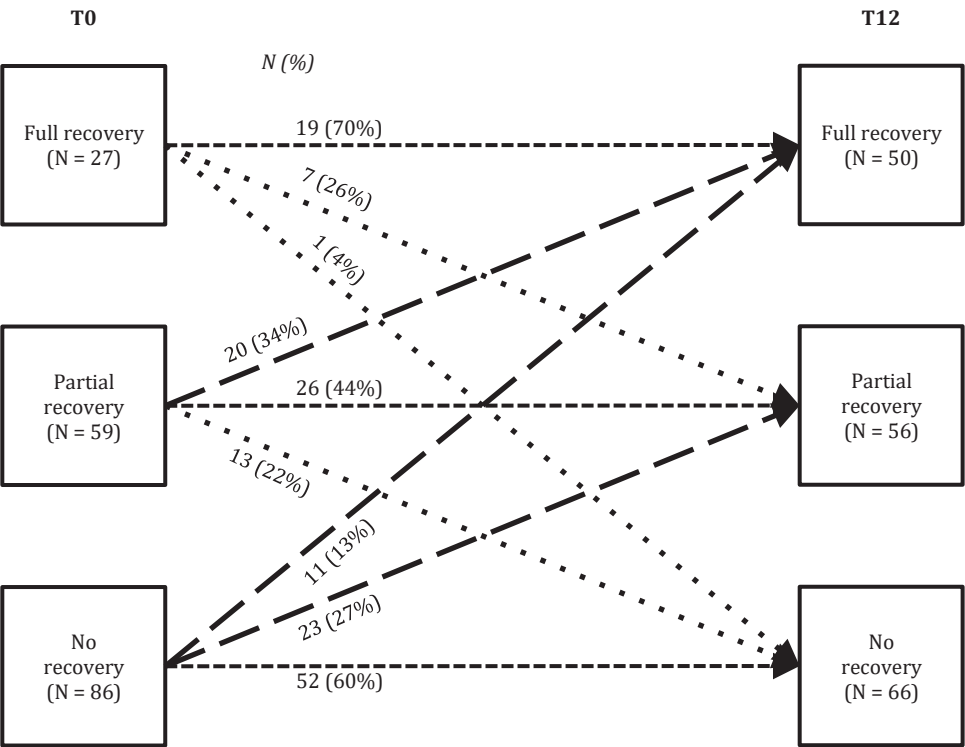
Our predictive models of recovery after a FEP with clinical, social and socioeconomic characteristics at first presentation yielded some significant predictors in our sample as a whole, but overall remained limited (chapters 2,3,4 and 6). Although a wide range of previously identified predictors was used, only a relatively small part of the variation in symptomatic and functional outcome was explained. To explore this finding further, we examined the different outcome trajectories in the main sample of this thesis. As illustrated by Figure 7.2, recovery in the first twelve months of outpatient treatment is heterogeneous. When classified into 'full recovery', 'partial recovery' and 'no recovery', 56% of patients did not change outcome category within 12-months, where 32% of patients transitioned to a better outcome category (e.g. from partial to full recovery), and 12% transitioned to a poorer outcome category (e.g. from partial to no recovery).

Examining our data from this perspective, the number of patients that apparently already qualified for the full recovery category at baseline (N=27) also raises some questions. Exploring possible confounders that resulted in this surprising number of 'fully recovered at baseline' patients, we did not find any significant differences on the assessed demographic variables between these patients, and those in the other two groups.

Looking further into possible differences between these groups, we did observe a trend in the route by which these patients had reached our department. As is shown in Figure 7.3 (first column), these patients were referred to our department slightly more often (trend level) after clinical hospitalisation or after a crisis intervention than those

from the no recovery group (Figure 7.3; second column). A plausible explanation here could be that the treatment as provided by the mental health hospital or crisis response unit was effective at reducing psychotic symptoms.

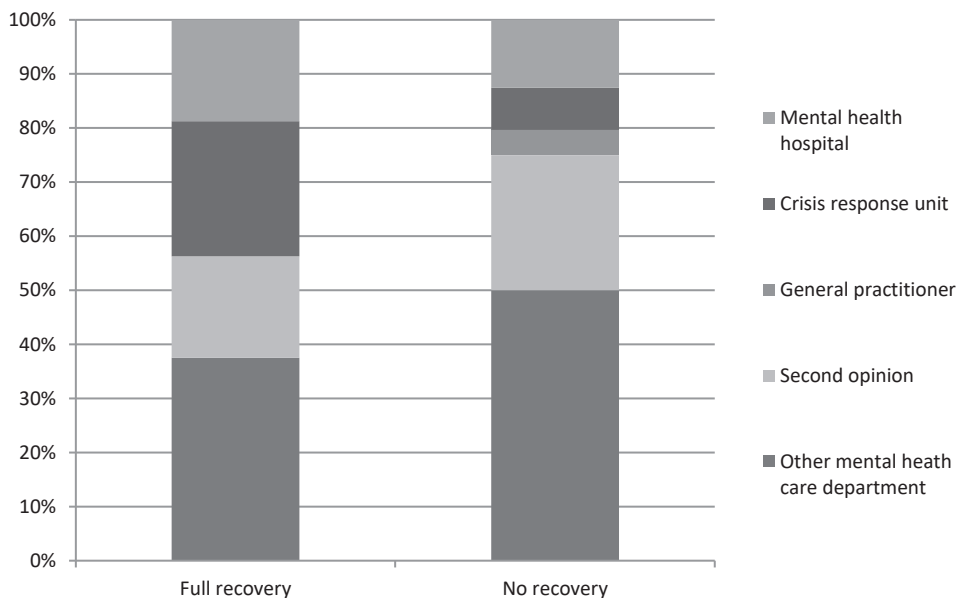
**Figure 7.2** Illness trajectories ('full recovery'; 'partial recovery', i.e. either symptomatic recovery or functional recovery; 'no recovery') within the 12-months follow-up period in the main sample presented in this thesis (chapters 2, 3, 4 and 6)



We further observed that a relatively large portion of individuals that experienced both symptomatic- and functional problems at baseline (i.e. 'no recovery') were referred to us by another mental health care department (Figure 7.3; second column), either as a direct referral, or for a psycho-diagnostic second opinion. In other words, they were included into a different secondary mental health program (e.g. depressive or anxiety disorders) before being referred to a specialised early psychosis program. When comparing the full

recovery and no recovery groups, this ‘secondary route’ was much more evident in the no recovery group (75%) compared to the full recovery group (57%). These findings are in line with previous meta-analytic work that showed that a majority of patients are treated in secondary mental health services *prior* to the onset of psychosis, namely for mood and anxiety disorders (Rietdijk *et al.* 2011), and also that this ‘within-care’ delay before enrolling in specialised treatment for their psychosis is clearly not beneficial to them (O’Callaghan *et al.* 2010; Rietdijk *et al.* 2011).

**Figure 7.3** Method of referral for patients with full recovery and no recovery at baseline, and method of referral for ‘improved’ and ‘declined’ patients (main sample; chapters 2, 3, 4 and 6)



Another plausible explanation for this observation could be that this difference does not represent a delay in treatment, but simply reflects a process by which a more severely ill group of patients reaches specialised FEP care. For these patients, the care they received from their initial mental health care program has had limited effect in most cases. As a result, they tend to have had their symptoms for a longer period of time, *a priori* reducing their chances of recovery.

### *Unexplained variance and clinical significance*

Although our comprehensive assessment of plausible predictors of outcome yielded some statistically significant predictors, the large heterogeneity of outcome trajectories between these patients makes the *clinical* significance of these findings rather limited; e.g. we are still not able to accurately predict outcome on the individual level for the majority of our patients.

These findings suggest that other contextual, (epi-)genetic, biological and psychosocial factors should be included in prediction models, in order to explain enough variance to reach clinical significance for the individual. Subsequently, it seems clear that multifactorial approaches should be applied not only to predictor variables, but also to outcome domains in patients with FEP (Menezes *et al.* 2006; Lin *et al.* 2013a), incorporating clinical factors (e.g. diagnoses, relapse, remission, symptom reduction, hospitalization, treatment compliance, suicidal behaviour and mortality) as well as dimensions of recovery (e.g. employment status, academic performance, social functioning, role functioning, self-care, self-esteem, independent living, cultural and identity development, sexual functioning and overall quality of life).

Our investigations of differences between patient groups from different ethnic backgrounds clearly showed that psychosis appears to manifest similarly across Dutch, first- and second-generation immigrants (Van Der Ven *et al.* 2012), despite differences between these groups concerning higher incidence rates (Veling *et al.* 2006; Bourque *et al.* 2011) and higher male-female ratios in immigrants (van der Ven *et al.* 2016)

Neurocognitive and social cognitive performance appear to be the only factors that differentiated clearly between ethnic groups. Functional limitations over the first year after baseline also appear to be comparable between ethnic groups. Nevertheless, the observed differences in functional change over the 12-months follow-up, and the observation that this change may have different predictors across ethnic groups, might indicate different mechanisms underlying functional problems in first-episode psychosis patients from various ethnic backgrounds (van Os *et al.* 2010).

The large differences in cognitive deficits both between and within ethnic subgroups, indicate the necessity of integrating a form of cultural assessment in both diagnostic measures and treatment programs for first-episode psychosis patients to expand our knowledge on cross-cultural differences in psychotic disorders and to optimize accuracy and effectiveness of clinical diagnoses and treatment. From a research perspective, these findings further strengthen the need for the development of either truly cultural neutral psychometric tools, or the development of standardized versions for



every subgroup, or at least subgroup-specific normative data for every instrument. The drawbacks and complications of these various pursuits are complex and outside of the scope of this discussion. We just argue the need to find a practical and psychometric sound approach to this issue that will allow future researchers to investigate these cross-cultural between- and within-subgroup effects.

Notwithstanding the fact that culture- and language-related effects on our cognitive-, symptomatic- and functional measures cannot be ruled out, this does not change the fact that these patients live in the Dutch society, an environment where they experience these culture- and or language-related difficulties every day. From a clinical perspective, the observed deficits therefore are likely to accurately reflect cognitive difficulties these patients experience in daily life.

## Limitations

The following limitations should be taken into account. First, no medication records were available at the time of this study, so possible effects of medication use on cognitive performance, symptoms and outcome could not be taken into account. However, besides the short period of time that patients could have used antipsychotic medication before cognitive assessments, meta-analytic data suggest that the negative impact of antipsychotic medication specifically on cognition is likely to be small (Mishara & Goldberg 2004; Woodward *et al.* 2007). Furthermore, there are also studies indicating that the (prolonged) use of anti-psychotic medication in the early stages of the disorder might not be beneficial for patients altogether, since AP use does not appear to be strongly related to better functional outcome (Menezes *et al.* 2006), and may even be associated with poorer long-term functional recovery in FEP patients (McGorry *et al.* 2013; Wunderink *et al.* 2013). An issue that clearly warrants further study.

Second, no data on cannabis (or other substance) use were available at the time of the study. Based upon previous work from our department, the lifetime prevalence of cannabis use in FEP patients can be as high as 60% (Veling *et al.* 2008b). Various studies have indicated that cannabis use can precipitate psychotic experiences and generally has a negative impact on illness trajectories (Meier *et al.* 2012; D'Souza *et al.* 2016). Not negating the limitations of not structurally assessing cannabis use, we still argue that any effect of cannabis use in our data is likely to be ambiguous, as cannabis appears to have negative effects but also some modest positive effects on cognitive performance in FEP (Yücel *et al.* 2010) and on the level of psychotic symptoms (Schubart *et al.* 2011). Although

the latter positive effect on cognition is likely to be driven by a subgroup of “neurocognitively less impaired” patients, who only developed psychosis after cannabis use. These patients as a group will have had superior cognitive functioning before illness onset compared to non-using patients, accounting for the ‘positive association’ between cannabis use and cognitive performance (Yücel *et al.* 2010).

Third, the quality of available normative data varied between the cognitive instruments. However, we note that this is an intrinsic and inevitable limitation of using such a wide scope of cognitive measures. In addition, the standardized cognitive scores were not used in any of the regression analyses and were only provided to enable comparison of the scores between the cognitive measures.

An related issue that should be considered here, is that one of the key strengths of this study (i.e. all baseline measures completed within three months after first contact) might also have affected some of our cognitive measurements. As we showed in chapter 2 (Table 2.4), some cognitive domains showed to be related to both positive symptoms (e.g. Attribution and inference bias and General social cognition) and negative symptoms (e.g. verbal processing speed). In other words, if you assess someone who is experiencing psychotic symptoms (or has just recovered), test scores will be impacted by the magnitude of these symptoms. The procedure we used provided some insight into this process. For example, assessment and diagnostic procedures used in this study were undertaken over a number of separate appointments, which enabled clinicians to assess whether or not a patient was able to undergo cognitive testing prior to the cognitive assessment appointments (as these were generally scheduled last). If clinicians deemed an individual patient was unable to undergo cognitive testing procedures at that time, this part of the assessment was postponed to a later time within the 3-month window. Although we do argue that all assessed patients were able to understand the test instructions and perform the test procedures correctly, we also think it is plausible that their current or recent psychotic experiences will have had some impact on cognitive test outcomes.

Furthermore, we note two limitations that apply specifically to the investigations presented in chapters 5 and 6. First, although the normative data that was used to standardize and compare cognitive performance scores between groups was corrected for the demographic variables age and gender, the use of either ethnic subgroup specific normative data or descriptive data obtained from healthy control subjects for all various subgroups in this study would have been preferable. Unfortunately, no such data sets were available, so investigations were limited to normative-, between- and within-

subgroup comparisons. Second, we have not obtained the completed years of education from those who did not complete cognitive assessment. Therefore, we are unable to investigate the extent of which this selection effect has influenced our results.

## **Strengths**

The presented samples are highly representative for early psychosis as it includes all consecutive patients with a first-episode psychosis who made first contact with specialized mental health services in an urban area during the study period.

Also, as all data were collected within the first 3 months after referral, possible impact of confounding variables associated with chronic psychosis and long-term treatment (particularly, long-term use of antipsychotic medication) is considered negligible in the presented samples.

Another strength is that we used a wide clinical scope. We included positive and negative symptoms, anxiety and depression, and used 15 separate psychometric tools to assess neurocognition and social cognition, and finally, assessed one general and four specific domains of psychosocial functioning.

A prospective design (excluding chapters 2 and 5) was used for our investigations. This design enabled assessment of both baseline and short-term follow-up (12 months) psychosocial functioning, but also the amount of functional change between these points. It further enabled identification of a cluster of interrelated factors at baseline that characterize those who are likely to recover in the early stages of psychosis (chapter 6).

There are a number of additional strengths that specifically apply to the investigations presented in chapters 5 and 6. The main strength of the study presented in chapter 5, is that it, to our knowledge, presents the largest sample of representative first episode schizophrenia spectrum patients to date that examines cognitive deficits and migration. Also, it is the first to compare cognitive measures between seven different ethnic subgroups and multiple generations from one urban area. The major strength of the investigation presented in chapter 6 is that, to our knowledge, it is the first study to assess ethnic differences in psychopathology, neurocognition, social cognition and psychosocial outcome in one large FEP sample. Furthermore, it is the first study to explore the prospective impact of six key symptom dimensions across these three ethnic groups in the first 12 months after diagnoses.

## Clinical implications

Our study showed that outcome is very heterogeneous in FEP patients. Going through the experience of a first psychotic episode used to be viewed (by both patients and clinicians alike) as an irreversible step towards neurodegenerative decline. However, in line with previous work, our data show that a majority of patients show marked recovery or even full recovery in the first year after illness onset. Reason enough to *feel* hope as a clinician treating these young people going through this experience, but more importantly, to *give* hope to those in our care.

Large cognitive diversity was evident in our samples, where we also found various specific and general ways that cognitive performance related to outcome. Since these effects were overall moderate to small, standard comprehensive cognitive assessment in FEP cannot be recommended. However, clinicians should keep a sharp eye out for both obvious (e.g. severe attention & memory problems) and more subtle (e.g. not being able to 'problem-solve' or missing key information in social context) cognitive problems. When evident, these problems should be assessed, so related functional problems are not overlooked and patients can be supported to challenge and overcome these obstacles. This might be especially relevant in patients with a migration background, since both neurocognitive and social cognitive problems tend to be more severe in these groups.

The majority of patients in our sample was 'clinically depressed' based on their BDI scores. And yet, only a minority had a(n additional) mood-related diagnosis, making it easy to overlook this 'co-morbid' psychopathology. Although depressive symptoms did not predict functional or symptomatic outcome, it obviously is an important predictor of quality of life. Obviously, initial FEP treatment should have a main focus on reducing (the negative impact of) psychotic symptoms. We do argue however that depression needs clinical attention, as it is very common, disabling, and still easy to overlook in everyday clinical practice treating FEP patients, especially since depressive symptoms have been shown to exacerbate psychotic symptoms (Kramer *et al.* 2014; Veling *et al.* 2016).

## Implications for future research

### *Differentiate between predictors of outcome and predictors of change*

The findings presented in this thesis showed that psychotic symptoms (positive and negative), neurocognitive and social cognitive deficits and affective problems all

contribute to psychosocial difficulties in the early course of psychosis. The investigation in presented in chapter 3 further showed that the magnitude of this influence not only varies substantially between different areas of psychosocial functioning, but also changes considerably over time. These changes were most notable for psychotic symptoms and cognitive deficits, as impact of baseline psychotic symptoms on psychosocial functioning was initially strong but decreased over time, where the opposite was true for the impact of baseline cognitive deficits.

Our findings indicate valid predictors of both general levels of psychosocial functioning at different points in time (e.g. PSP at T0; PSP at T2) as well as functional change (e.g. +10 points or +20% difference between PSP at T0 and PSP at T2). Yet, they also indicate that these predictors are not necessarily the same. This finding emphasizes the need for future researchers to differentiate between ‘absolute’ and ‘relative’ outcomes in the exploration of mechanisms underlying psychosocial problems in the early stages of psychotic disorders.

### *Ethnicity*

The symptomatic manifestation of psychosis is similar across patient groups with different ethnic backgrounds. However, we found two key differences between ethnic groups, (a) that neurocognitive and social cognitive problems are much more evident in patient groups with a background of migration, and (b) that functional recovery is predicted by different factors in these groups. Based on these findings, it seems advisable to at least assess social cognition and neurocognition when examining descriptive and prognostic differences between these groups.

### *Classification to staging: clinical dimensions*

As presented previously (see ‘general introduction’), McGorry and colleagues have recently conceptualised a clinical staging model that encompassed the various manifestations of psychosis in five stages, ranging from ‘stage 0’, i.e. at risk but no current symptoms or functional problems, to ‘stage 4’, i.e. severe and persistent symptoms, neurocognitive problems and functional disability (McGorry *et al.* 2010) (see also ‘general introduction’, Table 1.2). The work presented in this thesis has been undertaking in a ‘stage 2’ setting (i.e. FEP), assessing patients after the onset of their first-episode psychosis and following them through their first year of treatment. The presented data, but mainly it’s comparison with both ‘stage 1b’ (Ultra High Risk; UHR) and ‘stage 3’ and ‘stage 4’ groups (Recurrent psychosis; chronic illness), has yielded clear differences

between these groups, obviously in the expression of specific illness components and functional problems, but moreover in the associations between these factors. As such, the studies presented in this thesis clearly underline the practical and scientific applicability of such an approach to psychopathology in general and to psychosis in specific.

A good working example of the potency of the clinical staging model is currently in progress in the '1b stage' (UHR): a brief and effective tools have been developed to identify those individuals in the early stages of the model ('at risk'; Ising *et al.*, 2012), who are subsequently offered a brief psychological treatment program that has been proven both effective at preventing transition to the next stage in the model (Van Der Gaag *et al.* 2012) as well as cost-effective (Ising *et al.* 2015). A net result of reduced (or prevented) individual suffering for less money than it costs to do nothing. This methodology has demonstrated the potential power of a conceptual model that allows the clinician or researcher to demonstrate not only the presence or absence of pathology, but also the degree to which the disorder is manifested in a particular individual, and treat them accordingly.

Although based on the above, the need for a full paradigm-switch towards a staging approach to psychopathology appears evident, the route to take to obtain this objective is not. However, much research effort is being conducted to improve our current classification-paradigm and slowly mold it towards its future by attaching clinically relevant illness dimensional to each classification, preferably dimensions that can be impacted by therapeutic interventions. This will allow future clinicians and researcher not just to state that a classification is applicable to an individual, but moreover the degree to which the illness is manifested in that individual and provide treatment accordingly. This development towards a dimensional approach to psychopathology is seen across the full board of psychiatric disorders and is already yielding promising results for various disorders (Hudziak *et al.* 2007; Keshavan *et al.* 2011). For example, the core symptom dimensions generally associated with psychosis are positive symptoms, negative symptoms, cognitive deficits, depression and mania (Van Os & Kapur 2009). Within this framework, higher levels of negative symptoms and cognitive deficits at illness onset are associated with developmental impairment and a more insidious onset (and poorer outcome), where higher levels of mania and depression are associated with affective dysregulation and a more acute onset (and better outcome). Findings presented in this thesis showed that all these dimensions all provide valuable information when attempting to predict outcome. However, they also showed that the majority of variance in outcome is not explained by these five illness dimensions. What are we missing here?

Unfortunately, the data did not provide many leads to further address this question. Based on our observations during our work with these young individuals suffering from psychosis, we would hypothesize that a number of personal dimensions (that are not routinely assessed in early psychosis care,) might interact strongly with environmental stressors to have a major influence on symptom expressions on these five illness dimensions. Moreover, these interaction effects might have a strong shaping effect on illness trajectories and recovery. We argue that systematically incorporating personal psychological characteristics as well as environmental parameters into diagnostic and subsequent treatment procedures could greatly improved both symptomatic and functional outcome for these people. In the following two section, we will discuss a 'top 5' of both personal and environmental factors that could be considered here:

### *Personal factors*

(1) *The 'Big Five'*. The Big Five personality traits model is a widely examined theory of five broad dimensions used to characterize the human personality (Goldberg 1993). The five factors have been defined as openness to experience (O), conscientiousness (C), extraversion (E), agreeableness (A), and neuroticism (N) (Costa & McGrae 1992). Meta-analysis of these traits and their interrelation with psychosis found that patients with schizophrenia tend to have a higher score for N and lower scores for E, O, A and C compared with healthy subjects (Ohi *et al.* 2016). The effect sizes of these personality traits, as studied in this meta-analysis, ranged from moderate to large.

(2) *Attachment style*. Attachment theory is a psychological model that attempts to describe the dynamic facets of long-term and short-term interpersonal relationships between human individuals. The theory primarily differentiates between 'secure' and 'insecure' attachment styles, where the latter is divided into three substyles: anxious-resistant, anxious-avoidant and disorganized/ disoriented. As these styles develop in infancy and early childhood, they precede most forms of non-biological psychopathology. Attachment theory can therefore enable the development of lifespan models of how adverse developmental environments may increase the risk for all forms of psychopathology, including psychosis (Berry *et al.* 2007a; Korver-Nieberg *et al.* 2014; Mathews *et al.* 2014; Sheinbaum *et al.* 2015). Since these personal attachment styles develop the early developmental stage, they are ideal candidates for prophylactic intervention or other early harm-reduction strategies. Also, it can facilitate understanding of interpersonal difficulties and empathy, and the subsequent quality of the therapeutic alliances needed for optimal treatment of these individuals when they seek help (Gumley

*et al.* 2014; Pos *et al.* 2015). And last but not least, incorporation of attachment style may help to integrate key subjective domains of illness and recovery, like self-esteem, into account (Ringer *et al.* 2014).

(3) *Cognitive reactivity*. A term traditionally associated with depression-research, cognitive reactivity refers to the relative ease with which a mild dysphoric state or trigger reactivates core negative thinking patterns that are central to affective pathology. This mechanism has been found to play a causal role in depressive relapse (Elgersma *et al.* 2015; Figueroa *et al.* 2015). It seems plausible that such a concept that models increased cognitive reactivity to (mild) negative experiences or social stressors might be highly relevant in understanding the development and course of psychotic symptoms across the stages of psychosis.

(4) *Stress reactivity*. Recent work in the field of early psychosis used virtual reality-based social environments to demonstrate that heightened sensitivity to environmental and social stress may also play an important role in the development and recurrence of paranoid symptoms and subjective distress in the onset and course of psychotic disorders (Veling *et al.* 2016).

(5) *Coping style*. Coping refers to the process of expending conscious effort to solve personal and interpersonal problems, and seeking to master, minimize or tolerate related stress. More effective coping has been found to have a direct effect on quality of life in individuals who experience chronic stress (Brenner *et al.* 2011) and reduced internalized stigma and depression in people with persecutory delusions (Espinosa *et al.* 2016). Previous work in the coping styles in people with psychosis confirmed that this patient group as a whole tended to cope with stress in a relatively avoidant and ineffectual manner, where they tended to avoid stressors rather than involve in problem solving or have difficulties solving problems effectively when attempted (Lysaker *et al.* 2003, 2004; Lysaker & Taylor 2007). Overall, an ineffective or avoidant coping style could be considered a risk factor for poor prognosis in FEP. Inversely, proactive coping tendencies could also help to protect patients against poor prognosis. For example, a recent study showed that patients who are generally more open to (new) experiences (i.e. trait level) are more likely to make use of the available ambulatory FEP care (Scholte-Stalenhoef *et al.* 2016), and are subsequently more likely to increase their chances of good outcome. The issue of coping styles is highly relevant in the context of psychosis, since insufficient stress regulation is considered one of the key factors that elicit psychotic symptoms.



### *Environmental factors*

Onset of psychosis is associated with various environmental risk factors (van Os et al. 2010). For example the risk for psychosis in individuals who have experienced serious childhood adversity is more than double the risk observed in individuals who have not had such experiences (Varese et al. 2012). But as these and other environmental factors increase the risk of psychosis onset, little is known about how these factors impact illness development and outcome over time. And yet, it is very unlikely that the adverse effect of these environmental stressors will cease to impact the individual simply because they have 'transitioned to stage 3'. These risk factors are likely to have a complex and interactive impact not just on illness onset, but also the course of these disorders through all stages (Davis et al. 2016). As mentioned previously, we will present a 'top 5' of well-studied environmental risk factors that we consider likely to impact FEP patients well beyond illness onset.

(1) *reduced social support*. It has long been established that the social networks of individuals with psychosis have fewer members (Hammer et al. 1978; Cresswell et al. 1992) and give less satisfaction (Bengtsson-Tops & Hansson 2001) than those of individuals without a serious mental illness. Recent work further shown that these social problems are already evident in UHR samples (Robustelli et al. 2017) and are generally well established and severe by the time of first hospitalization (Horan & Subotnik 2006). Furthermore, the quality and size of social networks are directly related to objective and subjective illness outcome (Thomas et al. 2016; Robustelli et al. 2017). Also, recent meta-analytic work on effects of social support in young adults with mental problems suggests that it might be valuable to differentiate between general benefits and specific stress-buffering benefits that result from social support (Rueger et al. 2016).

(2) *childhood adversity*. A recent review of the FEP literature found that that childhood adversity and trauma substantially increases the risk of psychosis with an OR of 2.8, where emotional abuse (OR = 3.40), physical abuse (OR = 2.95) and neglect (OR = 2.90) yielded the highest odds ratios (Varese et al. 2012). The authors concluded that all types of adversity were related to an increased risk of psychosis, indicating that exposure to adverse experiences in general increases psychosis risk, regardless of the exact nature of the exposure. These effects appear to be evident across various stages of psychosis. A recent meta-analysis of UHR individuals showed that childhood trauma is highly prevalent among these individuals and that childhood trauma is related to UHR status, where recent life-events are not (Kraan et al. 2015b).

(3) *minority group position*. Minority group position as a potential risk factor for psychosis has received a lot of scientific attention in recent years. This body of work indicates that being part of a minority group with a disadvantageous socio-environmental position (e.g. *non-heterosexual orientation*, Gevonden *et al.* 2013; *hearing impairment*, van der Werf *et al.* 2011; *childhood adversity*, van Dam *et al.* 2012; Kraan *et al.* 2015a; *discrimination*, Veling *et al.* 2008a; *social marginalization*; van der Ven *et al.* 2016) increases the risk for psychosis. It seems likely that the impact of such factor does not stop at illness onset, but will likely affect illness trajectories.

(4) *cannabis use*. Cannabis use is very common in The Netherlands. A national survey done in 2014 indicated that of all Dutch people (between 15 and 64 years old; 4.1 million individuals) one in four has used cannabis at least once, and that one in twenty qualifies as 'current user' (cannabis use in last month). Furthermore, 1,3% of all respondents reported to use cannabis daily (Trimbos Instituut 2014). A large body of research on the effects of cannabis use shows mostly damaging (namely concerning cognitive and functional problems) but also some protective effects of cannabis use (Broyd *et al.* 2016). Concerning psychosis, cannabis use clearly increases the risk for psychosis two-fold on average, depending on the amount of cannabis used (dose-response effect) (Moore *et al.* 2007). Í

(5) *urbanicity*. Epidemiological data clearly shows that living in an urban environment is associated with increased risk for psychosis (Krabbendam & van Os 2005). However, it is still unclear why this is the case. It is clear however that this 'urbanicity' represent a multi-dimensional proxy that encompasses both biological, environmental and psychological components and their interactions (van Os *et al.* 2010), some of which have been discussed in these thesis. Since the combined effect of all these components has a large effect on psychosis risk (about a two-fold increase) further elucidation of these components seems of paramount importance.

### *Cognitive change and work outcome*

The present thesis replicated findings of significant functional *improvement*, rather than the stable or gradually expanding functional deficits, in FEP patients. The fact that these functional problems are subject to change (i.e. are impacted by socio-environmental factors and changeable rather than the net result of neurodevelopmental factors and stable / deteriorating) underlines them as a key research priority. This in turn emphasizes the need to expand out understanding of the mechanisms that account for these initial functional problems, but also of the mechanisms that account for these *changes*.

In the presented studies, we have demonstrated that cognitive deficits play a significant, yet unspecified, role in the mechanism that contributes to the functional problems that people suffering from psychosis experience. Fortunately, scientific studies and randomized controlled trials (RCT) that have been done in recent years have yielded many promising interventions that have proven to be effective to address these issues. Examining this body of research, looking for potential interventions that might improve the largest functional problems (i.e. vocational and academic functioning) and largest untreated symptom domain (i.e. cognitive deficits) observed in our sample, two have specifically targeted these problems and have been proven to be effective: (I) Individual Placement and Support (IPS): a treatment model that offers standardized Supported Employment to improve employment prospects in persons with severe mental illnesses (Crowther *et al.* 2001), and (II) Cognitive Remediation Treatment (CRT): Cognitive remediation is a rapidly developing treatment approach that targets the cognitive impairments of psychotic disorders (Wykes & Spaulding 2011). To quote Till Wykes, one of the founders of CRT:

*“Cognitive factors are essential to consider as part of recovery. We know from studies over the last century that recovery, measured by independent employment or a fulfilling social life, is poor in at least half the people with a diagnosis of schizophrenia. We need to improve these outcomes, and one of the barriers seems to be cognitive difficulties. Not only are these same difficulties directly related to outcomes but they may also have an effect on moderators such as medication adherence.”* (Wykes & Reeder 2005)

Furthermore, CRT has been found to provide a neurobiological enhancing effect of increased activation in various brain regions (mainly in frontal - especially prefrontal - and also in occipital and anterior cingulate regions during working memory and executive tasks) and improved functional connectivity (Isaac & Januel 2016).

Although both CRT and IPS treatment methods have been proven to be effective by themselves (McGurk *et al.* 2007; Killackey *et al.* 2008; Wykes *et al.* 2011; Michon *et al.* 2014; Revell *et al.* 2015), recent related studies show that they might be even more effective when combined (McGurk *et al.* 2007; Penadés *et al.* 2012; Allott *et al.* 2013). Although both the CRT and IPS approaches have market limitations (namely generalizability of cognitive improvement, or ‘transfer’, for CRT; limited longitudinal evidence of positive treatment outcome for IPS), outcome improvement demonstrated as a result of these intervention in FEP samples to date show much promise.

Moving forward from our own data towards this two-fold treatment approach, we argue that a number of our findings could be used as targets to investigate specific efficacy, process- and mechanism effects behind these deficits through randomised-controlled examination. For example, we found that both the general cognitive factor *verbal processing speed*, but also the more specific cognitive domain *visual learning* predicted vocational functioning, two cognitive components that might be central to language- and communicational skill development, and in fact might be much closer related than their verbal-visual nosological distinction suggests (Clerkin *et al.* 2017).

## Conclusions

In conclusion, this thesis provides insight into a wide range of neurocognitive and social cognitive domains, symptom profiles and psychosocial functioning in early psychosis patients. Moderate neurocognitive and social cognitive deficits were found in the majority of FEP patients, and these deficits proved to be largely independent of (other) domains of psychopathology. Of all illness dimensions, negative symptoms, neurocognition and social cognition showed the strongest cross-sectional association with psychosocial problems (chapter 2). Psychotic symptoms, both neurocognitive and social cognitive deficits, and affective problems at baseline were all indicative of psychosocial problems one year after baseline (chapter 3). Better functioning, lower levels of positive symptoms, negative symptoms and mania symptoms, and better social cognitive functioning at baseline discriminated between patients with full recovery from those who were not recovered in the first year after baseline (chapter 4). Furthermore, this thesis showed that immigrant patients have larger cognitive deficits compared to Dutch patients, and that first-generation immigrant patients have larger cognitive deficits than second-generation immigrant patients (chapter 5), and that these groups all have different predictors of functional outcome (chapter 6).



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## **Nederlandse samenvatting**



In het eerste deel van dit proefschrift werden symptoomprofielen, cognitieve prestaties en psychosociaal functioneren bij patiënten met vroege psychose onderzocht.

In **hoofdstuk 2** werden verschillende vragen behandeld met betrekking tot cognitieve tekorten bij FEP-patiënten, dat wil zeggen welke neurocognitieve en sociale cognitieve factoren kunnen worden geïdentificeerd die cognitieve prestaties in patiënten met een Eerste-Episode Psychose (EEP) accuraat weerspiegelen? Hoe zijn deze cognitieve factoren gerelateerd aan (andere) psychopathologie dimensies in EEP patiënten? Dragen deze cognitieve factoren bij tot het begrip van de psychosociale problemen van deze patiënten? Onze resultaten wezen uit dat de EEP-patiënten in ons sample gematigde neurocognitieve en sociale cognitieve tekorten hebben, die grotendeels onafhankelijk waren van (andere) domeinen van de psychopathologie. Onze cross-sectionele analyse van de gegevens van het eerste meetmoment toonde aan dat negatieve symptomen, neurocognitie en sociale cognitie gematigd gerelateerd waren aan psychosociale problemen, terwijl affectieve en positieve symptomen niet indicatief waren voor psychosociale functionaliteit op het eerste meetmoment.

In **hoofdstuk 3** is de impact van basis-predictoren (e.g. psychotische symptomen, affectieve problemen en tekorten in specifieke neurocognitieve en sociale cognitieve subdomeinen) op het huidige en toekomstige psychosociale functioneren onderzocht. Psychotische symptomen, cognitieve tekorten en affectieve problemen hebben allemaal invloed op het psychosociale problemen van patiënten in de vroege stadia van psychose. Uit de bevindingen blijkt dat de omvang van deze invloed niet alleen sterk verschilt tussen verschillende gebieden van psychosociaal functioneren, maar ook aanzienlijk verandert tussen de eerste meting en de meting 12 maanden later. Deze veranderingen waren het meest opvallend voor psychotische symptomen en cognitieve tekorten, waarbij de invloed van de psychotische symptomen op psychosociaal functioneren in eerste instantie sterk was maar in de loop der tijd afnam, waar het tegendeel waar was voor de invloed van de cognitieve tekortkomingen. Ook laten de bevindingen zien dat voorspellers van absolute niveaus van psychosociaal functioneren niet noodzakelijkerwijs voorspellers zijn van *veranderingen* in die niveaus (en vice versa). Op basis hiervan wordt gesteld dat het noodzakelijk is om onderscheid te maken tussen deze onderling verbonden paradigma's bij het onderzoeken van mechanismen die psychosociale problemen bij patiënten in de vroege stadia van psychose kunnen verklaren.

**Hoofdstuk 4** behandelt het probleem of het mogelijk is om te voorspellen welke EEP-patiënten functioneel herstel dan wel symptomatisch herstel bereiken binnen 12

maanden na het eerste meetmoment, waarbij de bij de eerste meting verzamelde gegevens als voorspellers worden gebruikt. Welke symptomatische en cognitieve variabelen differentiëren tussen patiënten die volledig herstellen in de eerste 12 maanden na de eerste meting en de patiënten die niet zijn hersteld in deze periode? En welke factoren differentiëren tussen patiënten die psychotische symptomen blijven ondervinden maar goed functioneren van degenen die grotendeels vrij zijn van symptomen maar slecht functioneren? Uit onze bevindingen bleek dat een derde van de patiënten volledig herstelde binnen een jaar na de eerste meting, waarbij een derde niet was hersteld en een derde zich gedeeltelijk herstelde. In het algemeen liet de hele groep patiënten verbeteringen zien wat betreft positieve, negatieve en algemene symptomen. Ook verbeterden zij tezamen genomen in beroeps- en/of academische prestaties, sociaal en algemeen functioneren, en lieten zij minder verontrustend gedrag zien. Beter functioneren, lagere niveaus van positieve symptomen, negatieve symptomen en manie symptomen, en beter sociaal cognitief functioneren op het eerste meetmoment differentieerde tussen patiënten met volledig herstel van degenen die niet herstelden in de eerste 12 maanden na de eerste meting. Binnen de groep patiënten die gedeeltelijk herstel vertoonden, hadden degenen die verbeterde symptomatische uitkomst hadden kortere DUP en meer voltooide opleidingsjaren dan degenen die verbeterde functionele uitkomst toonden na 12 maanden.

In het tweede deel van dit proefschrift werden etnische verschillen in cognitieve prestaties, symptoomexpressie en herstel in vroege psychosepatiënten onderzocht.

In **hoofdstuk 5** werden niveaus van neurocognitieve prestaties vergeleken tussen Nederlandse patiënten, eerste-generatie migranten en tweede-generatie eerste-generatie migranten. Alle groepen lieten matige cognitieve beperkingen zien op onmiddellijke herroeping, vertraagde herroeping en vastgehouden aandacht. In het algemeen hadden migranten grotere cognitieve tekorten ten opzichte van Nederlandse patiënten, en eerste-generatie eerste-generatie migranten hadden grotere cognitieve tekorten dan tweede-generatie eerste-generatie migranten (allemaal gecontroleerd voor verschillen in het niveau van onderwijs en het gebruik van cannabis). Over het geheel genomen lieten de Marokkaanse, Turkse en andere niet-Westerse migranten de grootste cognitieve tekorten zien. Post-hoc analyses gaven aan dat deze verschillen niet kunnen worden verklaard door effecten van de onderzoeks-taal, d.w.z. mogelijke verschillen in testuitkomst die het

gevolg kunnen zijn van verschillen in de beheersing van de Nederlandse taal tussen patiëntengroepen.

In **hoofdstuk 6** werden verschillen in symptoomuitdrukking, neurocognitieve en sociale cognitieve prestaties onderzocht tussen Nederlandse, eerste-generatie migranten en tweede-generatie migranten eerste-episode psychose patiënten, en in hoeverre deze factoren verschillende domeinen van psychosociaal functioneren in deze groepen beïnvloedde in de eerste 12 maanden na de eerste meting. Resultaten toonden aan dat niveaus van positieve symptomen, negatieve symptomen, opwinding en emotionele nood niet significant verschilden tussen Nederlandse patiënten, eerste-generatie migranten en tweede-generatie migranten. Op neurocognitieve en sociale cognitieve taken presteerde Nederlandse patiënten beter dan de tweede-generatie migranten, die op hun beurt beter presteerden dan de eerste-generatie migranten. De drie etnische groepen lieten verder ook vergelijkbare niveaus van functionele problemen zien op de gebieden werk / studie, opbouwen en onderhouden van sociale relaties, persoonlijke verzorging en zorg voor hun persoonlijke omgeving en agressief of anderszins verontrustend gedrag. Echter wat betreft verandering in psychosociaal functioneren lieten deze drie groepen verschillen zien. Zo veranderde het gemiddelde niveau van psychosociaal functioneren bij Nederlandse patiënten in de vervolgperiode niet significant. In contrast, verbeterde het opbouwen en onderhouden van sociale relaties bij eerste-generatie migranten. In tweede-generatie immigranten verbeterden zelfs alle functionele domeinen (met uitzondering van zelfverzorging).

**Tabel I** Voorspellers van vooruitgang (vs. achteruitgang) in psychosociaal functioneren, per domein, per subgroep

Groep	Discriminatoren voor functionele verbetering vs. achteruitgang per domein				
	Algemeen	Werk/studie	Relaties	Zelfzorg	Verontrustend gedrag
Nederlands	NEG	NEG	NEG + SC	NEG	EXC
Tweede-generatie migranten	SC	SC	YoE	SC	-
Eerste-generatie migranten	POS + NC	NC	NEG + POS	NEG	EXC

POS = positieve symptomen; NEG = negatieve symptomen; SC = sociale cognitie; NC = neurocognitie; EXC = opwinding; YoE = aantal voltooide opleidingsjaren

Hiernaast werden differentiële voorspellers van functionele veranderingen tussen etnische groepen onderzocht. Deze onderzoeken, zoals weergegeven in tabel I, toonden aan dat de waarden van negatieve symptomen, sociale cognitie en opwinding op het

eerste meetmoment de functionele verbetering voor Nederlandse patiënten voorspelden. Bij tweede-generatie migranten was sociale cognitie de enige symptoom dimensie die de functionele verbetering voorspelde. In tegenstelling hiermee waren vier van de zes symptomen dimensies (d.w.z. positieve symptomen, negatieve symptomen, neurocognitie en opwinding) van voorspellende waarde voor functionele verbetering in eerste-generatie migranten. Deze effecten bleven significant na het controleren voor het niveau van psychosociaal functioneren op het eerste meetmoment.



## Dankwoord

*“Life teaches us its small lessons, and we move on.”*

- Terry Pratchett, *The Fifth Elephant*

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## **Publications**



### **Peer-review, published**

**Stouten LH, Veling W, van der Helm M, Laan W, & van der Gaag M** (2013). Cognitive deficits and ethnicity: a cohort study of early psychosis patients in The Netherlands., *Social psychiatry and psychiatric epidemiology* **48**, 37–47.

**Stouten LH, Veling W, Laan W, van der Helm M, & van der Gaag M** (2014). Psychotic symptoms, cognition and affect as predictors of psychosocial problems and functional change in first-episode psychosis., *Schizophrenia research* **158**, 113–119.

**Stouten LH, Veling W, Laan W, van der Helm M, & van der Gaag M** (2017). Psychosocial functioning in first-episode psychosis and associations with neurocognition, social cognition, psychotic and affective symptoms., *Early intervention in psychiatry* **11**, 23–36.

**Stouten LH, Veling W, Laan W, van der Gaag M.** (in press). Psychopathology, cognition and functional recovery in Dutch and immigrant first-episode psychosis patients. *Early intervention in psychiatry*.

### **Peer-review, submitted**

**Stouten LH, Veling W, Laan W, van der Gaag M.** Predicting recovery after a first-episode psychosis.

### **Abstracts**

**Stouten LH, Veling WA.** (2010). Cognitief functioneren en etniciteit bij eerste psychose. *Tijdschrift voor Psychiatrie*, 52, suppl. 1, 39

**Stouten LH, Veling W, van der Gaag M.** (2010) Cognitive functioning and ethnicity in first episode psychosis. *Early Intervention in Psychiatry*, 4, suppl. 1, 82

**Stouten LH, Veling W, van der Helm M, Laan W, van der Gaag M.** (2012). Differential associations between cognition and outcome in early psychosis: A cohort study of early psychosis patients in The Netherlands. *Schizophrenia Research*, 136, suppl. S272

**Stouten LH, Veling W, Laan W, van der Helm M, van der Gaag M.** (2014). Dimensional profiles of psychopathology as differential predictors of psychosocial functioning in Dutch and immigrant first-episode psychosis patients. *Early Intervention in Psychiatry*, 8, suppl. 3, 139

**Stouten LH, Veling W, Laan W, van der Helm M, van der Gaag M.** (2014). Psychotic symptoms, cognition and affect as predictors of psychosocial problems and functional change in first-episode psychosis. *Early Intervention in Psychiatry*, 8, suppl. 3, 103

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## Curriculum vitae



Luyken Stouten was born on the 20<sup>th</sup> of October, 1980 in The Hague. After completing the gymnasium secondary education at the Van Maerlant Lyceum in The Hague, he moved to Delft to study Systems Engineering, Policy Analysis and Management at the Delft University of Technology for two years. In 2004, he relocated to Leiden to study Psychology at Leiden University, where he obtained his Bachelor degree in 2007. He pursued his Master studies in Clinical Psychology at Leiden University and completed an extended clinical internship at the Parnassia Centre for Early Psychosis (CEP) in The Hague. He graduated cum laude for his Master of Science degree in Clinical Psychology in 2009.



After obtaining his Master's degree, Luyken quit his 10-year part-time job, working as an outdoor-sport equipment salesman, and was employed at the CEP as a PhD candidate to investigate cognitive problems as predictors of outcome in the early stages of psychosis under supervision of prof.dr. Mark van der Gaag and prof.dr. Wim Veling. During this period, he also worked as a diagnostician and therapist, providing (neuro)psychological assessment and cognitive-behavioural therapy to patients suffering from psychosis. After completing the four-year research project, Luyken stayed on fulltime at the CEP to continue his diagnostic- and therapeutic work.

In 2015, Luyken enrolled in a two-year training program at the RINO Group in Utrecht to become a health-care psychologist (GZ-psycholoog). In the course of this program, Luyken worked in the The Hague area with patients suffering from addiction at Brijder Addiction Care (both outpatient and inpatient treatment) and with patients suffering from affective problems at PsyQ Depression (team bipolar disorders). He also worked at the PsyQ Psycho-Diagnostic Centre (PDC) to receive training in specialized psycho-diagnostics, focusing on complex pathology. After completing this two-year training program in 2017, Luyken resumed his employ at the CEP in The Hague as a health-care psychologist.

