Understanding cognitive heterogeneity in psychosis and high risk individuals
Meijer, J.H.

Citation for published version (APA):
Meijer, J. H. (2012). Understanding cognitive heterogeneity in psychosis and high risk individuals

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
SUMMARY AND GENERAL DISCUSSION
1. SUMMARY

In **Chapter 1** a background was provided on the nature, course and clinical correlates of cognitive alterations in patients with psychotic disorder and individuals with an increased genetic risk for psychosis. The outline of this thesis was presented including the research questions.

**Chapter 2** focused on the association between current and lifetime cannabis use and cognitive functioning in patients with psychotic disorder, their unaffected siblings and controls. Two main findings resulted from this study that seemed contradictory at first sight. Although current cannabis use was associated with worse processing speed and working memory, lifetime use was associated with better acquired knowledge and social cognition. Associations between cannabis use and cognition did not differ between patients, siblings and controls. Results in patients corroborate the existing hypothesis that different pathways to psychosis exist, depending on level of genetic risk in combination with early and late environmental risk factors.

In **Chapter 3** it was investigated whether the use of stimulants (cocaine, ecstasy, amphetamine) was associated with different cognitive performance in patients with psychosis, their unaffected siblings and controls. We found that current and lifetime frequent stimulant use was associated with more deficits in verbal learning, working memory and acquired knowledge in comparison to never users. Lifetime infrequent use was associated with a general pattern of better cognitive functioning in comparison to never users, however these results did not reach significance. As with cannabis, the relation between stimulant use and cognition did not differ between patients, siblings and controls. Findings suggest that cognitive deficits in lifetime stimulant users depend on the frequency of use.

**Chapter 4** examined the existing premise that schizophrenia patients with and without obsessive-compulsive symptoms (OCS) may be distinguished based on cognitive performance. In the largest study to date we found that patients and unaffected first-degree relatives with and without OCS did not perform different on a range of cognitive domains. Cross-trait cross-relative analyses neither yielded a clear association between OCS and cognitive performance in patients and their unaffected relatives. Therefore, results do not support the existence of a “schizo-obsessive subtype” associated with cognitive impairment. Although OCS was associated with a moderately worse clinical state, results may be explained by a continuum of symptom severity instead of a categorization.

In **Chapter 5** we assessed whether the identification of odours, a higher-order olfactory process, is associated with symptoms of parkinsonism in patients with non-affective psychosis. We found that olfactory identification deficits were associated with more parkinsonian and negative symptoms. These preliminary results suggest that dopaminergic disbalance may contribute to the pathophysiology of olfactory identification deficits in patients with psychosis. Olfactory identification deficits may be used as an early risk marker of increased sensitivity of the dopaminergic system, as it already is in patients with Parkinson’s disease. This may be of use for early identification of ultra high risk (UHR) individuals in the true prodromal phase as well as for prediction of antipsychotic response and adverse effects.

**Chapter 6** focused on the identification of cognitive endophenotypes in patients with psychotic disorder and their unaffected siblings and parents. We found that the familial predisposition to psychotic disorder is associated with alterations in immediate verbal learning,
processing speed, reasoning and problem solving, acquired knowledge and working memory. The distribution of cognitive alterations in patients and their first-degree relatives suggests a continuum of neuropsychological functioning, with 30% of the patients and 50% of the relatives displaying no clinically manifest (-1 SD) deficit. Severe cognitive impairments (-2 SD) seem to be restricted to a minority of patients (30%) and unaffected relatives (10%).

In chapter 7 we identified four profiles of social and academic adjustment in patients prior to psychosis onset: normal adjustment, isolated social problems, academic decline from childhood through late adolescence and poor overall adjustment. These clusters of premorbid adjustment proved to have convergent validity with regard to clinical correlates after disease onset. Moreover, patients in the academic decline and poor overall clusters showed a generalized decline in cognitive performance on domains of attention, problem solving, processing speed, working memory, acquired knowledge and social cognition. Findings illustrate a valuable approach to improve our understanding of the cognitive and clinical heterogeneity in psychotic disorders. The premorbid clusters in patients could not be validated by different associations with cognitive and subclinical functioning in their unaffected relatives.

In chapter 8 we described the first assessment of the Measurement And Treatment Response Initiative to Improve Cognition in Schizophrenia (MATRICS) test battery in a Dutch sample of first episode psychosis patients. Also we included a group of individuals at ultra high risk (UHR) of developing psychosis. With the current Dutch translation of the MATRICS test battery we were able to differentiate patients with first episode psychosis from control subjects on six out of seven domains, with the exception of visual learning. Second, a preliminary finding was that the MATRICS seems sensitive to assess cognitive alterations in UHR individuals, who performed intermediate to patients and controls. The size of the UHR sample in this study was too small to obtain significant results however.

Chapter 9 focused on the question whether lower semantic and phonological verbal fluency performance correlate with grey matter density (GMD) in UHR subjects with and without subsequent transition to psychosis. Using voxel-based morphometry we found that lower semantic fluency scores correlated significantly with reduced GMD in the right superior and middle temporal gyrus, the right insula and the left anterior cingulate cortex. This correlations were only present in UHR patients that developed psychosis during follow-up. This study suggests that the association between semantic fluency performance and GMD in task-related areas may be of use to improve psychosis prediction in UHR subjects.

2. CONCLUSIONS

The central objective of this thesis was to increase our knowledge on what explains the cognitive heterogeneity in patients with psychosis, their unaffected relatives and individuals who are in the putatively prodromal phase of psychosis. In the following paragraphs I will summarize and reflect on our main results and finish with a discussion and recommendations for future research.

1. Although sub-acute effects of cannabis impair processing speed and working memory, lifetime cannabis using patients with psychosis seem to have a higher cognitive potential compared to non-users.
2. Cognitive deficits associated with lifetime stimulant use are dependent on the frequency of use in patients with psychosis, their unaffected siblings and controls.

3. While 50% of genetic high risk individuals may experience some degree of cognitive impairment relative to controls (−1 SD), severe cognitive impairment (−2 SD) seems to be restricted to a minority (10%).

4. Olfactory identification deficits may reflect dopaminergic imbalance and therefore could be a valuable risk marker in psychosis prediction.

5. Cognitive functioning seems a promising candidate endophenotype with first-degree relatives performing intermediate to patients and controls. The specificity of the cognitive deficit is however under debate.

6. The MATRICS cognitive consensus battery is a valuable initiative to standardize cognitive assessment in patients with psychosis and possibly in UHR individuals, although the inclusion of tasks with less cognitive density would promote clinical utility.

7. Poor premorbid academic functioning before the age of nineteen is predictive for a broad-based cognitive impairment after psychosis onset.

8. Combining cognitive measures such as verbal fluency with structural brain imaging techniques may improve psychosis prediction in UHR individuals.

**3. DISCUSSION**

The search for aetiological factors in schizophrenia has been hampered by phenotypic variability and genetic heterogeneity ever since the diagnostic category was introduced. There has been a longstanding debate as to whether schizophrenia is a single process with pleiotropic manifestations at the level of cerebral organization, or a collection of aetiologically unrelated but dynamically interacting processes (Jablensky, 2006). The objective of the Genetic Risk and Outcome of Psychosis (GROUP) study, that provided data for most of the studies in this thesis, underlines the broader definition of the psychosis definition (Korver et al., 2012; van Os and Linscott, 2012). This was reflected in the inclusion of patients with a range of psychotic disorders, e.g. schizophrenia, schizo-affective disorder, schizophreniform disorder, psychosis not otherwise specified and substance-induced psychosis.

Although agreeing that schizophrenia does not seem to demarcate a homogeneous disease entity may be one step forward, the need to arrive at a better understanding of the heterogeneity of this broader psychosis phenotype remains vital. The current DSM-IV-TR criteria distinguish between different psychotic disorders on the base of duration, dysfunction, associated substance use, bizarreness of delusions and presence of depression or mania (APA, 2000; van Os and Kapur, 2009). Beside the limited stability of the different psychosis diagnoses within patients over time (Schwartz et al., 2000), the current classification of schizophrenia and other psychotic disorders is not associated with robust aetiological, prognostic, or therapeutic validity (Korver-Nieberg et al., 2011; Laursen et al., 2009).

This thesis focused on cognitive impairment in an attempt to unravel the diverse clinical picture in patients with psychotic disorders and in people at increased risk for psychosis. In order to do so, we examined whether cognitive dysfunction was associated with several clinical
features. Two studies associating cognition with substance use (chapter 2 and 3) revealed that especially recency of cannabis use and frequency of stimulant use was associated with worse cognitive functioning in domains of verbal learning and working memory. The small effect sizes suggested that, despite clear psychotomimetic effects of both cannabis and stimulants (Fiorentini et al., 2011), the cognitive effects may be limited. Moreover, findings that substance using patients display better cognitive functioning than never users is in line with recent findings (Leeson et al., 2011; Schnell et al., 2009; Jockers-Scherubl et al., 2007). In contrast to previous studies (Löberg and Hugdahl, 2009; Jockers-Scherubl et al., 2007) our results do not support the hypothesis that substance use may have a stimulating or neuroprotective effect in patients, since superior intellectual ability was only associated with lifetime (instead of current) use, and with infrequent (instead of frequent) use.

Alternatively, our results may indicate different pathways to psychosis in substance using patients. People who develop schizophrenia in the absence of cannabis use may have prevailing early (genetic or environmental) risk factors, which may be reflected in poorer premorbid adjustment. Contrarily, patients who develop psychosis in response to a late environmental factor such as substance use may have less impaired early development due to more cognitive reserve capacity. Findings by Leeson and colleagues supported this proposition as they found that superior cognitive functioning in patients with a history of cannabis use was probably the result of higher premorbid IQ (Leeson et al., 2011). Since cross-sectional studies like ours can not infer about causality, hypotheses on cognitive reserve and substance use should be confirmed by longitudinal studies.

In chapter 6 and 8 we investigated cognitive profiles of patients with non-affective psychosis in comparison to individuals at increased genetic and clinical risk. Both studies found a broad-based deficit in patients. Cognitive alterations in high risk samples were smaller, while the pattern was similar to that in patients. These findings add to the long-term discussion whether the cognitive heterogeneity in patients with schizophrenia-related psychosis is better accounted for by a generalized deficit of varying degree, or by specific cognitive impairments (Joyce and Roiser, 2007). The magnitude of particular cognitive deficits such as declarative memory and processing speed has led researchers to characterize them as specific to schizophrenia (Ragland et al., 2009; Dickinson et al., 2007). Others however argued that schizophrenia is represented by a generalized cognitive deficit (Blanchard and Neale, 1994; Heinrichs and Zakzanis, 1998). Two different explanations may account for these findings. The first explanation is that there is indeed no cognitive deficit specific for schizophrenia. A second explanation is that we are currently unable to reliably identify a specific deficit due to methodological difficulties that we will discuss here.

If the first explanation proves to be true, this would correspond with findings from neuroimaging studies that the neurobiological substrate of cognitive impairment affects almost all brain regions (Joyce and Roiser, 2007). Further support for a non-specific impairment can be derived from findings from recent cross-diagnostic studies on cognitive impairment in various psychiatric populations. Comparisons of patients with schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder demonstrated a similar pattern of neurocognitive performance across groups, including deficits in memory, attention
and processing speed. Schizophrenia patients were however the most impaired, suggesting that cognitive differences between patients with schizophrenia and other major psychiatric disorders may be more quantitative than qualitative (Reichenberg et al., 2009; Weiser et al., 2008). If however the second possibility is true that we have been unable to detect a specific impairment that is actually there, we should identify and address methodological pitfalls that may have accounted for this type of error. First, there is a problem of task heterogeneity common in the research field. In this thesis, task heterogeneity is illustrated by the fact that the test batteries of the GROUP study (chapter 6) and the MATRICS (chapter 8), both designed to assess domains typically affected in schizophrenia, did not have one cognitive task in common. Correspondingly, when we look at a meta-analysis on a specific cognitive deficit in schizophrenia, e.g. “working memory”, this single domain was assessed by 36 different cognitive measures (Forbes et al., 2009).

A second methodological difficulty is the cognitive density of neuropsychological tests that are currently being used. The majority of conventional neuropsychological tests in schizophrenia, including those in our studies, probably tap many basic processes simultaneously (Carter and Barch, 2007). For example, the “verbal fluency” task like the one used in chapter 8 and 9 may reflect multiple cognitive sub-processes. Different studies using this particular task have referred to its content as “executive functions and attention”, as “executive functions and working memory”, as “processing speed”, or as a cognitive domain on its own (Pukrop and Klosterkotter, 2010). These various assignments to cognitive functions imply inconsistencies in the communication of results leading to scientific ambiguity. Moreover, when cognitive performance tasks rely on diverse cognitive processes this may confound results on the specificity of the cognitive deficit. For example, processing speed is one of the two domains frequently mentioned as the most impaired in schizophrenia (Dickinson et al., 2007). Nevertheless, the MATRICS assesses domains of visual learning, attention/vigilance and reasoning/problem solving by means of speeded tasks. The fact that even a standardized and very well-considered measure like the MATRICS consensus battery has incorporated several cognitively dense tasks may illustrate that basic neuropsychological assessments are still sparsely used. Likewise, with the GROUP test battery, performance on tasks of reasoning/problem solving, working memory and set shifting ability may have also been confounded by lower processing speed in patients compared to controls. These observations emphasize the need for an update of the current testing material, for example by computerized tasks that parse sub processes more clearly (Brewer et al., 2006).

4. IMPLICATIONS AND FUTURE DIRECTIONS

Our results provide promising leads to increase our understanding of cognitive diversity in non-affective psychosis and high risk samples. For this purpose we investigated associations with clinical variables (e.g. substance use, obsessive-compulsive symptoms and motor symptoms), trajectories of premorbid functioning, and structural brain imaging. However, in order to proceed from here, the development of psychometric tools to operationalize cognitive constructs with more comparability and reliability is warranted. Doing so may aid
the cognitive endophenotype approach to improve understanding of the genetic base of the disorder (Gur et al., 2007). From a therapeutic perspective, the use of homologous cognitive models is required for the development of drugs that may enhance cognitive functioning (Carter and Barch, 2007). Beside the poor comparability of current cognitive assessments, face validity is also limited. This may hamper the understanding of how cognitive functioning may be influenced by clinical symptomatology and vice versa. Promising approaches include the development of paradigms that link relevant cognitive processes with specific symptoms of psychosis. Such studies have investigated associations between reality or source-monitoring deficits and auditory hallucinations (Ditman and Kuperberg, 2005), or between abnormalities in emotional perception of stimuli and delusions (Holt et al., 2006).

Future studies should focus on a dimensional approach to psychotic disorders and psychiatric disorders in general. There has been a long tradition of efforts to categorize patients based on clinical variables. For example several studies described in chapter 4 of this thesis refer to an aetiological different subtype based on the presence of one clinical symptom (OCS). However, these were all small studies with a high risk of sampling bias and results were not confirmed in the present study. Currently, there is a paradigm shift toward a more continuous approach of non-affective psychosis that may also stimulate the understanding of cognitive heterogeneity in this population. Categorization of patients may lead to artificial distinctions that actually exist on a severity continuum (Goldberg and Weinberger, 1995). Rather than trying to establish the deficits of a non-existent ‘average’ patient, it may be more fruitful to consider the factors which do or do not co aggregate with different patterns of cognitive impairment (Palmer et al., 2009).

Finally, the results of the studies described in this thesis raise new questions that highlight the importance of longitudinal studies. The GROUP study is such a longitudinal cohort study. While our analyses were based on the baseline assessment, the second and the third wave of this longitudinal study will allow to further investigate hypotheses that we have proposed. For example: will current users who stop using cannabis during the three and six- year follow-up period demonstrate an increase in cognitive ability as suggested by the cognitive reserve hypothesis? And: will patients with poor premorbid adjustment also show a worse disease course during follow up, which would support the hypothesis that these are the developmentally most impaired patients?

5. LIMITATIONS

The following limitations should be taken into account. Although our studies on cognitive functioning and substance use (chapter 2 and 3) yielded consistent results, analyses might have benefited from a more detailed assessment of the frequency of substance use. The current subdivision of the Composite International Diagnostic Interview (CIDI) into daily, weekly and less than weekly could have precluded a dose-response relationship between frequency of cannabis use and cognition that may be actually present. Therefore, we would recommend the use of a continuous scale of substance use to be incorporated into future studies (e.g. number of cigarettes or amount of money spent). Moreover, the prerequisite for patients to have
family members able and willing to participate in the GROUP study may have excluded the more isolated and impaired patients. Together with the wider inclusion criterion of all non-affective psychotic disorders, this may explain why the cognitive impairment in patients was lower (ES -0.7) than the average cognitive deficit normally reported (ES -1.0) (chapter 3). Another limitation is that the size of the UHR samples that we included was limited. In chapter 8, insufficient power may account for the fact that the difference in semantic fluency between converters and non-converters did not reach statistical significance. In addition, findings that the MATRICS may be sensitive to the cognitive alterations in UHR individuals should be regarded as preliminary for this reason (chapter 9).

6. STRENGTHS

Due to the multicenter nature of the GROUP-study, we were able to test our hypotheses in a substantial sample of patients, unaffected relatives and controls. This provided the analyses with sufficient power to solve contradicting findings from previous studies. For example, we did not find evidence for a schizo-obsessive subtype associated with cognitive performance (chapter 4) or for abnormal childhood and adolescent adjustment in unaffected siblings (chapter 7).

In addition, the inclusion of unaffected relatives of patients enabled us to investigate associations between cognitive functioning and clinical variables without disease-related confounding. Another strength of the studies in this thesis is the extensive cognitive test battery that was assessed in the GROUP study and in the MATRICS study. The thesis also includes exploratory studies that address some new and relevant topics for the field of psychosis and UHR research. For example, the association between parkinsonism and olfactory identification deficits in patients with psychosis has not been assessed previously. Moreover, it was for the first time that a Dutch translation of the MATRICS was assessed in patients with first episode psychosis and UHR individuals.

In conclusion, results of this thesis underline the value of examining cognitive functioning as a core symptom of psychosis that may offer a window into brain development and functioning. Future studies concerning cognition and psychosis should focus on longitudinal aspects of cognitive functioning and on improving domain-specificity and face validity of cognitive measures.

REFERENCE LIST


