Statistical approaches to explore clinical heterogeneity in psychosis

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CHAPTER 8

Summary and General Discussion

Aims of the thesis

The clinical presentation of psychotic disorders (e.g. on positive, negative symptoms or cognitive impairment) is heterogeneous and symptoms differ in origin, structure and in clinical expression. Although this notion has been widely acknowledged (Markova and Berrios, 1995), symptom differences are still overlooked in clinical practice and proper statistical analysis in research is lacking. The heterogeneity of psychotic disorders calls for adequate statistical approaches to clarify the underlying structures. Clustering techniques or group-based trajectory techniques have been implemented to form meaningful homogeneous symptom subtypes of subjects using longitudinal data (Goldstein and Shemansky, 1995; Jablensky, 2006; Joyce and Roiser, 2007; Dawes et al., 2011; Quee et al., 2014). The main aim of the thesis is to explore heterogeneity in cognitive functioning and in clinical symptoms in schizophrenia patients and their unaffected siblings using both cross-sectional *and* longitudinal data.

To reach the objective of the thesis, a number of different steps were taken. Firstly, I compared the performance of 14 cluster indices to identify the right number of cognitive subtypes. For this, I performed simulations of various number of clustering scenarios, based on a real case study with cognitive measures (**Chapter 2**). Secondly, I explored the heterogeneity of clinical symptoms and of cognitive functioning in patients with psychosis and their unaffected siblings in a longitudinal setting by implementing the group-based trajectory modeling approach (**Chapter 3** and **4**). Thirdly, I examined also the unobserved heterogeneity of symptoms by using factors (neuro and social cognition) to predict the development of psychotic experiences over time by applying mixture of generalized linear mixed effects modeling (**Chapter 5**). Fourthly, I described the heterogeneity in the domain of comorbid diseases among patients with schizophrenia, their unaffected siblings, and healthy controls. The effects of gender, age and familial liability on the prevalence of multimorbidity were also investigated (**Chapter 6**). Finally, I studied the risk factors that were associated with the duration of untreated psychosis (DUP) in a large sample that represented the treated prevalence of non-affective psychotic disorders (**Chapter 7**). All studies in this thesis were performed within the framework of the Genetic Risk and Outcome of Psychosis (GROUP) project, a longitudinal multicenter cohort study in the Netherlands and Belgium.

Summary of main findings

The first major challenge was to correctly identify the number of clusters in a complex heterogeneous dataset. Over the last decades, different indices have been developed to quantify the number of clusters. In **chapter 2**, I investigated the most promising indices for detecting the correct number of clusters on the basis of hierarchical clustering (with Ward's agglomerative method) in cross-sectional data. The indices were investigated on *(i)* how well they would discriminate between a single and multiple cluster solution and *(ii)* on how well they can predict the number of clusters in a multi cluster solution. I showed that, out of fourteen indices, the Duda and Hart (DH), Hartigan (H), and Gap/pc indices were best performing in the simulation study involving eight-dimensional cognitive outcome variables taken from a real case study of schizophrenic patients. These indices predicted with high probabilities the simulated number of clusters within the range of one cluster difference from the real case (actual number of clusters). The DH index was the most consistent, while Gap/pc

in combination with WGap/pc was capable of answering the question if a multiple cluster solution was present or not.

Next, I derived subtypes of patients with schizophrenia and their unaffected siblings longitudinally in terms of cognitive functioning (composite score) and in terms of clinical symptoms. For this, in **chapter 3,** I applied group-based trajectory modeling. Five trajectories of patients were found. These trajectories were labeled as 'normal' (26.7%) as their z-scores for the composite cognitive measures were in the standard normal range; 'mild alterations' (30.4%) as their performances were 0.5 SD below normal; 'moderate impairment' (28.4%) as their z-scores ranged 1 SD below normal; 'severe impairment' (10.7%) as their z-scores were more than 1 SD below normal. A small group of patients was labeled 'high performer' (3.8%), as they performed better than healthy controls. In a similar vein, four trajectories for siblings were identified. They were labeled as 'normal' (37.6%), 'mild alterations' (25.1%), 'moderate impairment' (13.0%) and 'high performer' (24.2%). These distinct trajectories of both patients and siblings turned out to be stable and persistent over time. Impaired patients and siblings were from ethnic minorities, younger age, low IQ and exhibited poorer premorbid functioning compared to the normal group. Severely impaired patients with schizophrenia also had more severe symptomatology, (*i.e.* poorer performance on PANSS five-factor model). Next, I hypothesized that subtype of patient predicted the subtype of sibling within the sibling-patient analysis. I considered sibling subtype (multi-category) as dependent and patient subtype as independent categorical variables. Given the family structure of the data (as siblings-patients belong within the same family), clustered multinomial logistic regression analysis was conducted taking into account family membership as a random effect. Results showed the familial correlation (*i.e.* the intra-class correlation coefficient between pairs of index patients and their unaffected siblings) accounted for 27 percent of total variation. I showed that cognitive subtypes of patients significantly predicted the cognitive subtypes of siblings. The poorer the cognitive profile of a patient, the better it predicted (OR 10.07, 95% CI 4.15-24.44) that of a more cognitively impaired sibling. Similarly, patients with moderately impaired cognition predicted his/her unaffected siblings to be moderately cognitive impaired (OR 5.7, 95% CI 2.77-11.70). Another finding was that severely impaired patients predicted much less (OR 0.24, 95% CI 0.09-0.63) the sibling to be a higher performer. The relative risks of mild alterations and moderate impaired group of patients also offered less predictive value to the high performance profiles of siblings. It is conceivable that the high performance of unaffected siblings is unlikely to be predicted given the status of their paired probands.

Besides investigating the cognitive heterogeneity, I also further explored the heterogeneity in negative symptoms. Recent literature has revealed that in fact there are two subdomains of negative symptoms, typically known as social amotivation (SA) and expressive deficits (ED) (Messinger et al., 2011; Foussias et al., 2014; Liemburg et al., 2013). To date, there are few studies describing the longitudinal course of SA and ED, and conclusions are mixed (Ergul and UCok, 2015; Norman et al., 2015; Galderisi et al., 2013). In **chapter 4**, I investigated *i)* whether the course of SA and ED changed during the course of six years. Using linear mixed models, I found that both SA and ED displayed a small but significant decrease in severity over time. Next, I examined *ii)* whether baseline levels of SA and ED could predict functioning and quality of life six years later. Multiple linear regression analysis

was conducted and the results indicated that lower baseline levels of SA symptoms predicted higher levels of global functioning, of social functioning, better quality of life and more engagement in work or study activity six years later. In the same line, lower baseline levels of ED symptoms predicted higher levels of global and social functioning six years later.

I then aimed *iii)* to identify subgroups based on the course of SA and ED over a period of six years. Here, I again applied group-based trajectory modeling in order to identify the correct number of subgroups. Each of the two subdomains yielded four subgroups with differing courses of negative symptom levels. Within both subdomains, a large group of patients (±60%) with steady low levels of symptoms and two subgroups (both ±15%) with either symptom-level increase or symptom-level decrease were found. Furthermore, within SA, a small subgroup (±6%) showed decreasing symptom levels over time after having started at a higher symptom levels, whereas within the ED subdomains, another small group (±6%) was continuously experiencing high symptom levels.

I further investigated *iv)* the relationship between subgroups within SA and ED and functioning and quality of life over the course of six years. Linear and generalized linear mixed effects modeling were conducted to unravel the relationships. The stable-low SA group had better functional outcome as measured by the Global Assessment of Functioning (GAF), Social Functioning Scale (SFS) and World Health Organization Quality of Life (WHO-QOL) at all time points. The stable-low ED patient-group also performed way better on the GAF and SFS, at baseline and after three years of follow up, but not six-years after baseline. People with decreased-to-low SA-symptoms had a significantly lower chance of living independently after three years of follow up and reported higher levels of both, global functioning and quality of life after six years compared to low SA symptoms. People with an increased SA had lower chance to have a regular work activity and reported lower functioning and lower quality of life over the course of six years. In a similar way, patients with increased ED showed significantly lower chance of work activity and lower levels of functioning than low ED over time. In addition, decreased ED was associated with better global functioning over the course of six years.

In summary, results show that there is considerable heterogeneity in the course of subdomains over time and suggest that negative symptoms are less stable than was previously assumed. Subgroups were identified within SA and ED, showing a different course of symptoms over time. Moreover, the two domains are clinically relevant as they differentially relate to the level and course of outcomes.

Besides cognitive and symptoms heterogeneity, I also studied psychotic experiences in relatives of individuals with psychotic disorders. Psychotic experiences are heterogeneous over time and this heterogeneity may be explained by different factors (e.g. neuro- and social cognition). To learn more about the development of psychotic experiences over three years, I investigated factors that were known to predict psychosis. To this end, in **chapter 5**, I applied mixture of generalized linear mixed effects models to examine the reported development of psychotic experiences in siblings of people with psychosis and its relationships to neuro- and social cognition. Poorer verbal learning performance (operationalized as the score on immediate recall) predicted the occurrence of PE after three years and also the distress associated with these psychotic experiences. Moreover, better baseline performance on a hinting task, representing Theory of Mind (ToM) was associated

with a decrease in psychotic experiences three years later. Baseline distress was associated with poorer recognition of angry and neutral faces and strikingly, with better performance on the Benton facial recognition test at baseline. In conclusion, verbal learning and ToM were found to be predictive of frequency and course of psychotic experiences over three years respectively. In addition, verbal learning and ToM were also predictive of the distress that psychotic symptoms were causing.

In **chapter 6,** the heterogeneity in the domain of somatic diseases and complaints among patients with schizophrenia, their unaffected siblings and subjects from the healthy population is described. I investigated the effect of familial liability to psychosis along with gender and age on the prevalence of multimorbidity of diseases and complaints. In summary, familial liability had a significant effect on multimorbidity of complaints and lifetime diseases (with/without psychiatric comorbidity) respectively. Moreover, multimorbidity was strongly associated with female gender overall. In people with psychosis, multimorbidity was not limited to the elderly but also affected young individuals. The risk of multimorbidity caused by familial liability for psychosis was consistent across gender and age group, meaning that familial liability for psychosis is in itself a strong independent determinant of multimorbidity.

Finally, in **chapter 7,** I identified risk factors that were significantly associated with the duration of untreated psychosis (DUP). DUP is defined as the time from the emergence of the first psychotic episode to the initiation of adequate treatment. Migration status, age at onset of psychotic disorder and gender were significantly associated with DUP. In conclusion, first generation immigrant patients, individuals with an early onset of their psychotic disorder and male patients were at risk of a longer DUP. Our findings were in line with the results of a number of smaller studies (Sterk et al., 2010; Boonstra et al., 2012; Nerhus et al., 2015; Schimmelmann et al., 2008; Cotton et al., 2006). First generation immigrants seem to be less familiar with the concept of mental illness and also with mental health services (Wolff et al., 1996). They may be less likely to perceive themselves as having a psychiatric problem or to be in need for treatment (Commander et al., 1999).

From heterogeneity to endophenotype

Cognitive impairment and negative symptoms are core features of the presence and severity of psychosis (American Psychiatric Association, 2013). There is ample evidence for significant cognitive heterogeneity in schizophrenia. This heterogeneity is explained by a general loss of function, varying from patient to patient, or by impairment over the various cognitive abilities (*e.g.* executive function and working memory) (Joyce et al., 2005; Joyce and Roiser, 2007). Previous literature reported that the cognitive test performance of patients with schizophrenia was extremely heterogeneous (Goldstein, 1990; Joyce et al., 2005; Joyce and Roiser, 2007). So far, only two studies demonstrated cognitive heterogeneity in the *relatives* of patients with schizophrenia (Quee et al., 2014; Sautter et al., 1995). I extended the findings of Quee *et al*. (2014) by showing that cognitive heterogeneity in people with schizophrenia and in their unaffected siblings was stable for the long-term course.

Another type of heterogeneity (*i.e.* negative symptom heterogeneity) has also been observed in psychosis (Seaton et al., 1999; Seaton et al., 2001; Liemburg et al., 2013; Stiekema et al., 2016). In both cases, I confirmed the stable groupings of patients. The heterogeneity was confirmed by examining the relationships with course of illness, clinical, and functional outcomes. Therefore, these groupings may be considered as candidate subtypes.

Furthermore, I underpinned the arguments for cognitive subtypes to be considered good "endophenotypes" by fulfilling the following criteria (Miller and Rockstroh, 2013; Ritsner and Gottesman, 2011; Hasler et al., 2006):

i) stable trait: cognition as well as cognitive subtypes were shown to be highly stable over time and associated with illness of schizophrenia, *ii*) familial liability: the cognitive performance of family members of patients with schizophrenia is located in between cognitive performances of patients and healthy population (i.e. familial correlation), *iii*) cognitive subtypes were correlated with other clinical and socio-demographic parameters, and *iv*) cognitive functioning cannot be seen by the "naked eye". Thus, unraveling the heterogeneity of cognition yielded meaningful cognitive subtypes for both patients and their unaffected siblings, so called endophenotypes, being located somewhere between the genotype (DNA) and the phenotype (clinical symptoms).

Regarding negative symptoms as well as symptom subtypes: they are less stable but still persistent over time. Their significant relationships with other external parameters define them as subtype. However, they cannot be considered as endophenotype of schizophrenia, as they are part of the phenotype.

Not one but many forms of schizophrenias

A number of analytical techniques have been used to address the issue of cognitive heterogeneity. One option is to categorize cognitive functioning into neuro-psychologically normal and impaired subgroups based on standard cut-off scores for cognitive batteries or expert's judgment of cognitive profile (Seaton et al., 2001). However, categorizing patients into normal or impaired groups supposedly underestimates the actual heterogeneity in schizophrenia based on expert's cut-off scores. This limitation is addressed adequately using exploratory or model-based statistical techniques. Therefore, an alternative and more objective option is the application of clustering, like the model-based trajectory techniques to classify homogeneous cognitive subtypes to identify disease severity (Goldstein and Shemansky, 1995; Seaton et al., 1999; Seaton et al., 2001; Jablensky, 2006; Joyce and Roiser, 2007; Dawes et al., 2011; Quee et al., 2014). A number of studies in literature used cluster analysis (*e.g*. hierarchical or K-means) while other used latent profile analysis and reported four or five-cluster subtypes of patients with schizophrenia. These findings were stable and consistent although different studies used different test batteries (Goldstein, 1990; Heinrichs and Awad, 1993; Heinrichs et al., 1997; Goldstein et al., 1998; Seaton et al., 2001; Joyce et al., 2005; Joyce and Roiser, 2007; Bora et al., 2016). Likewise, several researchers investigated at least four potential subtypes of clinical symptoms (*e.g*. on the PANSS) of schizophrenia such as positive, negative, mixed and disorganized symptoms (Dollfus et al., 1996; Lykouras et al., 2001; Seaton et al., 2001). Moreover, there is also evidence that the negative symptoms are heterogeneous, yielding two subdomains *i.e.* social amotivation (SA) and expressive deficit (ED) (Liemburg et al., 2013; Stiekema et al., 2016). By group-based trajectory modeling, I confirmed that indeed patients are heterogeneous in both subdomains supporting the two dimensional approach of Liemburg *et al.* However, the DSM-V (American Psychiatric Association, 2013) favours one dimension.

Together with neurocognition and clinical symptoms, psychotic experiences of siblings of patients with schizophrenia are heterogeneous and are explained by neuro- and social-cognition (Appels et al., 2003; Kremen et al., 1994; Meijer et al., 2012; Quee et al., 2014; Snitz et al., 2006). In

line with the findings of our study (**chapter 5**), one study found that poorer theory of mind predicted the experience of delusions in children with auditory hallucinations after three years (Bartels-Velthuis et al., 2011). Fragmenting frequency of psychotic experiences and distress according to their true distributions and their associations with neuro-and social cognition, I conclude that psychotic experiences are heterogeneous over time. Apart from heterogeneity of clinical symptoms, I conclude that domains of somatic diseases and complaints are heterogeneous according to familial liability group as the prevalence of multimorbidity of complaints and lifetime diseases in siblings fall in between the prevalences of patients with schizophrenia and member of healthy population. One study showed the familial liability (controls<siblings<patients) as a risk factor for cognitive functioning (Krabbendam et al., 2001), although this is not the same as my conclusions on multimorbidity.

Based on findings from chapter 2 to 5, I conclude in line with Bleuler's hypothesis (1950) that there are many "schizophrenias" rather than a single form of schizophrenia (Bleuler, 1950). There are several considerations that would favor the cognition or symptom subtypes in schizophrenia rather than a continuum form of schizophrenia. First of all, the cluster analysis and trajectory modeling showed both level and pattern differences *on external variables* such as age, education, IQ, age of onset and premorbid functioning. Secondly, although there are clear differences in level of performances, the differences in average standardized cognition scores between patients and siblings are often dramatic, making it hard to imagine that there would be one underlying continuum of cognitive performance. Therefore, current data are in favor of cognitive heterogeneity containing multiple subtypes.

Methodological considerations

The strengths and limitations of the studies in this thesis have been addressed chapter-wise. Overall, the clustering techniques are appropriate to identify subtypes. The methodological strength in chapter 2 is that of applying extensive simulation studies that were based on a case study of eight dimensional measures to determine the number of clusters, making this a "real world" exercise. So far, performances of indices were studied mainly with artificial low dimensional simulated data (Milligan and Cooper, 1985; Tibshirani et al., 2001). In general, I studied only the indices which would fit best with the relative simple but frequently used methods of clustering. Thus, the study investigated the proposed indices using a sequential stopping criterion for hierarchical clustering. This means cutting the branches in the dendrogram horizontally. However, cutting branches can also be performed more dynamically making cuts higher and lower in the tree and not at the same height for the whole tree. It would be challenging and highly interesting to find out whether dynamic cutting would improve the performance of certain indices. Moreover, I focused only on Euclidean distance measure and Ward's agglomerative technique for identifying the number of clusters. It may be possible that some of the indices will provide different results when other distances or dissimilarity measures are used to merge subgroups within hierarchical clustering.

The strength of group-based trajectory modeling (GBTM) (Nagin, 2014) for analyzing developmental cognitive trajectories over time is that it is easily understood graphically and it provides simple and straightforward tabular data summaries. This method does take into account the missing outcome, covariates and patterns within the same model (Haviland et al., 2011) whilst other techniques such as growth-curve modeling or latent profile analysis do not.

Some limitations should also be mentioned in this regard. Sometimes GBTM provides a very small group of individuals which will not be representative for further analysis. For example, I found five meaningful subtypes in patients according to logged Bayes factor, but a small group of patients (3.8%) with high cognitive performance did not predict moderate impairment of siblings using sib-pair analysis. This may imply that the high performers in patients are a cluster artifact, but this is difficult to establish in unsupervised clustering.

Composite scores were computed using mean z-scores for all eight cognitive measures that were age and gender specific. We did not adjust for education as we believe that years of education is a measure, albeit rough, of "prodromal" cognitive functioning in schizophrenia. For that reason, it would not make sense to artificially control for years of education (Seaton et al., 2001).

Generating composite cognition scores might have an impact on finding meaningful trajectories instead of using multivariate cognitive tests. This is one of the limitations of trajectory modeling (Jones et al., 2001) which may deal with only one variable at a time measured over at least three assessments. Thus, here information may have been lost by using a composite score.

There may have been some selection bias in data collection with respect to patients or siblings compared to controls, as most of the controls were selected by random mailing.

Several additional limitations should also be mentioned on the subtypes for negative symptoms that were presented in chapter 4. We do not know whether changes in negative symptoms are due to relief of secondary negative symptoms, for example by reduced positive symptoms, depressive symptoms or antipsychotic medication (Carpenter and Kirkpatrick, 2015). Further, the duration between assessments is three years, which is large. Short interval may provide a clearer picture of negative symptoms persistency instead of observing at three years interval.

More importantly, there is a distinction between clusters and subtypes. If one conducts cluster or trajectory analysis and clusters/trajectories are determined, it does not mean that they reflect actual subtypes because cluster membership may be determined largely by level of performance. An extensive external validity must be established when cluster/trajectory becomes a subtype. For example, in schizophrenia, we usually want to see clinical, cognitive, neurobiological, and genetic evidence of the stability of the cluster/trajectory under study.

The assessment of psychotic experience at three-year follow-up might have been biased, resulting in observed decreases in frequency and distress of psychotic experiences. There may also be reporting bias since psychotic experiences are very personal experiences and thoughts which were assessed with a self-reported questionnaire.

The overall strength of the study is the use of a broad range of neurocognitive variables together with social cognition of healthy siblings of patients with schizophrenia, providing a comprehensive picture of the possible factors related to psychotic experiences. The methodology of using a mixture of generalized linear mixed effects models is unique for the predictive values of neuro- and social cognitive parameters on psychotic experiences. Measuring psychotic experiences in siblings yielded lot of zeros (i.e. no experiences) together with psychotic experiences ranging from 'sometimes' to 'nearly always'. In this situation, the weighted scores of psychotic experiences displayed a highly heterogeneous distribution function. Dealing with the heterogeneous outcomes, a

mixture of generalized linear mixed effects models (Tooze et al., 2002) would provide unbiased results.

The multimorbidity study was mainly based on self-reported diseases, clinical complaints and medication history. There might be a reporting bias regarding the diagnosis of the disease. The operational definition of multimorbidity is another concern. The majority of studies have defined multimorbidity as two or more, whereas others counted three or more concurrent diseases (Fortin et al., 2005; Jacobi et al., 2004; Fuchs et al., 2012; Willadsen et al., 2016). In this thesis, multimorbidity is defined as two or more diseases or complaints. Another concern is that I considered only gender, age and familial liability, leaving out other reported multiple risk factors (Agborsangaya et al., 2012; De Hert et al., 2011) for multimorbidity.

One of the strengths of this study was statistical methodological point of view. I applied generalized linear mixed effects models taking into account family structure as random effect to identify the risk factors for multimorbidity in psychosis. Additionally, this is the first study which has dealt with a comprehensive list of diseases, either somatic or psychiatric, in schizophrenia patients while counting multimorbidity in a cumulative way rather than focusing only on pairwise comorbidities (Nuyen et al., 2006; Oreski et al., 2012). The most informative feature of this study was the sibling model; whereas most studies emphasized multimorbidity either in healthy subjects or the disease population.

A major strength of duration of untreated psychosis (DUP) is the use of a statistical model that takes into account the effect of other candidate factors. I applied ordinal logistic regression for categorical DUP and a sensitivity analysis using Cox-proportional hazards model for time-to-event DUP. Modeling the data with equally valuable tools and then showing consistent results, makes the conclusion on the significant association of first generation migration status and age at onset of the psychotic disorder with DUP stronger than just using one analysis technique. One of the concerns is that categorization of DUP; there are no agreed-on cutoff points (Marshall et al., 2005). Other concerns of the results are that DUP was defined retrospectively and that data collection relied on self-reports.

There is a potential loss of statistical power and efficiency when missing data are present. This may lead to biases and incorrect statistical inferences. In chapter 4 and chapter 5, there were missing data both on outcomes and independent variables. Both chapters are assumed that the missingness is conditional on the observed data but independent of the unobserved values, which is called missing at random (MAR) (Allison, 2002). Maximum likelihood (ML) and multiple imputation (MI) (Rubin, 1987) methods usually handle the missingness under MAR. I employed a fully conditional specification (FCS) predicted mean matching (PMM) multiple imputation (MI) method to impute missing values for both continuous and categorical variables (van Buuren, 2007) and analyzed the data with appropriate statistical models. Apart from PMM, Bayesian MI method is another good approach to handle missingness under MAR assumptions. It uses an iterative algorithm to impute data and it splits the multivariate missing problem into a series of univariate problems based on the assumed distribution of the multivariate missing variables (e.g. multivariate normal for continuous variables, multinomial loglinear for categorical variables) (Schafer, 1997). However, if the missingness is Missing Not At Random (MNAR), i.e. missingness depends on the unobserved data and missingness

is no longer ignorable, a model for the probability of missing data needs to be specified. This probability model is then combined with a linear mixed model for the measurement process. Selection and pattern mixture models are two alternative and important approaches for dealing with MNAR. A selection model is the joint distribution of the measurement and the missing mechanisms into the marginal measurement distribution and the dropout distribution conditional on the measurements (Thijs et al., 2002; Verbeke and Molenberghs, 2000). A pattern-mixture model is the joint distribution of the measurement and response mechanisms into a different measurement model for all response patterns, and the marginal response distribution (Thijs et al., 2002; Michiels et al., 2002; Verbeke and Molenberghs, 2000). Pattern mixture model is a sensitivity analysis within a fully Bayesian modeling framework that could be used to handle the missingness under MAR (Little, 1995; Little, 1993; Michiels et al., 2002; Thijs et al., 2002).

Which clustering technique to use?

There are several clustering algorithms and each of them uses different induction principles. Literatures suggest that clustering methods are categorized into hierarchical, partitioning methods, model-based and grid-based methods (Fraley and Raftery, 1998; Han and Kamber, 2001; Fraley and Raftery, 2002; Estivill-Castro and Yang, 2000; Rokach and Oded, 2005).

A strength of hierarchical cluster analysis is that it always confirms that the most similar observations are in the same clusters. However, this is also its major weakness. Once a cluster is made, the observations within this cluster will never be relocated to other clusters. This problem does not occur with partitioning methods *e.g.* K-means or K-medoids. Additionally, partitioning methods are easy to interpret, simply to implement and faster to compute with large datasets. However, this method is sensitive to noisy data and outliers. Model-based or density-based methods, *e.g.* latent class/profile analysis, trajectory and growth-curve modeling, assume that observations would come from a mixture of distributions (Muthen and Shedden, 1999; Muthen and Muthen, 2000; Rokach and Oded, 2005). Latent class/profile analysis, trajectory or growth-curve modeling are subject-specific finite mixture modeling approaches, meaning that the focus is on the subject's unique pattern of characteristics and therefore focuses largely on identifying subtypes of individuals with similar patterns (Muthen and Muthen, 2000; Rokach and Oded, 2005; Jung and Wickrama, 2008). The model-based approaches assume a certain type of mixtures of distributions, while partitioning methods do not make any assumption on the distribution. Thus, the model-based approaches are theoretically superior to any other approaches when the distributional assumption is known. The algorithm takes into account the uncertainty when allocating observations to clusters. These approaches use to estimate the posterior probabilities that an individual will be categorized into a particular group of risk patterns (Shah et al., 2014). However, all approaches need a pre-defined number of clusters. Hierarchical clustering can be considered a prior analysis of K-means or latent profile analysis in cross-sectional studies and this thesis showed that it may be suitable to detect the number of clusters. Other clustering approaches e.g. decision trees, neural networks and grid-based methods are beyond the scope of this thesis.

Clinical implications

Cognitive functioning is moderately to severely impaired in patients with schizophrenia and their unaffected siblings and more than 80% of patients show significant impairment (Keefe and Fenton, 2007; Keefe and Harvey, 2012; Quee et al., 2014). This impairment group has an impact on outcomes such as occupational, social, clinical and economic functioning and emergent for treatment target. Research for pharmacological treatment is ongoing for improving cognitive function in schizophrenia but the results are not very convincing so far (Keefe and Harvey, 2012; Marder, 2006). The psycho-social intervention programs *e.g.* Cognitive Remediation (CR) is likely to be a safer way to improve cognitive functioning than pharmacologic treatment. The CR program produces modest improvements for patients with schizophrenia (Bora et al., 2009; Keefe and Harvey, 2012). Subtyping patients, especially severe cognitive impaired and severe symptom group, may be eligible for psychosocial interventions. A promising approach is cognitive adaption treatment (CAT), a method that takes into account the persistency of the cognitive impairments, while providing practical means to overcome these handicaps in real life situations (Quee et al., 2014).

Attention should be taken on subdomains of negative symptoms, especially when patients are severely ill. Evidence suggests there are deficits in anticipatory pleasure and defeatists beliefs from SA (Messinger et al., 2011; Foussias and Remington, 2008). Cognitive Behavioral Therapy (CBT) may be a suitable intervention for changing these beliefs. In addition, learning to anticipate on the experience of pleasurable events could possibly reduce SA. In this thesis, a significant association of ED with functioning was found after controlling for neuro-cognition. Therefore in chapter 4, we suggested that interventions targeting expressive skills such as Social Skills Training (Shean, 2009), could possibly improve ED. Though there is debate on the effectiveness of Social Skills Training, it has shown to be more effective in reducing negative symptoms than other psychosocial interventions (Turner et al., 2014).

Additionally, chapter 7 demonstrated that DUP was longer for patients being younger at onset of the psychotic disorder, for first generation immigrant patients and for male patients. Literature showed that longer DUP predicts worse symptoms at admission (Drake et al., 2000). Early implementation of intensive psychosocial intervention services may be necessary to shorten DUP, since the effect of DUP on recovery is greatest in the early stages of illness.

Future directions

Directions for statistical development

I elaborated the methodological aspects of several indices of hierarchical clustering technique using simulation studies in chapter 2. Overcoming some limitations of hierarchical and partitioning clustering, it would be of interest to use a multivariate finite mixture model, which classifies observations on the basis of probability estimated from Gaussian mixture modeling in cross-sectional studies. This method produces posterior distributions of all cluster parameters, proportions and cluster membership probabilities for all subjects (Kass and Raftery, 1995; Raftery and Dean, 2006). It would also be of interest to use clustering approach on multivariate non-normally distributed data (e.g. mixtures of other distributions).

Another focus would be extending clustering indices and apply those indices to trajectory modeling framework to confirm the number of subtypes (chapter 3 and 4). The performance of group-based trajectory analysis over growth-curve modeling and linear mixed effects modeling is less well known. Therefore, future studies may investigate the performance of group-based trajectory modeling on the selection of clusters using extensive simulations. So far, no one has investigated how well GBTM would detect the number of clusters and the trajectories in finite studies.

In longitudinal data, most methods deal with just one outcome variable over time to determine the number of clusters. It might be of a great interest to develop multivariate longitudinal clustering techniques, i.e. extending the group-based trajectory modeling to multivariate outcomes over time. For example, in this thesis, eight cognitive tests are formed into one composite measure to be able to identify the number of clusters and its trajectories. I would expect more subtle trajectories and different clusters if eight cognitive tests could be jointly incorporated into the trajectory modeling over time.

Another improvement area would be the integration of models for missingness with clustering or trajectory modeling. Throughout the thesis, I assumed the missing mechanisms to be MAR. It is not examined whether the missing mechanism is MAR or not, since it is impossible to verify if it would be MNAR. However, it would be highly interesting to model clustering technique in combination with MNAR models, but this requires more research on realistic missingness models in schizophrenia research.

Directions for clinical research

There is still abundant room for improving clinical research. Clustering cognitive functioning and symptoms longitudinally in such a way that all observations would be clustered at all time points separately, and transition between time points would be modeled by Markov transition matrices. This indicates that clustering of one time point will be affected by what chances at the adjacent time points (Franzen, 2008).

Phenotypically patients with schizophrenia and their unaffected siblings are cognitively heterogeneous. It may be beneficial to investigate the genetic effect on subtypes to confirm the true cognitive subtypes. This is an exciting, new chapter in research, now that polygenic risk scores have become available also for schizophrenia (Schizophrenia Working Group of the Psychiatric, Genomics Consortium, 2014). It would also be interesting to study whether the cognitive profiling approach is predicting functional and clinical outcomes over time.

It would be informative to use shorter follow-up times to study the effect of SA and ED on functioning, clinical outcomes and quality of life. In chapter 4, I demonstrated the effect of individual subtypes of SA and ED on outcomes over time. But symptoms of SA and ED tend to co-occur (Hartmann-Riemer et al., 2015) and may reinforce each other (Goekoop and Goekoop, 2014). Future studies should investigate in such interaction between subtypes of SA and ED, which may provide insight in the relationship with outcomes.

For future research it might be interesting to monitor psychotic symptoms of genetic high risk group more frequently (e.g. half-yearly) over time and study associations with neuro- and social cognition. Such analysis will be possible within the recently started Early Detection Study in the

Netherlands (see www.rgoc.nl/ontheroad). Additionally, one could study the discrete level of frequency and distress of psychotic experiences to observe the association with neuro- and social cognition instead of using continuum score of frequency and distress of psychotic experiences using generalized linear mixed effects modeling.

In chapter 6, I demonstrated that familial liability is one of the main determinants of multimorbidity which acts independently of the other major risk factors of age and gender. It was reported that the familial correlation between siblings and index patients were 11 to 16%. It should be essential to perform additional genetic analysis to distinguish between the effects of genetic liability and intra-familial environmental susceptibility on multimorbidity, applying polygenic risk scores for schizophrenia and other complex disorders in the same population.

Finally, it would be of interest to explore whether ethnicity plays part in the association between DUP and migration status. In addition, compelling literature indicates that there is an association between a shorter DUP and positive and negative symptoms, functional outcome and quality of life (Perkins et al., 2005; Boonstra et al., 2012). Therefore, a longitudinal study should be warranted to see whether an association between DUP and changes in functioning and symptoms exist.

Concluding remarks

The current thesis describes a number of new findings on the heterogeneity in cognitive functioning and clinical symptoms in schizophrenia patients and their unaffected siblings- with a special emphasis on the statistical approaches that were applied. In cross-sectional study-designs, hierarchical clustering with Duda and Hart (DH) index is the best approach to determine the number of clusters; however, model-based clustering approach would be preferable to confirm these clusters. In longitudinal studies, group-based trajectory modeling under finite mixture modeling is the best approach for summarizing and graphical representing of distinct trajectories.

Using these approaches, this thesis clearly underlined the validity of cognitive subtypes of patients and four subtypes of siblings, being stable and persistent over time and putting forward new clinical insights. Similarly, this thesis extent our knowledge on negative symptoms subtypes of SA and ED respectively, by demonstrating the performances of these subtypes being persistent on clinical and functional outcomes over time.

Another application of mixture of generalized linear mixed effects modeling on zero-inflated continuous outcome of psychotic experiences of siblings helped us to explain this outcome by the neuro-and social cognitive functioning, while at same time this yielded valuable insight in the clinical development of psychotic symptoms over a three-year time.

Psychotic experiences and symptoms may be on a continuum, reaching from the general non-ill population all the way to the schizophrenia spectrum disorders. Findings in patients and their non-affected siblings however confirm that for both cognition and negative symptoms heterogeneity exists and meaningful subtypes can be identified. These subtypes may provide new avenues to better understanding and more effectively treating people with psychotic disorders.

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