Obsessive compulsive symptoms in psychotic disorders

Swets, M.

Link to publication

Citation for published version (APA):
Summary and General Discussion
Chapter 12

SUMMARY

INTRODUCTION

The aim of the current thesis is to evaluate differences and similarities between schizophrenia patients with or without obsessive compulsive symptoms (OCS). Relevant sub-questions are: Can OCS in patients with schizophrenia be identified as a specific risk for other comorbid characteristics? Is treatment with antipsychotics associated with OCS in patients with schizophrenia? What is the 3-year course of OCS in patients with schizophrenia and are changes in OCS associated with other illness features?

To provide answers to these questions, we performed first of all a meta-analysis followed by a metatregression, which presents an overview and re-analysis of the results on prevalence rates of OCD and/or OCS from previous studies. All other papers use data from the Genetic Risk and Outcome of Psychosis (GROUP) study (1). The GROUP-study included approximately 1000 patients with schizophrenia or related disorders, 1000 un-affected siblings and parents of these patients, and 1000 healthy controls. A large set of tests was conducted, assessing a wide range of variables. When possible participants were reassessed after 3 and 6 years. In this thesis we identify cross-sectional and longitudinal associations between obsessive compulsive symptoms (OCS) and obsessive compulsive disorder (OCD) and other illness-related features in patients with schizophrenia or related disorders. We were able to adjust for illness related factors by repeating analyses in patient’s healthy siblings, when possible. Previous studies found that, in terms of psychotic symptoms and other schizophrenia related features, siblings score better than the patients but worse than the general population. Because siblings have not been exposed to medication and other illness related influences, exploring whether or not patients-features are also found on a sub-clinical level in their healthy siblings is important to “correct for” these potential influences.

The obsessive compulsive spectrum in schizophrenia, a meta-analysis and meta-regression, exploring prevalence rates

- What is the prevalence of OCS and OCD in schizophrenia according to the combined literature, and what variables influence this prevalence?

In Chapter 2 we performed a meta-analysis and meta-regression to determine a valid prevalence estimate of OCD and OCS in patients with schizophrenia and related disorders and identify factors influencing the prevalence. Our meta-analysis included 43 studies providing information on OCD or OCS prevalence rates in patients suffering from schizophrenia, and calculates a mean weighted prevalence rate of 12% for OCD and 30% for OCS. However, the difference in prevalence rates between the studies is very large. Five variables significantly influenced the prevalence of OCD: “sub-Saharan African study origin” and OCD assessment using the Diagnostic Interview for Genetic Studies (DIGS) are associated with a lower prevalence rate whereas a longer duration of psychotic illness, Y-BOCS assessment and
use of the DSM-IV instead of older DSM versions are associated with a higher OCD prevalence rate. Results show that in the case OCD was assessed in a more elaborate way, specifically when the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used, the prevalence rates are higher. Introducing these five variables, sub-Saharan African study origin, illness chronicity, use of DSM-IV, DIGS and Y-BOCS assessment, as confounding variables in the analyses results in a very significant reduction of heterogeneity, indicating the important influence of these variables on prevalence rate results. These results lead to the conclusion that the Y-BOCS is a reliable instrument to assess severity of OCS or OCD in patients with psychotic disorders. We assume in the case that no OCS-specific instrument is used, OCS or OCD are easily missed in patients with schizophrenia. Furthermore, a longer duration of psychotic illness is associated with more OCD, indicating that OCS prevalence in patients with recent onset schizophrenia is likely to differ from patients with a chronic illness. In fact this is an interesting ‘time’-effect. Very few longitudinal studies have been conducted on OCS in schizophrenia, so knowledge about OCS in schizophrenia is based on cross-sectional associations. However, the limited prospective data suggests that both schizophrenia symptoms and OCS both tend to change over time. With the evaluation of the results of the GROUP-study with its prospective design, I was able to shine some light on this aspect which will be further discussed in the discussion section.

The meta-analysis also showed that when different Y-BOCS cut-off scores are used in defining different levels of OCS severity, the prevalence of OCS is roughly inversely proportional to the value of the cut-off score used. OCS prevalence decreases as cut-off scores are set higher (more severe symptomatology). Put in a different way, like many co-morbid symptoms, OCS in schizophrenia tends to occur on a continuous Scale: having more severe OCS symptoms gradually becomes less prevalent (as opposed to a dichotomous presentation, with either no symptoms or a full-blown syndrome).

**The Group Data**

Facture structure of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) in a large sample of patients with schizophrenia or related disorders and comorbid obsessive-compulsive symptoms

- Is the factor structure of the Y-BOCS in schizophrenia patients with OCS is comparable to the factor structure found in OCD patients?

In Chapter 3, a factor analysis of the Y-BOCS reveals that OCS in patients with schizophrenia have a very similar OCS symptom pattern, compared to OCS in the general population. On the one hand there is a strong relation between obsession-related items, on the other hand, there is a strong relation between compulsion-related items. This two factor solution, with obsessions and compulsions as the two separate factors, is consistent with the originally proposed scoring structure of the Y-BOCS and provides the optimal fit in the GROUP patient population. Similar to results in the general population we also find some support for a three-factor solution, in which the two resistance items, resistance to
obsessions and resistance to compulsions, load on a third factor.
In sum, this study shows that the Y-BOCS is a reliable instrument to assess OCS severity in patient with non-affective psychotic disorders. Combined with the findings of the meta-analysis in chapter 2 we conclude that the Y-BOCS is a reliable instrument for assessing OCS severity in both patients with and without schizophrenia.

CROSS-SECTIONAL RESULTS

Evidence for a shared etiological mechanism of psychotic symptoms and obsessive-compulsive symptoms in patients with psychotic disorders and their siblings

- What is the prevalence rate of OCS in schizophrenia patients and their siblings? Do OCS cluster in families? Are (sub)clinical psychotic features in unaffected siblings associated with OCS in the related patient or the other way around?

After establishing that the Y-BOCS is a reliable instrument to assess OCS in patients with schizophrenia, we analyze the cross-sectional data from the first assessment of the GROUP study. In Chapter 4 we compare OCS prevalence rates in patient with prevalence rates in controls and in their unaffected siblings. In the healthy siblings, instead of psychotic symptoms, subclinical symptoms are assessed. The general hypothesis is that siblings hold an in-between position, with more frequent OCS and psychotic symptoms than in controls, but less frequent occurrence than in patients. We find the following prevalence rates of OCS in the GROUP-sample at the first assessment: 19% of the patients, 4.3% of the siblings and 2.9% of controls had Y-BOCS scores >9. Compared to controls the prevalence of OCS is significantly higher.

Furthermore the design enables cross-sib cross-trait associations on OCS and psychotic symptoms. The cross-sib cross-trait analysis studies the potential association between OCS in one sibling, comparing it with psychotic symptoms or subclinical symptoms in the other sibling. In case the presence of OCS in one sibling proves to be associated with psychotic or subclinical symptoms in the counter sibling, this would be compatible with a shared etiological mechanism between OCS and psychotic symptoms. In the GROUP data we find a cross-trait association in patients with schizophrenia and related disorders and their siblings on a trend level. In order to obtain enough power, OCS inclusion criteria were reduced to Y-BOCS score >0. In patients OCS is associated with more severe positive subclinical symptoms in siblings. However, the association lost significance after adjusting for confounders. If these results would reach significance in future studies, this would implicate that OCS and psychoses are genetically related or influenced by a shared environment.

Finally within trait, cross-sibling analyses show that if one sibling suffers from OCS, the counter sibling has a higher chance of having OCS as well. OCS clusters in families of patients with a psychotic disorder.
In this respect, OCS does not differ from the non-psychotic population, in which OCS tends to cluster in families as well. Apparently the fact that somebody also suffers from a psychotic disorder doesn’t alter this.

In summary, in line with results of previous studies, siblings of patients with schizophrenia have an elevated risk of developing OCS compared to controls. OCS in one sibling is associated with OCS in the counter sibling. Finally, without correction for confounders, OCS in patients with non-affective psychotic disorders is associated with more subclinical symptoms in their related healthy siblings. These last results, together with the fact that the OCS prevalence in sibs is higher than in healthy controls is an indication for a, probably genetic, etiological mechanism.

**Exploring associations of OCS with other co-morbid and illness related features:**

- **Obsessive-Compulsive symptoms in patients with schizophrenia: a naturalistic cross-sectional study comparing treatment with clozapine, olanzapine, risperidone and no antipsychotics in 543 patients**
  - Are different antipsychotics associated with different prevalence rates of OCS in patients with schizophrenia?

Anti-psychotic medication is known to influence OCS, sometimes aggravating, sometimes alleviating it. Clozapine specifically has been reported to cause OCS. Therefor in **Chapter 5**, the prevalence rates of OCS in patients with schizophrenia using clozapine, olanzapine, risperidone and those not taking antipsychotics are compared. Patients taking clozapine reported significantly more OCS (i.e., 38.9%) compared to the other groups (olanzapine (i.e. 20.1%), risperidone (i.e., 23.2%) or no antipsychotics (i.e., 19.6%)). This difference was particularly large in patients taking clozapine for a longer period of time (>6 months) (i.e., 47.3%), compared to patients taking clozapine for a short period of time (i.e. <6 months) (i.e., 11.8%). These results indicate that clozapine may play a role in the emergence of OCS in a subsample of patients with co-morbid OCS and that clozapine use should always be checked as possible etiological factor for the development of OCS.

- **Substance use in a large sample of patients with schizophrenia or related disorders and co-morbid obsessive-compulsive symptoms**
  - Does the prevalence of substance use differ between schizophrenia patients with OCS and without OCS?

**Chapter 6** addresses the association between OCS and substance abuse (i.e., use of nicotine, alcohol, cannabis and hard drugs) in patients with schizophrenia and related disorders. Lifetime prevalence of substance use disorder (SUD) in the general population is higher in patients suffering from OCD, with a possible exception for smoking. Substance abuse is strongly associated with schizophrenia. We expected the combination of OCS and schizophrenia to result in an even higher SUD prevalence. However, to our surprise, in our sample of patients with schizophrenia, unlike in the general population, no association
was found between OCS and substance use. The reason why OCS is not associated with substance use in a population suffering from non-affective psychosis is not clear. Both substance abuse and OCD are present much more frequently in a population suffering from non-affective psychosis compared to the general population. While it is plausible that tension caused by OCD in the general population prompts a patient to take, for instance, alcohol or other drugs in order to relieve tension, in psychotic patients, psychotic symptoms cause tension themselves and may thereby obscure the OCD effect on the propensity to use substances.

**Is a schizo-obsessive subtype associated with cognitive impairment?**
- Do patients with psychotic disorders and comorbid OCS show a specific cognitive profile?

Both schizophrenia and OCD are associated with cognitive impairment at specific tasks. In chapter 7 we evaluated the association between different cognitive performance tasks and OCS, in patients, unaffected siblings, their parents and controls. As was the case with substance abuse, we did not find a specific association between OCS and a set of 10 cognitive tasks. This contrasts with most previous studies, which tended to find an association between OCS and poorer cognitive functioning. The majority of those studies though, demonstrated a rather nonspecific cognitive profile, with marginally significant results, present in a single cognitive domain, possibly confounded by higher levels of symptomatology, such as more positive or negative symptoms.

In summary, in contrast to several previous studies, no specific associations were between OCS in a population suffering from non-affective psychosis was found with substance use or cognitive performance. Given the strengths of our study design (a large number of participants, a less select sample than in former studies, an elaborate set of assessments making it possible to explore associations in considerable detail, and correcting for relevant confounders), I think that our results are more robust and reliable than former findings.

**Longitudinal results; comparing baseline data and data at three year follow-up:**

After the release of the data of the first follow-up assessment, we were able to study the (in)-stability of OCS or co-occurrence in patients and their siblings. Secondly, this makes it possible to study longitudinal associations between OCS and other clinical variables. Patient groups are defined according to the course of OCS, as either stable with or without OCS at the two assessments or changing, with OCS at just one of the two assessments.

**Obsessive-compulsive symptoms and overall psychopathology in psychotic disorders:**
- Which psychotic symptoms are associated with OCS, and how do they evolve over time in patients with psychotic disorders and their unaffected siblings?
In **Chapter 8**, we compare positive and negative psychotic and affective symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS (2)) in patients and the Community Assessment of Psychotic Experiences (CAPE (3)) in siblings and general functioning as measured with the Global Assessment of Functioning (GAF (4))-scale between individuals with and without OCS at baseline and follow-up. At follow-up the results of *chapter 4* remain fundamentally unchanged; OCS is associated with poorer functioning as measured with the GAF and with more severe psychotic symptoms. In order to investigate the effect of the emergence and the remission of OCS on symptoms of schizophrenia, we divided the patient population into four groups according to the course of OCS: a no-OCS group, a OCS-remission group, with OCS only at baseline, an OCS de novo group, with OCS only at follow-up, and a persistent OCS group, with OCS at both assessments, making it possible to take a closer look at the ‘change’-groups. We assumed that co-occurring symptoms would co-vary over time. The remission of OCS is associated with an improvement of psychotic symptoms and functioning, while the de novo emergence of OCS is associated with higher clinical impairment, which was already present before the onset of OCS. In siblings we find similar results on a subclinical level. Psychotic symptoms and functioning and OCS do seem to co-vary, but not always simultaneously. The onset of OCS appears to develop over a longer period of time in patients with relatively severe psychotic symptoms.

**Longitudinal association between motor and obsessive-compulsive symptoms in patients with psychosis and their unaffected siblings**

- Is OCS associated with specific motor symptoms and how does this association develop over time in relation with the OCS in schizophrenia patients and their unaffected siblings?

In **Chapter 9** we look at the association between OCS and motor symptoms (i.e., parkinsonism, akathisia, dyskinesia and dystonia) in patients and siblings. Parkinsonism is a condition of tremor, motor rigidity and poverty of motion. Akathisia is a feeling of restlessness and an urgent need to move. Dyskinesia is a condition of involuntary repetitive dyskinetic movements. Catatonia is a state of immobility and dystonia consists of sustained or repetitive muscle contractions. Previous studies found that motor symptoms are associated with OCS in schizophrenia patients, but again different studies showed mixed results. Similar to the cross-sectional results, described in Chapter 6 and 7, which show no significant association between OCS and cognitive functioning or substance abuse, we find no specific association between OCS and any of the four assessed motor symptom domains. Surprisingly, at follow-up, we do find an association between OCS and akathisia and the composite motor scale. In siblings we find the same association, but at baseline.

Again, to evaluate covariation of OCS and motor symptoms in time we evaluated four groups, a no OCS group, OCS remission group, a OCS de novo group and a persistent OCS group. This reveals that at baseline the OCS-remission group has less severe akathisia, no more than the no-OCS group. Compared to the no-OCS group, the OCS de novo group already has more severe akathisia at baseline. At follow-
up the OCS de novo group remains having relatively more severe akathisia, while the OCS remission group remains having less severe akathisia at follow-up. Clinicians should be aware that in case of the presence of comorbid OCS schizophrenia patients may be at risk of developing akathisia, since akathisia can be misdiagnosed as psychosis related agitation (and thus needing a completely different treatment approach), and since akathisia causes great discomfort to the patient.

**Longitudinal association between cognitive performance and obsessive-compulsive symptoms in patients with psychosis and unaffected siblings**

- What is the longitudinal interrelation between OCS and cognitive functioning and are the patient results mimicked in their healthy siblings?

In Chapter 10 we studied the longitudinal association between cognitive functioning and co-occurring OCS. While Chapter 7 reports no significant association between OCS and performance in several cognitive tasks, longitudinal data on cognitive tasks are specifically interesting, because comparing performances over time provides information on cognitive improvement and learning abilities. In line with earlier cross-sectional results, group comparisons reveal no significant group differences at baseline or follow-up. Subsequently, changes in task performance were investigated and compared between earlier defined OCS groups. The OCS de novo group and the persistent OCS group show no significant improvement over time on cognitive task performance, whereas the no OCS group and the OCS remission group do improve. The no OCS group shows improvement on the Wechsler Adult Intelligent Scale (WAIS) tasks digit-symbol coding, block design, information and on the Word Learning Task (WLT) immediate recall (5). The OCS remission group shows significant improved cognitive performance on the digit-symbol test and the immediate verbal recall. The OCS de novo group shows no significant changes, but a significant decrease in the retention rate of the WLT. It appears that remission of OCS is associated with an improvement of cognitive performance.

**Patterns of obsessive-compulsive symptoms and social functioning in schizophrenia; a replication study**

- Can two distinct groups of schizophrenia patients with comorbid OCS be identified, one with poor functioning and one with superior functioning?

In Chapter 11 we perform a replication study. Lysaker et al. used cluster analysis and found that patients with schizophrenia spectrum disorders with comorbid OCS can be divided in two groups: one with good social functioning, less severe negative symptoms and good cognitive performance and one with poor social functioning, severe negative symptoms and worse cognitive performance. This provides a good explanation for the often contradictory results found in research examining the association between OCS and functioning, negative and cognitive symptoms. In an almost 10 times larger sample we partly replicated Lysaker et al.’s findings. We also found a comorbid OCS group with good functioning and less severe negative symptoms than other clusters with poor functioning. However unlike in Lysaker et al.’s study, we find no significant differences on the level of negative symptoms between the two good
functioning groups, while their study found that the comorbid OCS group with good functioning did have significantly lower levels of negative symptoms compared to the no-OCS good functioning group. Neither do we find more cognitive dysfunction in the comorbid OCS group with poor functioning. Moreover, we did not find evidence for a superior prognosis in the comorbid OCS good functioning group, as Lysaker et al. suggested might be the case. Taken together, our results support the idea that co-morbid patients can be clustered into groups with poor or good functioning and that the good functioning group shows less severe negative symptoms. However, in these patients having comorbid OCS doesn’t seem a marker of an exceptional good prognosis.

Taken together our longitudinal studies show that OCS is not a stable comorbid condition in patients with schizophrenia, but tends to fluctuate. It appears that remission of OCS is associated with better performance on cognitive tasks and with less severe psychotic symptoms, while more severe akathisia and poorer functioning is associated with the emergence of OCS at follow-up.

**Discussion**

At the beginning of the GROUP project in 2004, in concordance with many clinicians and researchers, I viewed psychiatric disorders mainly in a categorical way. Schizophrenia was regarded as a clearly defined disorder with distinct borders, as an entity that is stable over time and well distinguishable from other disorders. Diagnostic developments were directed at identifying and defining new and more refined (sub-)categories, with a distinct course of illness and a stable subset of co-existing variables. Researchers and clinicians assumed that this further refinement would lead to a more specific and adequate treatment. Because of the high co-occurrence between OCS and schizophrenia it was hypothesized that the “schizo-obssessive” subtype might be such a subtype. Over time, focus has shifted from clear-cut diagnostic categories toward a dimensional approach, which appears to be more in agreement with the broad and ‘messy’ pattern of psychopathological phenomena that occur both within and across different disorders that we see both in research and in clinical practice, which was confirmed in my own growing clinical experience. As pointed out by Owen et al. (6), research results indicate that genetic risk is multi-causal on the one hand and highly pleiotropic on the other. Pleiotropic means that “one gene can affect multiple seemingly unrelated phenotypic traits and does not map onto existing definitions of disease”. Studies show that there exists a significant sharing of risk factors between schizophrenia, ADHD, depression, autism and bipolar disorder. The same appears to be true for OCD. Meier et al. (7) found that a previous OCD diagnosis is associated with an increased risk of developing schizophrenia and offspring of parents with OCD have an increased risk of developing schizophrenia as well. This all seems to indicate that a genetic overlap between both disorders is plausible. Taking this into account it is not surprising that OCS and psychosis are frequent co-morbid features.

Despite the potential genetic overlap between OCS and schizophrenia and despite the fact that
symptoms in schizophrenia seem to be less stable than the criteria might suggest, the cluster of obsessive compulsive symptoms still are distinguishable from psychotic symptoms (with the exception of overlaps between obsessions, compulsions and psychotic symptoms that are sometimes found). Factor analysis shows that OCS in patients with schizophrenia behave in a similar way as OCS in the general population, indicating that OCS in patients with psychotic disorders are comparable to OCS in other populations. The fact that the content of obsessions is generally very different from the content of delusions helps distinguishing between the two. In conclusion: schizophrenia and OCS frequently co-occur and probably share some common etiological factors, but clinically they are well distinguishable in most cases.

The co-presence of OCS in schizophrenia should not be regarded as an expression of a distinct subtype, with a distinct course and set of co-occurring features, but rather as different expressions of psychopathological processes and/or interactions between symptoms. The results of the thesis indirectly support this hypothesis; first, OCS tends to fluctuate substantially, instead of being a stable set of accompanying symptoms. Second, we find no specific cognitive profile or other sets of stable co-occurring features. Although no specific set of co-occurring features is found, comorbid OCS are associated with general worse functioning, more depressive symptoms and more positive and negative symptoms. This is compatible with a more severe expression of the psychotic disorder. Despite the fact that the OCS-patient group as a whole shows more severe symptoms, there is a substantial subgroup of patients with OCS which is functioning relatively well. This indicates that major differences exist between patients within the “comorbid OCS” patient group.

**Obsessive compulsive symptoms in patients suffering from schizophrenia**

The results of these studies indicate that OCS in schizophrenia is associated with different origins. It may be treatment related, but a person who is liable to develop schizophrenia is also liable to develop other psychopathology such as OCD, and the associated disease processes are complex and diverse (6). I will now discuss a tentative model of the association between psychosis and OCS, in which our own findings are integrated. It is clear (though unfortunate) that not all questions have been answered, but I hope the work in this thesis will help to elucidate the interplay between these domains.

Medication related OCS. Clozapine is associated with OCS in schizophrenia particularly if administered for a longer period of time. The association between OCS and clozapine in patients with schizophrenia has been described before and is in GROUP it is one of the few associations we were able to replicate. Furthermore, we were able to make a distinction between recent and chronic clozapine use. We found that only chronic clozapine use is associated with OCS. It is estimated that patients taking clozapine for over 6 months have about a 3 times higher OCS prevalence compared to patients not taking antipsychotics.

Different presentations of OCS over time: We identified three groups of OCS-patients with potentially different course patterns. The first group consists of patients with OCS at baseline, but remission
of their OCS at follow-up, the second group consisted of patients with OCS only at follow-up and the third group of patients with persistent OCS. In general, the OCS remission group appears to have a relatively favorable illness course. After remission their performance and their symptoms improved. In case of motor symptoms, the OCS remission group had already fewer symptoms compared to the other OCS groups at baseline. Patients with OCS de novo, at the other hand, tend to have a less favorable course of illness. In case of the OCS de novo group, signs of a less favorable course are present even before the emergence of the OCS with, on average, poorer performance and more severe symptoms. In fact this result is in line with the result of our meta-analysis showing that chronicity of schizophrenia is associated with more OCS. The persistent OCS group, though smaller in number and with less significant results as a consequence, shows a pattern very similar to OCS de novo group. It has more severe symptoms and poorer performance compared to the no-OCS and the OCS remission group. Because of the similarities we propose that the OCS de novo group and the persist group best be regarded as one group. Possibly, these two different presentations of OCS over time do not share the same pathological pathways and might be the expression of different phenomena. In some cases, specifically early during the illness, OCS might be a transient phenomenon, not associated with poorer functioning or positive psychotic symptoms. At the other hand, persistent OCS and OCS developed after several years of illness may be associated with a severe form of schizophrenia. This expression of OCS could be a sign of a more extensive illness process indicating more substantial vulnerability to different expressions of psychopathology, OCS included.

**METHODOLOGICAL CONSIDERATIONS**

**Strengths**

The GROUP study has many strong points. First, the inclusion of over 1000 patients with schizophrenia or related disorders is a unique large sample, providing very substantial statistical power to evaluate relevant associations. Second, the GROUP population is a reasonably well representation of the general patient population with psychotic illnesses following treatment and who are willing to collaborate with researchers. It is likely that part of the differences in results found in the previous studies is a result of differences in the study sample. Because the GROUP population is a reasonably well representation of out and inpatients with psychotic illness in general, results will better apply to the general patient population. Third, the GROUP study has a longitudinal design with assessment at baseline, 3 and 6 years follow-up. Again, the fact that such a large cohort of patients is followed over a period as long as six years is very unique and provides information on the course of illness and enables the evaluations of associations between variables at two different time-points during the course of illness. Previous observational studies were almost all cross-sectional. This results in a “frozen” image of the assessed symptoms and confounders. Such an image is thought to be a continuous state. The longitudinal design is able to partially correct this image. The co-presence of OCS changes over time, as do other symptoms.
Looking at changes and stability helps to present a more accurate image of schizophrenia and related disorders.

Fourth, a very elaborate set of assessments has been used, enabling the exploration of associations in considerable detail, correcting for a wide variety of relevant confounders. Because of the large size of the sample many variables can be included in our analyses without causing power problems. Previous contradictory findings from the literature were addressed in a more elaborate way with the GROUP results, and robust and reliable answers have been given. Moreover, the inclusion of healthy siblings and controls makes it possible to investigate associations between OCS and other features without the confounding effect of disease related variables, such as medication.

**Limitations**

Each of the studies discussed in this thesis has its own limitations, discussed separately in the previous chapters, but some limitations are more general, and I discuss them here. It is clear that the pathogenesis of OCS and psychotic symptoms is complex and changes in psychotic symptoms have a cascade of implications at many different levels. For instance, more psychotic symptoms may lead to a change in medication, e.g. clozapine, resulting in less motor symptoms but more OCS. Unfortunately, the descriptive design of the GROUP study makes it impossible to identify such subtle interactions. As a consequence, it is impossible to draw conclusions concerning causality from the identified associations.

Another major limitation is that only information from two assessments with a substantial three year time interval, is available. Although one of the major conclusions is that change is a prominent feature of OCS in schizophrenia, and this change is a major focus of many articles, the conclusions of this thesis are based on only these two assessments.

Furthermore, although roughly a thousand siblings are included, some symptoms or combination of symptoms are so rare that no reliable analysis could be performed. Siblings were included in an effort to correct for the effect of the illness process and its treatment. Unfortunately, this was not possible in some cases, due to the problem mentioned above problem. This applies even to a greater extent to the healthy control population.

Finally the GROUP-sample has significantly more male patients, while the male/female distribution in the sibling and control group is more or less even. The duration of illness at baseline is relatively short. A substantial portion of participants was lost to follow-up. Moreover, participation in research is demanding, and patients with a severe illness tend to be underrepresented in the GROUP sample. All these factors imply that findings should be interpreted cautiously.
Summary and General Discussion

Scientific implications:
OCS in schizophrenia should not be regarded as a distinct subtype. Results of previous studies and of the GROUP study indicate that OCS in schizophrenia is multi-causal and has different implications as to how it may affect the course. Future studies should, as we were able to do in the GROUP study, always correct for the influence of clozapine. Our results indicate that the duration of illness has an effect on the prevalence of OCS and that if OCS is present in patients with chronic schizophrenia, this is associated with a more severe course of illness. As a consequence duration of illness should also be corrected for in future studies.

Clinical Implications:
OCS is well distinguishable from psychotic symptoms and may need specific interventions. Persistent OCS and OCS de novo are an unfavorable sign and are associated with poorer functioning and more severe psychotic symptoms, among others. Furthermore, moderate to severe OCS is a cause of additional suffering. Remission is associated with better functioning. Thus, the recognition and treatment of OCS is of great importance. The Y-BOCS is the instrument of choice when assessing OCS in patients with schizophrenia or related disorders. When starting clozapine treatment, OCS should be monitored on a regular basis over a longer period of time. Patients with OCS might be at risk of developing akathisia.

Future research directions:
Shorter assessment intervals of future observational studies would provide valuable information on the variability of OCS in schizophrenia and co-morbidly associated features. Replication of our result that the OCS remission group differs significantly from the OCS de novo group and persistent OCS group, would help to identify different implications of the presence of OCS. Of course, not only narrowing of the intervals would provide valuable information, but also lengthening the follow up, would be of great interest. In short, shifting focus from cross-sectional to detailed longitudinal studies would provide answers to yet unsolved questions.

Second, I hope that future intervention studies will provide guidelines to optimize the treatment of OCS in schizophrenia, by performing medication and therapeutic trials, focusing on the treatment of OCS, such as testing the effect and the acceptability of anti-depressants and CBT. Third, although we did only partially replicate Lysaker et al.’s findings in distinguishing a good and a poor functioning OCS group, Lastly, exploring differences in susceptibility to develop OCS may provide information on the causality of previously identified associations.

In summary:
This thesis reveals that OCS frequently occurs in patients with non-affective psychotic disorders, and fluctuates during the course of the illness. Meta-regression indicates that the way OCS is assessed significantly influences its prevalence. The best way to assess OCS in schizophrenia is the Y-BOCS. Chronicity of the psychotic illness is associated with a higher prevalence and possibly sub-Saharan origin.

In summary:
This thesis reveals that OCS frequently occurs in patients with non-affective psychotic disorders, and fluctuates during the course of the illness. Meta-regression indicates that the way OCS is assessed significantly influences its prevalence. The best way to assess OCS in schizophrenia is the Y-BOCS. Chronicity of the psychotic illness is associated with a higher prevalence and possibly sub-Saharan origin.
of the patient population is associated with a lower prevalence.

In a large patient cohort we evaluated the relation between OCS and psychotic symptoms, social functioning, motor symptoms, substance use, use of medication and cognitive symptoms. In general, results show that OCS is associated with more psychotic symptoms and poorer functioning. We also find an association between OCS and clozapine use, which has been identified in previous studies as well. This affect is even larger when clozapine is used for more than six months, which asks for close and prolonged monitoring of OCS in patients started on clozapine.

We did not replicate previous findings that OCS is associated with cognitive symptoms, motor symptoms and less nicotine use. The extensive GROUP-design makes it possible to include a series of confounders in the analyses which previous studies were unable to include. This might account for the differences in results. Perhaps publication bias is partially responsible for the fact that relatively few studies reporting no associations between OCS and other symptoms or signs were published. Moreover, former studies relied on small and selected samples, therefore I propose that our findings are the most valid and robust thus far.

The results of the studies described in this thesis do not support the existence of a specific “obsessive-compulsive subtype”, with a specific course and set of specific comorbid symptoms other than poorer functioning and more positive and depressive symptoms.

Our results seem to indicate that individuals who develop psychosis are also susceptible for other psychiatric symptoms, OCS among others. Taken together, we find that poorer functioning, more severe psychotic symptoms or akathisia at baseline is a risk for the development of OCS three years later. Remission of OCS is associated with clinical improvement and development of OCS during the course of illness or persistent OCS is associated with a less favorable course. In general, findings in patients are mimicked in their healthy siblings at a subclinical level.
REFERENCES


