Obsessive compulsive symptoms in psychotic disorders

Swets, M.

Citation for published version (APA):
GENERAL INTRODUCTION
Chapter 1

GENERAL INTRODUCTION

This thesis is about Obsessive Compulsive Symptoms (OCS) in non-affective psychosis. The studies described in this thesis are, except for one, all part of the Genetic Risk and Outcome of Psychosis (GROUP) study. The GROUP study is a unique cohort study, investigating more than 1000 patients with schizophrenia or schizophrenia related disorders, their unaffected siblings and healthy controls at three assessment waves with two 3 year follow-up intervals. Unaffected siblings have a 4-10 fold (1) higher risk of developing a psychotic disorder compared to the general population. The inclusion of unaffected siblings enables the investigation of psychotic symptoms on a subclinical level without the disturbance of the illness and treatment related confounding effect.

Non-affective psychotic disorders

Non-affective psychotic disorders, of which schizophrenia is the most prominent representative, are arguably the most severe and disabling mental disorders and are common disorders with a prevalence rate around 0.7%, affecting about 26 million people worldwide (2).

According to the DSM-5 (3) psychotic disorders feature the following symptoms: delusions, hallucinations, disorganized thinking, disorganized or abnormal motor behavior (including catatonia), commonly referred to as positive symptoms and negative symptoms, such as diminished emotional expression or social withdrawal and loss of initiative. The prevalence of psychotic symptoms is not uncommon, affecting about 5% of the general population of which 75%-90% resolve over time, without specific treatment (4). Sometimes though symptoms persist, affect general functioning and are accompanied by for instance negative symptoms and develop a disorder with need for care. In this case we speak of a disorder: psychosis and if symptoms persist for at least 6 months, schizophrenia. From now on I will use the term schizophrenia, implying all disabling non-affective psychotic disorders, not directly caused by psychotropic substances or somatic conditions.

Schizophrenia has a high heritability of 80% and often clusters in families, but it has proven difficult to find high impact genes (5). Except for the “pure” gene-effect, the heritability also “contains” genotype-environment interactions. Genetic factor increase the vulnerability for certain environmental risk factors. Cannabis use (6), childhood trauma (7), urban environment (8) and for instance social isolation and prenatal influences (9) are identified as such risk factors.

The pathophysiology of schizophrenia is complex. In interaction with environmental influences subtle dysfunctions of several neurobiological systems are implicated. The heterogeneity of these pathophysiological dysfunctions is probably as extensive as the clinical heterogeneity of psychotic disorders. Changes in the prefrontal cortex are associated with cognitive deficits (10). “Subtle reduction of grey matter and abnormalities of white matter have been reported in many brain regions, some related to antipsychotics use, some not, but up till now no circumscribed anatomical or functional abnormality
specific for the disorder have been identified" (11). Dopaminergic dysfunction is implicated in the emergence of hallucinations and delusions (12). The glutamatergic system, among others is involved in negative and cognitive symptoms (13). Furthermore neuronal connectivity appears to be disturbed (14).

Schizophrenia has been studied extensively in the past. Although most patients suffer marked to severe impairment, there are many differences in manifestation and course between individuals. Comorbidity, such as depression and anxiety disorders in patients with non-affective psychotic disorders is very common, but not all co-morbid mental disorders are equally common (15). The difference in prevalence of an obsessive compulsive disorder (OCD) in the psychotic population, about 12% (16), compared to about 1.6% (17) in the general population is particularly high.

Schizophrenia is known to affect many aspects of functioning and is known to be associated with several co-morbid features. I will shortly address those discussed in my thesis:

In schizophrenia deficits are present in several cognitive domains (18), such as lower IQ, problems with executive functioning, attention and working memory and general memory, processing speed and motor speed. Compared to controls, impairments were greatest for verbal memory, followed by executive functioning and IQ (18).

Motor symptoms are common in schizophrenia. For a long period they were thought to be caused by antipsychotics medication, until the prevalence of motor symptoms in an antipsychotics naïve cohort of patients was found to be almost as high as in medicated patients (19). The main movement disorders related to schizophrenia are: a) parkinsonism, consisting of tremors, slowness of movement, rigidity and postural instability; b) dyskinesia, characterized by involuntary, predominantly facial muscle movements; c) akathisia consisting of inner restlessness and a compelling need to be in constant motion, and d) dystonia, sustained or repetitive muscle contractions, usually of the eyes or neck.

Substance (ab)use is very common in schizophrenia (20) and much more prevalent compared to the general population. The mechanisms underlying this comorbidity are still poorly understood. Imaging studies suggest that both chronic cannabis users and patients with schizophrenia show reduced volumes in the amygdala and hippocampus (21, 22). The mesolimbic dopaminergic system though, is implicated in both the rewarding mechanism for drugs, but also in the occurrence of positive symptoms in schizophrenia (20). Psychotic symptoms are common “side-effects” of “drug-trips” (20). On the other hand the same system appears to play a role in the feeling of anhedonia, part of the negative symptoms, and drugs are thought be used as self-medication to (temporarily) elevate this gloomy feeling. Unfortunately, in the long run, drugs tend to aggravate anhedonia (23, 24).

The treatment of non-affective psychosis consists primarily of antipsychotics medication. Those usually work well on the positive symptoms, but they have much less effect on the negative symptoms and cognitive problems (10).
Chapter 1

Obsessive compulsive disorder

OCD is the 10th leading cause of disability of all medical conditions in the industrialized world (25). The prevalence is estimated at about 1.6% (26). The mean age of onset is 20 years and the course of the disorder is often chronic.

According to the DSM-5 OCD features the following symptoms:

- **Obsessions:** recurrent and repetitive thoughts or images that are experienced as intrusive and cause anxiety. They are not simply excessive worries about real life issues. The affected person tries to ignore or neutralize those thoughts with another thought or action, and this person recognizes that these thoughts are a product of his own mind.
- **Compulsions:** repetitive behaviors or mental acts that the affected person feels compelled to do in response to an obsession, or according to rigid rules. Compulsions are aimed at preventing or reducing distress, or preventing some dreaded event. The amount of insight into the fact that the obsessions or compulsions are excessive or unreasonable, varies. Therefore a specifier signifying the degree of insight can be added: with “absent insight/delusional beliefs” at the poor end of the spectrum (3).

To fulfill the diagnostic criteria for OCD, obsessions or compulsions cause suffering, are present for at least one hour a day and must interfere with normal functioning. If obsessions or compulsions are not severe enough to meet criteria for OCD, they are classified as obsessive compulsive symptoms (OCS).

The heritability of OCD is less than for schizophrenia, around 50% in children and around 30% in adults (27). Less is known about environmental risk factors although a recent study identified prenatal influences (28).

In OCD primarily the serotonergic system is implicated, but other evidence points to an additional involvement of the glutamatergic and dopaminergic system (29). Brain imaging has implicated the involvement of the frontal orbito-striatal area including the nucleus caudate and the dorsolateral and prefrontal cortex.

Similar to schizophrenia OCD is associated with a diversity of comorbid disorders (30). At least 50% of OCD patients have comorbidity, most commonly, anxiety disorders and depression. Alcohol abuse and tics are specifically associated with OCD. In terms of social characteristics, people with OCD are less likely to be married than patients with depression and anxiety disorders, are more likely to be unemployed and report more social impairment (31). Similar to all psychiatric disorders, OCD is a syndromic concept with considerable overlap with other psychiatric conditions and health. In relation to OCD specific illness features have been studied, such as cognitive profiles, in order to elucidate the cognitive pathways responsible for obsessions and the executive functioning problems related to compulsions. Motor symptoms have been studied as they are highly co-prevalent. Since inhibitory difficulties are a central issue in OCD, addiction has also been studied. I will shortly address what is known concerning the features studied in this thesis in relation to OCD.

The cognitive deficits found in OCD are more limited compared with schizophrenia. OCD is specifically
associated with memory dysfunction and with executive function problems (32). OCD is partly explained by impairment in inhibitory processes (33). Deficits in executive functioning have been proposed to underlie many of the symptoms in primary OCD (34). Vice versa severe OCD will interact with cognitive tasks, for instance by prompting the patient to keep on checking, which by itself will influence results on cognitive tasks (35, 36).

Motor symptoms in OCD are most often tics. Gilles de la Tourette’s syndrome is a condition with combined tics and OCS (37, 38). Neurological disorders with motor symptoms such as Huntington’s disease, Sydenham’s chorea and PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) are specifically associated with OCD.

Substance use disorder (SUD) is associated with OCD although studies show mixed results (39). The association is certainly less pronounced than in schizophrenia. Noticeably, whereas schizophrenia is associated with the highest prevalence of nicotine dependence, OCD has been found to be associated with an even lower prevalence of nicotine dependence than in the general population (40).

The treatment of OCD normally consists of a combination of psychological treatment and pharmacotherapy (29). According to meta-analyses, CBT and pharmacotherapy are more or less equally effective in treating OCD, but not all patients respond. In case of severe OCD a combination of both treatment modalities is the treatment of choice (41). The addition of antipsychotics medication can cause an additional improvement. Patients with comorbid tics react particularly well to antipsychotics (42).

Schizophrenia and obsessive compulsive symptoms (OCS)
The co-occurrence of OCS and schizophrenia has been described for over a century (43). At first, OCS in patients suffering from psychosis was believed to be associated with a favorable course of illness and better to be left untreated. After the introduction of more systematic research on the topic, new insights revealed poorer global functioning and more severe psychotic symptoms in case of comorbid OCS (44). Those systematic studies found prevalence rate up to 37% (45), while the lifetime prevalence for OCD in the general population is estimated at 1.6% (17). Buckley et al. (46) calculated a weighted average and estimated the prevalence of OCD in schizophrenia to be 23%. These rates made OCD a common co-morbid disorder in schizophrenia, with an about tenfold raise in prevalence compared to the general population.

Both OCD and psychotic disorders have puzzling similarities: delusions are illogical, intrusive thoughts which are held to be true, while obsessions are often equally illogical and intrusive thought, but are believed by the patient to be untrue. Still, as pointed out, it is rather common for OCD patients to also have poor insight into the incorrectness of their obsessions, which can result in difficulties distinguishing between both conditions (47).

On the other hand, it is rare that an obsession develops into a delusion and most of the time they do not
“change sides”. Confusing obsessions with delusions has been described but is rare. A study addressing insight in OCS in patients suffering from schizophrenia found that the percentage of patients with lack of insight was comparable to that in “pure” OCD. Good insight in the OCS was positively correlated with awareness of schizophrenia, but not with awareness of delusions, indicating that obsessions and delusions are distinct and distinguishable phenomena, even when occurring simultaneously (48). The typical content of delusions and obsessions usually is very different from each other and aids in distinguishing between the two. A recent article has drawn attention to the doubt-certainty continuum on which OCS and psychosis take opposite sides. It is argued that delusions can also be regarded as thoughts with too much conviction. In OCD at the other hand, persistent doubting and rechecking is one of the core features (49). In summary OCS and psychosis show similarities, but there are enough differences to distinguish between the two.

The high co-occurrence of OCS in schizophrenia (16), has evoked the interest of researchers. Several concepts have been proposed to explain the frequent co-occurrence of which one is the “schizo-obsessive subtype” (50). This subtype of schizophrenia is assumed to have a distinct set of co-appearing features apart from the co-existing OCS and a specific course of illness and liability to treatment (50). As a result many studies tried to identify those co-occurring features such as cognitive functioning and co-occurring phenomena such as motor symptoms, addiction and effect of psychotropic medication. Unfortunately, results tended to differ between studies, although most studies found OCS to be associated with poorer functioning, more depressive symptoms and often more positive symptoms (51). No further persistent co-occurring features were identified.

The relation between OCS and the course of schizophrenia was studied, showing that OCS could either precede or coincide or follow the start of psychosis and that symptoms tended to fluctuate over time (52). This led to the hypothesis that possibly the moment OCS emerged in relation to the psychotic illness, has different implications. Pre-existing OCD in schizophrenia could perhaps best be regarded as independent disorders, while OCS emerging simultaneously with the psychotic disorder might indicate as specific stress reaction or a “true” schizo-obsessive disorder, while OCS emerging later in the course of a severe psychotic illness might be the result of an increase in vulnerability of the mind for all kind of psychopathology. In other words, OCS in schizophrenia might represent different phenomena.

Lysaker et al. tried to find an explanation for abovementioned differences by performing a cluster analysis. They identified four schizophrenia patient clusters. A good and poor functioning group of patients with OCS and a moderate and poor functioning group without OCS. The good functioning OCS group had fewer negative symptoms compared to all other groups, while the poor functioning OCS group had poorer concentration compared to all other groups (53). Their results indicated that in fact OCS comorbidity in schizophrenia consists of two distinct groups, one with superior functioning and one with very poor functioning compared to patients with schizophrenia without OCS.
General Introduction

The effect of medication on OCS in patients with schizophrenia was studied and proved to be ambiguous. Sometimes the antipsychotics treated both OCS and psychosis, sometimes it treated the psychotic symptoms but aggravated the OCS (54-58). Specifically clozapine is associated with the occurrence of OCS (59).

The earlier mentioned inconsistent results in studies trying to identify features specific to the OCS-psychosis condition and the strong fluctuation in the presence of OCS in schizophrenia did not support the hypothesis of a distinct, stable schizo-obsessive subtype.

Still, knowledge concerning OCS or OCD in schizophrenia is of great importance. First because OCD in schizophrenia causes additional suffering and OCD is a treatable disorder. Second, by studying the OCS-psychosis co-prevalence in relation to the abovementioned features I hope to enhance our insight into the implication of their co-occurrence and into the underlying psychopathological mechanisms involved in their co-appearance.

Research conducted on OCS-psychosis comorbidity has established the fact that the co-prevalence is high and in general associated with poorer functioning. Clozapine is associated with more OCS. Yet virtually all features that have been studied in relation with co-morbid OCS in schizophrenia have resulted in highly varying results, prevalence values included. Most likely these variations are at least partly the results of methodological inconsistencies and differences in patient samples. Most studies on OCS-psychosis comorbidity included relatively small number of cases. Many were conducted in specialized centers, focusing on a selection of schizophrenia patients. The larger studies, including over 100 patients, providing prevalence data seldom used the Y-BOCS to assess severity, resulting in suboptimal OCS evaluations. The Y-BOCS is a OCS-specific instrument assessing OCS severity and is generally regarded as the instrument of choice in assessing OCS or OCD. Furthermore, few studies had a longitudinal design (33, 35), which resulted in virtually only cross-sectional data. To the best of my knowledge only one previous study also included healthy relatives, but this study also had a cross-sectional design (60).

The GROUP project provided a unique opportunity to study the occurrence, associations and course of OCS in a large nonselective cohort of patients suffering from non-affective psychotic disorders and to compare different illness variables in patients with OCS to those without co-occurring OCS. Furthermore, the inclusion of non-affected siblings offered the unique possibility to evaluate the occurrence, associations and course of OCS in a large cohort of subjects at an increased risk to develop a psychotic disorder, and to evaluate cross-disorder and cross-sibling associations. The Y-BOCS was assessed in all patients, unaffected siblings and controls, providing detailed and thorough information on severity of OCS. Also, extensive information on medication, social situation, psychotic symptoms, cognitive functioning and motor symptoms was obtained.
Chapter 1

The aim of this thesis
Except for Chapter 2, which is a meta-analysis and meta-regression, all other research articles use the GROUP data and they all focus on the differences in patients with schizophrenia with and without OCS. The following topics are addressed in the subsequent chapters:

Chapter 2 addresses the question what the prevalence is of OCS and OCD in schizophrenia according to the combined literature, and what variables influence this prevalence.

Chapter 3 addresses the question whether the factor structure of the Y-BOCS in schizophrenia patients with OCS is comparable to the factor structure found in OCD patients.

Chapter 4 establishes the prevalence rates of OCS in schizophrenia patients and their siblings. It addresses the question whether OCS cluster in families and whether (sub)clinical psychotic features in unaffected siblings are associated with OCS in the related patient or the other way around. It also compares the prevalence of OCS in siblings with the prevalence in controls.

Chapter 5 addresses the question whether different antipsychotics are associated with different prevalence rates of OCS in patients with schizophrenia.

Chapter 6 addresses the question whether the prevalence of substance use differs between schizophrenia patients with OCS and without OCS.

Chapter 7 addresses the question whether patients with psychotic disorders and comorbid OCS show a specific cognitive profile.

Chapter 8 addresses the question which psychotic symptoms are associated with OCS, and how they evolve over time in patients with psychotic disorders and their unaffected siblings.

Chapter 9 addresses the question whether OCS is associated with specific motor symptoms and how this association develops over time in relation with the OCS in schizophrenia patients and their unaffected siblings.

Chapter 10 addresses the question what the longitudinal interrelation between OCS and cognitive functioning is and whether the patient results are mimicked in their healthy siblings.

Chapter 11 addresses the question whether two distinct groups of schizophrenia patients with comorbid OCS can be identified, one with poor functioning and one with superior functioning.
REFERENCES


