Depressive and psychotic symptoms in schizophrenia

Focus on networks and treatment

van Rooijen, G.

Publication date
2018

Document Version
Final published version

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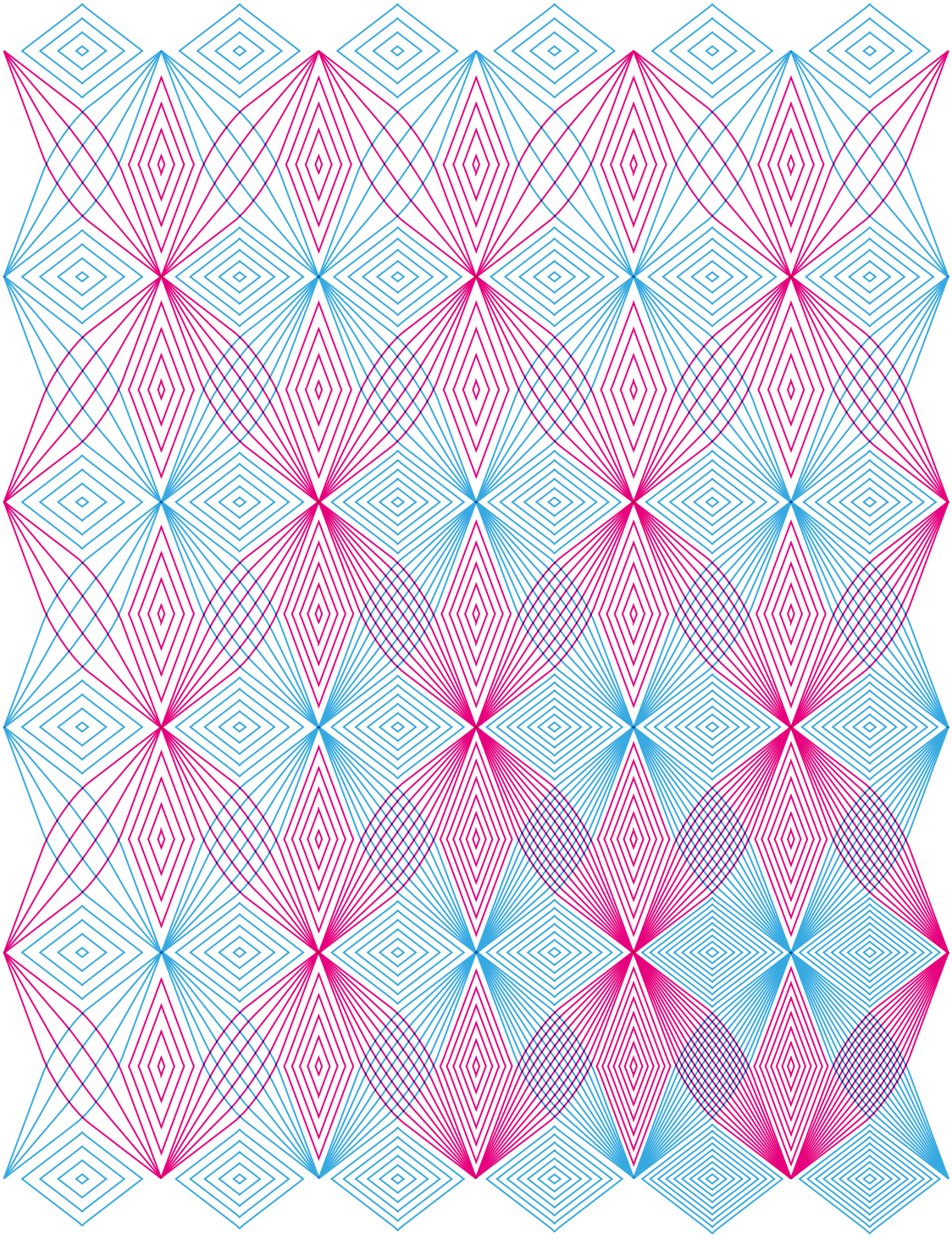

DEPRESSIVE AND PSYCHOTIC SYMPTOMS IN SCHIZOPHRENIA: FOCUS ON NETWORKS AND TREATMENT - GEESKE VAN ROOIJEN

Depressive and psychotic symptoms in schizophrenia: Focus on networks and treatment

Geeske van Rooijen

Colophon
Financial support for printing this thesis was provided by Amsterdam UMC.

Author: Geeske van Rooijen
Cover and layout: www.studioanne-marijn.com
Printed by: Netzodruk, Groningen

Depressive and psychotic symptoms in schizophrenia:
Focus on networks and treatment

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 5 oktober 2018, te 12:00 uur

door Geeske van Rooijen

geboren te Alkmaar

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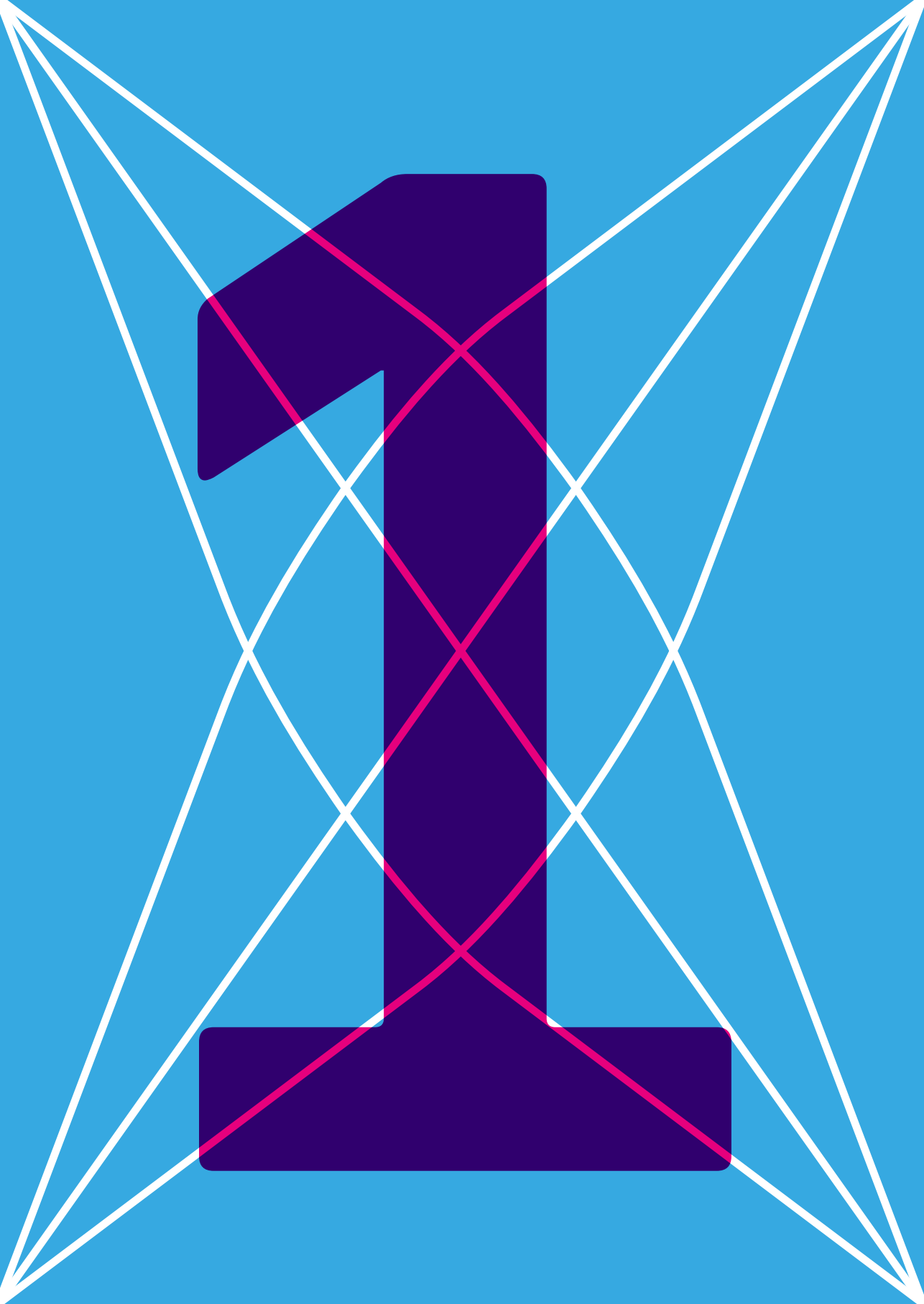

GENERAL INTRODUCTION

1. INTRODUCTION

Schizophrenia is a common mental disorder with a point prevalence of 4.6 per 1000 persons[1,2] and an average annual incidence of 15 per 100,000.[2] The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) classifies patients with a mental disorder based on the presence of a specific combination of symptoms. With respect to schizophrenia, at least 2 of the following symptoms must be present: delusions, hallucinations, disorganized speech, disorganized / catatonic behavior or negative symptoms (from which at least one of these two should concern delusions, hallucinations or disorganized speech). For a patient to meet the criteria for schizophrenia, the symptoms need to be present for at least one month (or shorter in the situation of receiving treatment), while the functional deterioration should exist for at least 6 months.[3]

A consequence of these broad diagnostic criteria is a substantial heterogeneity between patients diagnosed with schizophrenia. Nevertheless, positive symptoms (i.e., behavior that is usually *not* present in healthy subjects) and negative symptoms (i.e., the absence of behavior regularly present in healthy subjects) are considered core symptoms. Examples of positive symptoms are, for example, hallucinations and delusions. Negative symptoms include a flat affect, lack of spontaneity, anhedonia and emotional or social withdrawal.

Apart from these symptoms several other, sometimes subtle, symptoms or signs are frequently present such as anxiety, affective symptoms and neurocognitive deficits (e.g., difficulties with attention, memory, planning and organization).[4,5] For instance, approximately 25% of the schizophrenia patients suffer from a depression,[5,6] with a life –time prevalence of suffering from a depressed mood (≥ 2weeks) up to 83%.[7] Although, prevalence numbers vary widely between studies (which might be partly due to differences in selection of study samples and varying time intervals),[5] depressive symptoms have a more substantial impact on quality of life than positive symptoms.[8]

This introduction will start with 1) a historical overview regarding the concept of schizophrenia; 2) the network approach; 3) co-occurring depressive symptoms in schizophrenia; 4) an introduction of the process emotion regulation and 5) treatment aspects of schizophrenia. Lastly, the aims of the present thesis will be outlined.

1.1 The concept 'schizophrenia' from a historical perspective

The criteria for diagnosing patients with schizophrenia differed widely in the past decades. In the following paragraph a short historical overview is given regarding the concept schizophrenia, derived from Jablensky and Tandon et al.[9,10]

Kraepelin (1856-1926) and Bleuler (1857-1939) were the first describing a clinical picture, now known as schizophrenia.[11–13] Kraepelin described, based on his long-term observations

of patients, a clinical pictured called *'dementia praecox'*. This clinical picture consisted of impaired functioning that started during adolescence or early adulthood and eventually resulting in an inability to keep up with healthy peers due to severe cognitive and behavioural deficits. According to Kraepelin symptoms associated with this syndrome tended to persist and deteriorate in dementia. He distinguished this syndrome from manic-depression, which was characterized with a much better outcome compared to *dementia praecox*.

Eugen Bleuler (Switzerland) argued that there was a more variable course and outcome of schizophrenia compared to deteriorating course described by Kraepelin. Therefore, he considered the term 'dementia' confusing and he coined the name 'schizophrenia'. Contrary to current use in classification systems, both authors did not considered delusions and hallucinations as core symptoms (Bleuler described them as *accessory* symptoms). Bleuler considered 'loosening of association, blunt or incongruous affect, ambivalence and autism'[10] as fundamental symptoms. Blunt affect and the concept autism, as Bleuler defined it, are currently considered as negative symptoms.

Several decades later, Kurt Schneider (1887-1967, Germany) described 'first-rank symptoms' including, among others, commentary hallucinations, thought withdrawal, insertion and broadcasting. Schneider considered these symptoms, now known as positive symptoms, as pathognomonic for schizophrenia.[14,15] However, this does not appear to be valid, patients having such symptoms can nowadays also be diagnosed with other disorders (e.g., bipolar disorder).

In the decades following, several psychiatrists including Karl Leonhard (1904-1988, Germany) continued on the work of Kraepelin's and Bleuler's and developed a detailed classification of psychosis with sharp-defined disease entities.[16] By the 1960s, there were major differences between the rates of diagnosing between the USA and the rest of the world, which was demonstrated by the US-UK study.[17] This study flaunted that patients in New York, with similar symptoms, were often diagnosed with schizophrenia, while in the UK patients were mainly diagnosed with bipolar disorder. As a response, the third edition of the DSM that followed contained the most strict criteria ever.[18] In the editions following (i.e., DSM-III-R,[19] DSM-IV,[20] DSM-IV-TR)[21] these criteria became a little less stringent. For example, the number and type of symptoms as well as the criteria for the age of onset (i.e., onset before 45-years) changed over time.

Although there are several differences between the syndromes described by Bleuler, Kraepelin and Schneider, current classification systems still includes elements of them: the DSM integrate 'Kraepelinian chronicity, Bleulerian negative symptoms, and Schneiderian positive symptoms'.[10] Additionally, in order to refine the diagnosis, in the latest version, the DSM-5,[3] a novel dimensional assessment is added, next to the aforementioned diagnostic criteria of schizophrenia. This dimensional assessment contains 8 domains evaluating the primary symptoms (among others hallucinations, delusions, negative and depressive symptoms, disorganized speech, cognitive disabilities, abnormal psychomotor behavior and manic symptoms), which are rated on a 5-point scale.

Current classification systems (i.e., DSM-5[3] and the International Classification of Disease (ICD-10)[22] have led to an increase in the reliability of classifications. Nevertheless, the

validity of the categorical nature of this type of classification is debated.[9,23,24] Current classification systems describe the number of symptoms as a cut-off needed to diagnose patients with a specific psychiatric disorder and hereby assume that psychopathology and the occurrence of symptoms are a reflection of one underlying latent factor. The use of these static classification systems resulted in a high degree of heterogeneity within the group of patients with schizophrenia spectrum disorders as well as a high comorbidity between different psychiatric disorders. Fortunately, a new approach - the network approach has been developed.[25] Results from the network approach show that there is no empirical ground for one latent factor underlying specific disorders, in contrast the network approach assumes that psychopathology raise from the interactions between symptoms.[25,26]

1.2 Network approach

The network approach is based on a number of important assumptions:[26] i) psychopathology or mental disorders are the result of the causal interaction between symptoms. These symptoms and their interactions may come from different etiological backgrounds (e.g., a biological background in which insomnia leads to fatigue and change of appetite);[26] ii) all the interactions between symptoms result in so called symptom networks; iii) in an asymptomatic phase, there are no symptoms and, consequently, the symptom networks are latently present (in other words; they describe 'what would happen upon symptom activation, but not what does happen at that moment'[26]; iv) the presence of external factors (e.g., traumatic events and or genetic vulnerability, situated outside the symptom network) might trigger the activation of a symptom network. Depending on the already existing interactions between symptoms, activity will spread further through the network ultimately resulting in self-reinforcing feedback loops in which symptoms keep on activating each other. Due to these feedback loops the activation within a network keeps on going, despite the fact that an external trigger already disappeared. Moreover, the latter assumption describes that activation of strongly connected networks will happen more easily, compared to less – strongly connected networks; this is called the *hysteresis* principal.[26]

The network approach has already been applied in different psychiatric disorders, including posttraumatic stress disorder,[27,28] depression,[29–33] anxiety disorders,[34,35] complex bereavement,[36] autism,[37,38] substance abuse,[39] personality disorders,[40] eating disorder[41] and the structure of psychiatric symptoms in general.[23,42–45] Studies using the network approach investigating psychosis or psychotic symptoms have been performed as well.[46–50] For instance, Wigman and colleagues[48] compared the networks of adolescents with and without auditory verbal hallucinations. Although the children did not differ with respect to the severity of psychotic experiences, there were more connections between positive psychotic experiences within the symptoms network of the children with auditory verbal hallucinations. The authors hypothesize whether these differences in interconnectedness could reflect a 'liability' for psychosis. Another network study investigating psychosis was performed by Isvoranu and colleagues,[47] who constructed a cross-sectional network of psychotic and general symptoms in patients with non-affective psychosis. In these networks that also included items evaluating potential childhood trauma (when happened under the age of 17 years). They found direct connections between general psychopathology symptoms (e.g., depression) and childhood trauma; also general symptoms mediated the relationship between childhood trauma and positive psychotic symptoms. Despite the

cross-sectional nature of their data, their findings corroborated 'an affective pathway to psychosis after exposure to childhood trauma'[47] (i.e., due to childhood trauma patients will first develop affective symptoms, which might be followed by psychotic symptoms).

However, many questions remain when investigating the psychosis spectrum from a network approach. For instance, a cross-sectional network including a wide range of symptoms in patients with schizophrenia is currently missing. Therefore in chapter **2,** the network approach was applied to elucidate associations between individual symptoms in patients diagnosed with a non-affective psychotic disorder. Given the importance of depressive symptoms and earlier associations with positive symptoms,[51,52] we focussed on the associations between depressive and delusional symptoms. Moreover, there are also unanswered questions regarding the stability (e.g., the difference between acute symptomatic and remission states) of the network topology in patients, diagnosed with schizophrenia. Therefore, the stability of a network structure in patients with schizophrenia is investigated in which patients in psychotic remission are compared to non-psychotic remitted patients (chapter **3**). Moreover, also this network study focussed on the interactions of depressive symptoms with delusional symptoms.

1.3 Co-occurring of depression and its impact on the quality of life

Approximately 25% of the patients diagnosed with schizophrenia suffer from a co-morbid depressive episode.[5,6] The diagnosis of a depressive episode is highly important, considering its association with reduced treatment adherence,[53] more frequent use of mental health services,[53] higher probability of psychotic relapse(s),[54] increased substance abuse[55] and greater risk of suicide and suicide attempts.[56–59] These considerations contributed to the inclusion of depressive symptoms as one of the symptoms dimension to be assessed in the DSM-5.[3] Nevertheless, diagnosing a depressive episode in patients with schizophrenia might be difficult considering its similarities with other symptoms (i.e., negative symptoms or extra-pyramidal side-effects).

Given the high burden of depressive symptoms, effective treatment of this co-morbidity is highly relevant. National and international guidelines[60,61] summarizing current evidence of the treatment of depressive symptoms in patients with schizophrenia are out-dated and do not include the most recent insights.[62–65] Therefore, we summarized the current knowledge and, based on this, a clinical framework for the treatment of depressive symptoms and episodes is provided (chapter **7**).

Moreover, co-occurring depressive symptoms have been shown to be associated with a worse quality of life (QoL) in patients diagnosed with schizophrenia.[53,66–68] Although there is an ongoing debate regarding the precise definition of QoL, the WHO defines QoL as follow; "*a individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*".[69] Patients with schizophrenia generally report a poorer QoL, which may be further deteriorated by depressive symptoms. The improvement of QoL is considered as a crucial part within the long-term treatment of patients with schizophrenia.[60,61]

Identifying factors that are associated with worse QoL in patients with schizophrenia may provide valuable information for opportunities and targets of new treatments. There are several cross-sectional studies[53,66–68] that investigated the association between QoL and clinical variables (including depression), but due to the cross-sectional nature of these studies it is impossible to draw conclusion regarding the direction of these associations (i.e., does a lower QoL leads to depression or *vice versa*). Additionally, it could also be suggested that multiple variables play a role in the associations between depression and QoL (e.g., depression might influence the level of functioning, in stead of a direct association with QoL). Recently, Alessandrini and colleagues[70] used Structural equation modeling (SEM) to investigate the cross-sectional influence of different variables (i.e., functioning, depressive symptoms, schizophrenia symptoms and neurocognition) on QoL and showed that depressive symptoms were mostly associated with QoL. SEM is a statistical methodology that allows the inclusion of several variables, to estimate the order and the extent to which these variables influence each other.[71] However, the model by Alessandrini needs validation within a larger sample to improve the generalizability of the model, ideally within a longitudinal design because this will improve the validity of the original model.[70] Indeed, longitudinal studies investigating long term, potentially causal influences on QoL are scarce[7,53] and most of these studies did not use SEM. By applying the model by Alessandrini and colleagues[70] we will be able to verify whether this cross-sectional model was also applicable in the long-term follow-up data of the GROUP-sample.

1.4 Disturbed emotion regulation underlying depressive symptomatology

Emotion regulation in humans is considered as a higher order specific, complex process, comprising several aspects including not only the recognition of emotionally salient stimuli but also the generation and regulation of an emotional state. Abnormalities in emotion regulation (ER) are assumed to be important for the occurrence and maintenance of symptoms in major psychiatric disorders, including major depressive disorder (MDD) and schizophrenia.[72] For instance, depressed patients showed deficits in ER in terms of difficulties in understanding their emotions[73] or modifying aversive emotions successfully.[74] Moreover, emotion dysregulation is also known to cause problems in patients diagnosed with schizophrenia. As summarized by Phillips and colleagues,[72] neurocognitive deficits are frequently reported in these patients, with difficulties in attention and working memory. On top of these deficits, patients with schizophrenia report problems in perception of facial emotions, which is combined with the misinterpretation of other people's intentions (i.e., theory of mind) and a limited regulation of the 'resulting belief systems and emotional behaviour'.[72] Taken together, these abnormalities might be responsible for the difficulties during social interactions and specific symptoms (such as delusions) that patients with schizophrenia encounter.[72]

Phillips and colleagues[75,76] proposed a neuronal model of ER, based on the earlier findings by animal, human lesion and human functional neuroimaging studies. This model describes a *ventral* system (compromising the amygdala, insula, ventral striatum, ventral anterior cingulate gyrus and the ventromedial prefrontal cortex) responsible for the identification of emotional important stimuli and the generation of an emotional state and a *dorsal* system (compromising of the hippocampus, dorsal anterior cingulate gyrus and the dorsal prefrontal cortex) responsible for the regulation of an affective state.[76] Altered neural function in one

of these two neurobiological systems might be responsible for (or concur with) difficulties in emotions regulations as observed in different psychiatric disorders. However, to better map ER-strategies to these neurobiological systems and their interplay, they separated ER in automatic and voluntary ER and additionally distinguished behavioural, attentional and cognitive strategies.[76]

Phillips and colleagues[72] summarized the abnormalities in structures involved in ER in different psychiatric disorders including schizophrenia. For instance, structural abnormalities in the ventral system (i.e., decreased volume of amygdala, thalamus and anterior insula) as well as functional abnormalities (i.e., reduced activity within the amygdala, anterior insula and ventral striatum) have been found. With respect to the dorsal system structural and functional abnormalities have been found, mainly in the dorsal prefrontal cortex as well as in the dorsal anterior cingulate gyrus and hippocampus. Additionally, the aforementioned ventral abnormalities might lead to diminished (automatic) recognition of emotions in patients with schizophrenia, resulting in a limited range of identifiable emotions. Consequently, this may result in a diminished range of resulting affective states and behaviours. Also a misinterpretation of emotional salient stimuli (mainly with discriminating threatening from non-threatening) is frequently present in patients with schizophrenia. While the dorsal abnormalities may be responsible for difficulties during the voluntary regulation of emotions, as these neuroanatomical abnormalities may result in problems with reasoning and the voluntary regulation of affect states. Taken together, neuroanatomical abnormalities in patients with schizophrenia have been found in areas involved in emotion regulation.

At the same time emotional dysregulation (next to several other disturbed processes) is assumed to underlie the occurrence and persistence of depressive symptoms.[77,78] In the past decade several neuroimaging studies investigated the functional and structural changes in patients with a major depressive disorder during the performance on different emotion regulation tasks. Obtaining more insight into emotion regulation processes could contribute to our knowledge of the pathophysiology of depression. Therefore, by using the earlier proposed model of Phillips and colleagues[75] a systematic search on neuroimaging findings in patients with major depressive disorder during emotion regulation tasks was performed. Considering the involvement and the findings in this review (chapter **4**), on top of the importance of emotion dysregulation in different psychiatric disorders (including schizophrenia) we formulated hypotheses regarding neuronal abnormalities during emotional regulation in patients with schizophrenia with and without depressive symptoms (chapter **10**).

1.5 Treatment of schizophrenia

National and international guidelines exist to describe the treatment of patients with schizophrenia.[60,61] The treatment of schizophrenia spans multiple facets that should be personalized and continuously be re-evaluated, in order to prevent or intervene early in the case of relapses. Generally speaking, the treatment of schizophrenia consists of long-term care, in which the intensity will be determined depending on the course and possible psychotic relapse(s). The overarching goals of current treatment programs are directed at reducing the effects of the disease, encourage further personal and social development

and improve psychosocial functioning. So, the treatment of patients diagnosed with schizophrenia should include at least the following aspects: biological treatment of psychotic symptoms and other comorbid disorders (e.g., antipsychotics, adjuvant antidepressants), psychosocial interventions (e.g., cognitive behavioural treatment, social skill training, psycho-education and family interventions) and interventions intended to enhance social participation and rehabilitation.[61]

Regarding the biological treatment of psychotic symptoms: the effectiveness of antipsychotics compared to placebo has been proven undoubtedly, with a moderate pooled effect size for overall symptoms reduction of 0.51.[79,80] However, treatment with antipsychotics is associated with substantial (short and long-term) adverse effects, including extrapyramidal side-effects and an increase of cardiovascular mortality risk by weight gain, diabetes mellitus and dyslipidaemia.[81,82] Consequently, effectiveness and tolerability should be balanced in every patient. However, not using antipsychotics is associated with an increased risk of psychotic relapse(s) in turn associated with risky and potentially lethal behaviours (e.g., aggression, accidents and suicide). It is currently unclear whether the treatment of antipsychotics is associated with a lower long-term mortality risk compared to not using antipsychotics in this patient group. Therefore, we performed a systematic review and meta-analyses to give some guidance on this topic, described in chapter **8**.

More specific, clozapine has shown to be superior regarding efficacy compared to other antipsychotics,[83] especially with respect to treatment resistant schizophrenia (i.e., patients that did not respond to two adequate trails with other antipsychotics).[60,61] Also use of clozapine was found to be associated with a decreasing risk on suicide and suicidal behaviour.[84,85] However, due to its severe, but rare adverse effects (such as myocarditis and agranulocytosis) its use is restricted to treatment resistant patients. Additionally, clozapine (and olanzapine) are associated with a high risk of the metabolic syndrome and with the highest risk of inducing weight gain, dyslipidemia and Diabetes Mellitus Type II; all associated with an increase in mortality.[82] As a result, clinicians are sometimes reluctant when it comes to prescribing clozapine as was recently stated by Kane and colleagues.[86] Overall, the question arises whether the potential long-term harmful effects of clozapine outweigh the benefits of its superior efficacy in terms of mortality. This is of high clinical interest as this could lead to a re-evaluation of the restrictions and prejudices on the use and prescription of clozapine. To answer this question, we performed a system search and meta-analysis to determine long-term mortality rates in patients diagnosed with schizophrenia treated with clozapine and compare this to patients using other antipsychotics or no antipsychotics, described in chapter **9**.

Although antipsychotic medication is an important factor in the treatment of schizophrenia spectrum disorders. The quality of the provided care is important, as was underscored by different reports published in recent years.[87,88] However, measuring the quality of the provided care in psychiatry falls behind. In addition, psychiatric inpatients are consistently ignored in large studies that systematically assess quality of care,[89] while measurements of the quality of care provided, is necessary to identify areas for improvement. Therefore, a new method to assess the quality of provided care in inpatients is introduced, by combining process and outcome measures. This approach was applied to a group of patients admitted to a psychiatric ward and diagnosed with a non-affective psychosis, described in chapter **6**.

1.6 Aims of the present thesis

This thesis has two main aims. First, to review and increase knowledge concerning symptom interaction in patients with schizophrenia, with a specific focus on co-occurring depressive symptoms and its neural correlates in major depressive disorder (Part I and II). Second, to review and investigate different treatment aspects and outcomes in schizophrenia (quality of life, depressive symptoms and mortality) (Part III).

In Part I, the network approach is applied in patients diagnosed with schizophrenia to i) construct a network of symptoms within the psychosis spectrum and ii) examine potential differences in network connectivity between remitted and non–remitted psychotic patients. In both network studies the associations between depressive symptoms (including suicidality) and positive psychotic symptoms are put central. By doing so, the following research questions will be addressed in Part I:

1. *What can we learn from the associations between a wide range of symptoms when we apply the network approach in patients with schizophrenia?*

2. W*hat is the influence of psychotic remission on network topology in patients diagnosed with schizophrenia?*

In Part II, neuronal correlates during emotion regulation tasks in patients with a major depressive disorder are discussed. By doing so, the following research question will be addressed in Part II:

3. *What are the neurobiological correlates of disturbed emotion regulation in major depressive disorder?*

In Part III, different treatment aspects and outcomes of patients diagnosed with schizophrenia with/without comorbid depression are examined. First, the influence of depressive and psychotic symptoms on the QoL, as outcome measure, is investigated in patients diagnosed with schizophrenia. This chapter is followed by a study that offers a new method for measuring the quality of provided care in psychiatry, which is applied in a sample of inpatients diagnosed with schizophrenia. Part III ends with three treatment-focused reviews in which i) current knowledge regarding the effectiveness of different treatment strategies for comorbid depressive symptoms and/or depressive episodes in patients with schizophrenia are reviewed; ii) the association between mortality and the long-term use of antipsychotic medication compared to other or no-antipsychotic use in patients with schizophrenia is studied; and iii) the association between mortality and the long-term use of clozapine compared to other antipsychotics or no antipsychotic use is assessed. By doing so, the following research question will be addressed in Part III:

4. *What is the longitudinal relation between clinical variables (i.e., neurocognition, social functioning, depression and psychotic symptoms) and the quality of life?*

5. *What is the quality of the provided care of patients with schizophrenia admitted to a psychiatric ward?*

6. *What are the treatment options for patients with schizophrenia and co-morbid depressive symptoms or episodes?*

7. *What is the association between the long-term mortality risk and the treatment with antipsychotics compared to other antipsychotics or no antipsychotic treatment in patients diagnosed with schizophrenia?*

8. *What is the association between the long-term mortality risk and the treatment with clozapine compared to other antipsychotics or no antipsychotic treatment in patients diagnosed with schizophrenia?*

Chapter **10** provides a general discussion based on the findings in chapters 2-9.

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PART I

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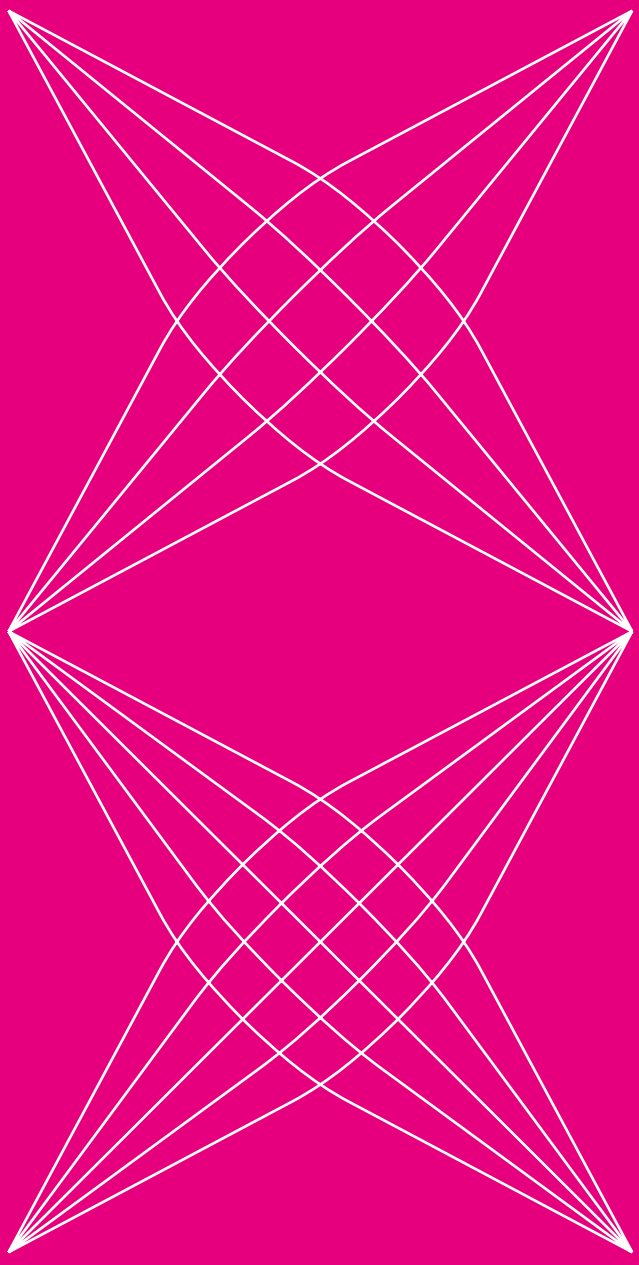
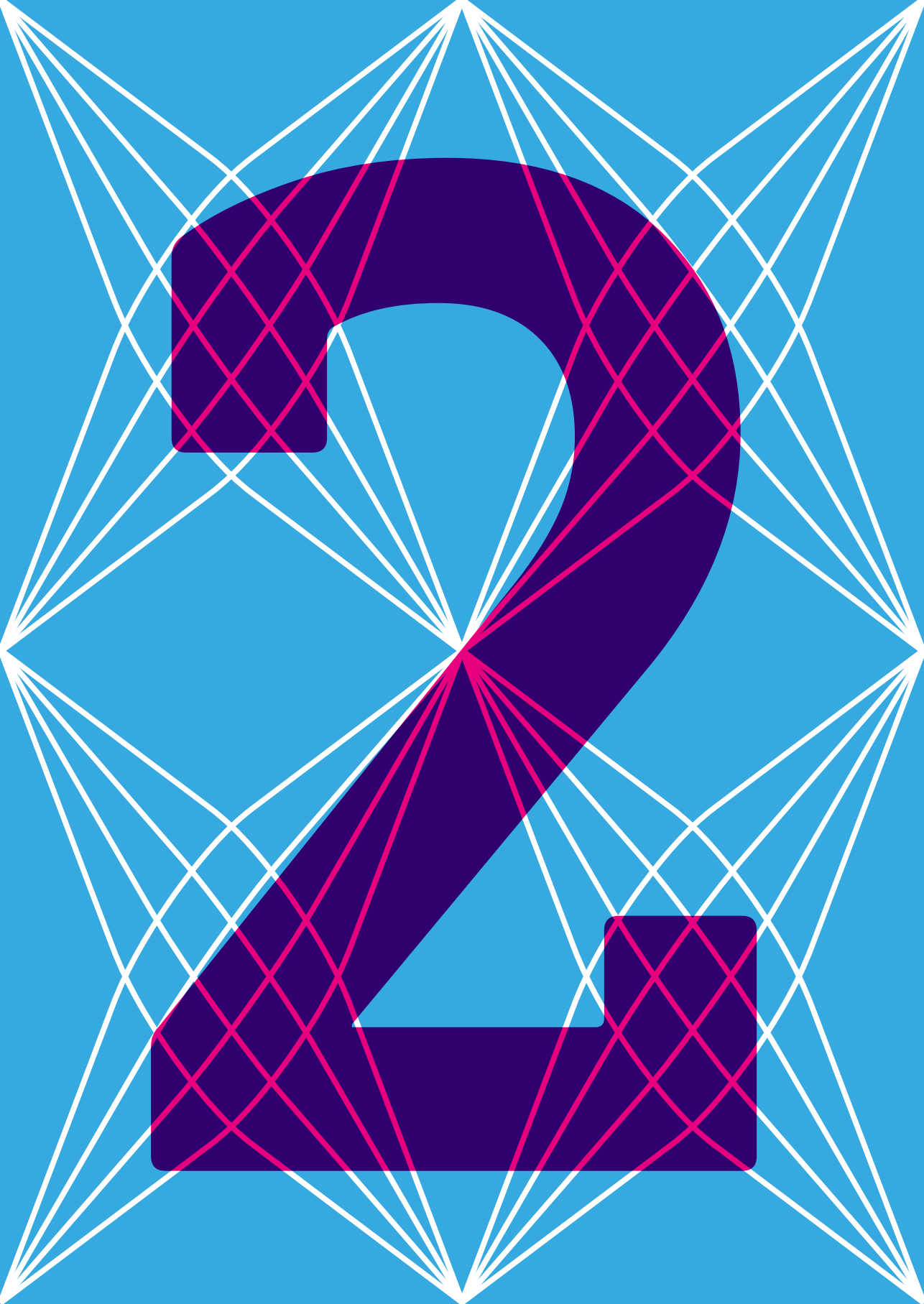
INVESTIGATING SCHIZOPHRENIA WITH A NETWORK APPROACH





A SYMPTOM NETWORK STRUCTURE OF THE PSYCHOSIS SPECTRUM

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Schizophrenia Research 2017; 189: 75-83

ABSTRACT

Current diagnostic systems mainly focus on symptoms needed to classify patients with a specific mental disorder and do not take into account the variation in co-occurring symptoms and the interaction between the symptoms themselves. The innovative *network approach* aims to further our understanding of mental disorders by focusing on meaningful connections between individual symptoms of a disorder and has thus far proven valuable insights to psychopathology. The aims of current study were to I) construct a symptom network and investigate interactions between a wide array of psychotic symptoms; II) identify the most important symptoms within this network and III) perform an explorative shortest pathway analysis between depressive and delusional symptoms.

We analysed interview data from n=408 male patients with non-affective psychosis using the Comprehensive Assessment of Symptoms and History (CASH). A network structure of 79 symptoms was computed to explore partial correlations between positive, negative, catatonia and affective symptoms.

The resulting network showed strong connectivity between individual symptoms of the CASH, both within- and between-domains. Most central symptoms included 'loss of interest', 'chaotic speech', 'inability to enjoy recreational interest in activities', 'inability to form or maintain relationships with friends' and 'poverty of content of speech'. The shortest pathway analysis between depressive and delusional symptoms displayed an important role for 'persecutory delusions'.

In conclusion, this study showed that individual psychotic symptoms are meaningfully related to each other not only within their own cluster, but also between different clusters and that important information may be acquired by investigating interactions at a symptom level.

1. INTRODUCTION

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM)[1] classifies patients with a specific mental disorder based on pre-defined combinations of symptoms. A more fundamental problem of the current classification system may however be its categorical nature. Therefore, current classification systems have been criticized extensively,[2,3] mainly because strong empirical evidence for the demarcations between symptoms is missing. Moreover, a slow progress in the identification of biomarkers[4] and specific genes[5] for disorders or symptoms illustrate the caveats of the current diagnostic classification system and potentially the absence of an underlying disease model. Thus, although it cannot be refuted that the DSM has contributed to more uniformity in the diagnostic process, the phenotypic heterogeneity and complexity to link symptoms to underlying pathophysiology remain substantial and problematic.

Besides the well-known categorical diagnostic criteria of schizophrenia, the DSM-5[1] incorporated a dimensional assessment to specify the severity of symptoms. The psychosis spectrum includes positive and negative symptoms as well as symptoms of disorganization and affective symptoms. Distinguishing between these symptoms is often difficult (e.g., negative symptoms are difficult to differentiate from depressive symptoms), which is partly due to the conceptual overlap between symptom domains. Nevertheless, this distinction is of great clinical relevance, since these symptom domains might require different treatments.

Previous factor analytic studies investigated this wide variety of symptoms within the psychosis spectrum by identifying factors underlying the symptomatology of schizophrenia. For example, a study by Derks and colleagues,[6] which included the present study sample, showed that variation in five dimensions (disorganization, positive, negative, mania, and depression) explained the largest portion of the variance within the psychosis spectrum. These results are in line with a review by Potuzak and colleagues[7] who concluded that most factor (analytical) studies reported four or five of the aforementioned dimensions within the psychosis spectrum. However, they also pointed out that symptoms often loaded on more than one factor and those factors often showed considerable overlap. Differences in applied instruments and methodology may explain part of this variability in findings. Moreover, since significant differences in symptom profiles between genders have been described in schizophrenia,[8,9] sample characteristics may also contribute to such variability. Overall, despite the relevance of factor studies in elucidating clusters of symptoms, their contribution to etiological research or valuable insights into psychopathology has been limited.[2]

Factor analytical studies are conceptually based on the 'common cause model' (i.e., an underlying latent factor 'causes' the associations among symptoms).[10] Within this view, the association between, for example, insomnia and loss of energy is attributed by a common latent factor 'major depressive disorder'. However, the possibility that the symptom insomnia might itself cause a lack of energy is ignored. As an alternative to the latent factor model, a novel network framework recently emerged. The network framework adopts a different perspective on psychopathology, by assuming that disorders are the result of the interactions between (specific) symptoms, i.e., that symptoms are able to influence each other.[10]

To date, the network approach has been applied to a wide variety of psychiatric disorders, including research in depression, social anxiety disorder, personality disorder and more recently psychosis.[11–14] For instance, a recent study investigated negative symptoms in patients with chronic schizophrenia at baseline and follow-up (i.e., 60-days later) and showed that (speech) symptoms remained strongly correlated, indicating that these symptoms were less influenced by treatment.[15] This study did not however include other symptoms (such as positive symptoms) to allow for the interpretation of negative symptoms in a wider spectrum of symptoms.

Here, we argue that exploring a network of a wide variety of symptoms is not only beneficial to identify interactions between an extensive range of symptoms, but also to explore the pathways and potential mediating items between symptoms and symptom domains. This can be done using shortest pathway analysis,[16] a recently developed hypotheses-generating technique. For the current paper, we chose to explore the shortest pathway between the depressive and delusional domains. Previous studies have identified that depressive symptoms are a central part of a psychotic episode[17,18] and argued that this association should be thoroughly investigated in further research. Thus, the aims of current study were to I) construct a symptom network and investigate interactions between a wide array of psychotic symptoms in a large cohort of male patients; II) identify the most important symptoms within this network and III) explore the pathway that connect depressive and delusional symptoms.

2. METHODS

2.1 Subjects

The data in this study was part of the Dutch multicenter study 'Genetic Risk and Outcome of Psychosis' (GROUP). The details of this study were described earlier.[19] In short, the full GROUP sample consists of patients, between 16 and 50 years old, meeting criteria for a non-affective psychotic disorder.[20] The patients were assessed at baseline and at three and six year follow-up. For the purpose of this study, baseline data was used. To avoid influences due to gender differences, we performed our analyses in only male participants. Due to the relatively low number of included women, we were not able to perform a network analysis in only female participants.

2.2 Measures

2.2.1 Symptom assessment

All symptoms were assessed with the Comprehensive Assessment of Symptoms and History (CASH)[21] in three of the four participating centers. The CASH is a structured interview, in which every item is rated on a scale ranging from 0 (none) to 5 (severe). The CASH includes lifetime rated and present state symptoms. For this study, the present state symptoms were chosen since this is more suitable for a network approach in which symptoms are assumed to influence each other. Moreover, it prevents the risk of recall bias. A total of 79 items (i.e., symptoms) were included in the statistical analyses. Since items that indicate a specification of a particular symptom (e.g., in the case of mania, state 'euphoric' or 'agitated' and in the case of depression state 'depressed' or 'anxious') were missing in approximately 20% of these cases we did not include these items.

The CASH includes thirteen a priori defined symptom domains (i.e., manic syndrome, major depressive syndrome, delusions, hallucinations, bizarre behavior, formal thought disorder, avolition - apathy, anhedonia - asociality, catatonic motor behavior, alogia, affective flattening and inappropriate affect), each including a different number of symptoms (Table 1).

2.2.2. Network construction

The details of the network approach and construction have been described earlier.[10,22] In brief, in our network, every item of the CASH (i.e., symptom) is represented as a *node*, whereas associations between nodes are represented as *edges*. Because, the current data were univariate not normally distributed, before performing analyses, we applied a non-paranormal transformation which is a tool for relaxing the normality assumption.[23]

We expressed associations in our network between two nodes by partial correlations between those two symptoms. Partial correlations are preferred over zero-order correlations because the latter might be spurious, i.e., resulting from indirect (via other symptoms) interactions. Moreover, the partial correlations were *L1-regularized*.[24,25] L1 regularization decreases the overall strength of some parameter estimates, while setting others to zero, thereby ensuring a more interpretable and sparse model. L1-regularization involves model selection with the Extend Bayesian Information Criterion (EBIC) to ensure accurate network estimations.[26–29] Model selection with EBIC involves the hyperparameter γ, which is commonly set to 0.5. Details of the association between γ and network connectivity have been published previously.[11] L1-regularization ensures an optimal balance between parsimony and goodness of fit of the network model. The network was estimated with *R* package *qgraph*.[30,31]

2.2.3. Network visualization

For the layout of the graph, the Fruchterman-Reingold algorithm was used, which calculates the optimal layout so that symptoms with less strength and less connections are placed further apart and those with more and/ or stronger connections are placed closer to each other.[32] The associations are either green indicating positive partial correlations or negative, coloured red. The thickness of an edge represents the strength of the association, with thicker lines representing stronger associations.[33] Association with- and between-domains were described.

2.2.4. Network analyses

First, we analysed our network by assessing three centrality measures for each node within the network, namely betweenness, node strength and closeness (Supplementary material Figure S3).[34–36] 'Betweenness' is the proportion of shortest paths of all possible empirical paths between two symptoms that have the node of interest in the path. It is measured by calculating how often a particular symptom lies on the shortest path between any combination of two nodes. 'Node strength' is calculated as the sum of the weighted number and strength of all connections of a specific node relative to all other nodes. Lastly, 'closeness' is the average distance from the node of interest to all other nodes. Closeness is calculated as the inverse of the sum of all the shortest paths between the index symptom and all other symptoms. In other words, a high closeness index indicates a short average distance of a specific node to all other symptoms.

Second, we carried out a more in-depth, concentrated analysis by computing shortest pathways between depressive and delusional symptoms. Although there are several options to reach one node from other nodes, there is only one shortest route, which is highlighted in the shortest pathway figure.[16,37,38] This analysis allows for the identification of shortest pathways from delusional symptoms to depressive symptoms (or vice versa) and shows possible mediating symptoms between these domains.

2.2.5 Network stability

There is no clear consensus regarding the minimum number of participants per parameter needed to generate stable networks.[39] Therefore we performed a stability check as described by Epskamp and colleagues.[22] More specific, we estimated the accuracy of edge-weights, by drawing bootstrapped confidence intervals (CIs) and performed the 'bootstrapped difference test' for edge-weights and centrality measure 'node strength' (for more information regarding this procedure, see methods section in the Supplementary Material).[22]

3. RESULTS

3.1 Study sample

Since the CASH was only assessed at three of the four centers, a total of 861 subjects completed the interview. From a total of 559 patients data was complete, with 408 male patients meeting the criteria for non–affective psychosis. In this sample, the mean age was 27.4 (SD=7.5) years, with a mean age of onset of 22.3 (SD=7.2). Of our sample, 306 participants (75%) were diagnosed with schizophrenia (Table 2).

3.2. Network analysis

3.2.1 Network structure and stability

The symptom network, based on the 79 symptoms, is presented in Figure 1. As described above, the CASH contains thirteen a priori defined symptom domains that could be largely identified in the network structure. Symptoms within the same a priori defined symptom domains are shown in the same color. By applying a stability check,[22] we demonstrated that our network can be interpreted as relatively stable. A detailed description of these additional analyses is presented in the Supplementary Material, figures S1–S3.

3.2.2. Associations of symptoms within a priori defined symptom domains

An overview of the associations of symptoms between and within these domains is shown in Table 3. Within-domain associations between symptoms were in general stronger than between-domain associations. For example, the symptoms of affective flattening (AF) were associated to almost all symptoms within the affective flattening domain (i.e., 93.3% of all possible connections). This was comparable for symptoms of anhedonia (AS) (i.e., 83.3% of all possible connections), which means that the priori defined domains by the CASH correspond with distinguishable subnetworks of symptomatology. Symptoms within the domains bizarre behavior (BB) and avolition (AP) were however less strongly connected within clusters (i.e., 16.7% respectively 33.3% of all possible connections).

Table 1. Abbreviations of a priori defined symptom domains and associated items (i.e., symptoms) as well as mean scores per item

Item label	Item description	Male participants (n = 408) Mean (SD)
	Manic Syndrome (MS) (red)	
MS 1	Euphoric mood	0.10 (0.47)
MS 2	Increase in activity	0.11 (0.56)
MS 3	Increased talkativeness / Pressure of speech	0.09 (0.49)
MS 4	Racing thoughts	0.23 (0.74)
MS 5	Inflated self esteem	0.13 (0.61)
MS 6	Decreased need for sleep	0.07 (0.49)
MS 7	Distractibility	0.29 (0.81)
MS 8	Reduced judgment	0.08 (0.46)
	Major depressive syndrome (MD) (orange)	
MD 1	Depressive mood	0.74 (1.24)
MD 2	Change in appetite	0.36 (0.94)
MD 3	Weight gain	0.18 (0.67)
MD 4	Weight loss	0.15 (0.64)
MD 5	Sleep disturbances	0.47 (1.07)
MD 6	Insomnia	0.21 (0.71)
MD 7	Hypersomnia	0.38 (0.98)
MD 8	Psychomotor agitation	0.34 (0.88)
MD 9	Psychomotor retardation	0.33 (0.84)
MD 10	Loss of interest or pleasure	0.87 (1.34)
MD 11	Loss of energy	0.93 (1.33)
MD 12	Feelings of worthlessness	0.57 (1.10)
MD 13	Diminished ability to think or concentrate	0.89 (1.33)
MD 14	Recurrent thoughts of death / suicide	0.43 (0.98)
	Delusions (DL) (yellow)	
DL 1	Persecutory delusions	1.15 (1.55)
DL 2	Delusions of jealousy	0.08 (0.42)
DL 3	Delusions of sin or guilt	0.25 (0.78)
DL 4	Grandiose delusions	0.52 (1.13)
DL 5	Religious delusions	0.38 (1.02)
DL 6	Somatic delusions	0.36 (0.98)
DL 7	Ideas and delusions of reference	1.10 (1.51)
DL 8	Delusions of being controlled	0.37 (1.01)
DL 9	Delusions of mind reading	0.57 (1.15)
DL 10	Thought broadcasting / Audible Thoughts	0.44 (1.12)
DL 11	Thought insertion	0.39 (1.02)
DL 12	Thought withdrawal	0.31 (0.93)
	Hallucinations (HA) (green)	
HA 1	Auditory hallucinations	1.02 (1.52)
HA 2	Voices commenting	0.68 (1.31)
HA 3	Voices conversing	0.50 (1.19)
HA 4	Somatic or tactile hallucinations	0.27 (0.82)
HA 5	Olfactory hallucinations	0.18 (0.67)
HA 6	Visual hallucinations	0.46 (1.10)

	Bizarre behavior (BB) (dark green)	
BB 1	Received comments about clothing and appearance	0.18 (0.58)
BB 2	Received comments about (inappropriate) behavior	0.27 (0.76)
BB 3	Aggressive or agitated behavior	0.36 (0.92)
BB 4	Ritualistic or stereotype behavior	0.29 (0.82)
	Formal thought disorder (FTD) (cyanogen)	
FTD 1	Disorganized speech	0.31 (0.88)
FTD 2	Pressured speech	0.46 (0.99)
FTD 3	Derailed speech	0.39 (0.93)
FTD 4	Chaotic speech	0.51 (1.11)
FTD 5	Incoherent speech	0.12 (0.50)
FTD 6	Illogical speech	0.22 (0.68)
FTD 7	Circumstantial speech	0.62 (1.11)
FTD 8	Distractible speech	0.21 (0.73)
FTD 9	Clanging	0.03 (0.33)
	Avolition - Apathy (AP) (light grey)	
AP 1	Impersistence at work or school	1.15 (1.50)
AP 2	Physical anergia	1.32 (1.47)
AP 3	Less attention to grooming and hygiene	0.54 (1.04)
	Anhedonia - Asociality (AS) (light blue)	
AS 1	Inability to enjoy recreational interest and activities	1.07 (1.49)
AS 2	Loss of sexual interest and activity	0.83 (1.38)
AS 3	Ability to feel intimacy and closeness	0.80 (1.34)
AS 4	Inability to form or maintain relationships with friends	1.24 (1.58)
	Inatttention (AT) (dark blue)	
AT 1	Social inattentiveness	0.63 (1.08)
AT 2	Inattentiveness during mental status task	0.91 (1.34)
	Catatonic motor behaviour (CMB) (pink)	
CMB 1	Stupor	0.17 (0.46)
CMB 2	Rigidity	0.10 (0.37)
CMB 3	Waxy flexibility	0.01 (0.12)
CMB 4	Excitement	0.08 (0.31)
CMB 5	Posturing and mannerism	0.08 (0.33)
	Alogia (AL) (purple)	
AL 1	Poverty of speech	0.71 (1.16)
AL 2	Poverty of content of speech	0.56 (1.01)
AL 3	Blocking of speech	0.18 (0.66)
AL 4	Increased latency when responding	0.60 (1.04)
AL 5	Perseveration	0.16 (0.57)
	Affective flattening or blunting (AF) (soft red)	
AF 1	Monotone facial expression	1.26 (1.36)
AF 2	Reduced spontaneous movement	1.00 (1.23)
AF 3	Paucity of expressive gestures	1.09 (1.30)
AF 4	Poor eye contact	0.59 (1.06)
AF 5	Affective non-responsivity	0.58 (0.94)
AF 6	Lack of intonation	0.76 (1.16)
	Inappropriate affect (IA) (dark grey)	
IA 1	Inadequate affect	0.28 (0.78)

Table 2. Demographics and clinical characteristics of (male) participants

	Study group (n = 408)
Age, years (Mean, SD)	27.41 (7.5)
Age of onset, years (Mean, SD)	22.3 (7.2)
Episodes (n)	1.8 (1.3)
Diagnosis, n (%)	
Schizophrenia	306 (75.0)
Schizoaffective disorder	39 (9.6)
Schizophreniform disorder	16 (3.9)
Delusional disorder	4 (1.0)
Brief Psychotic disorder	4 (1.0)
Psychotic disorder NOS	39 (9.6)
Antipsychotics	
Atypical	255 (62.5)
Typical	44 (10.8)
Antidepressants (%)	130 (31.9%)

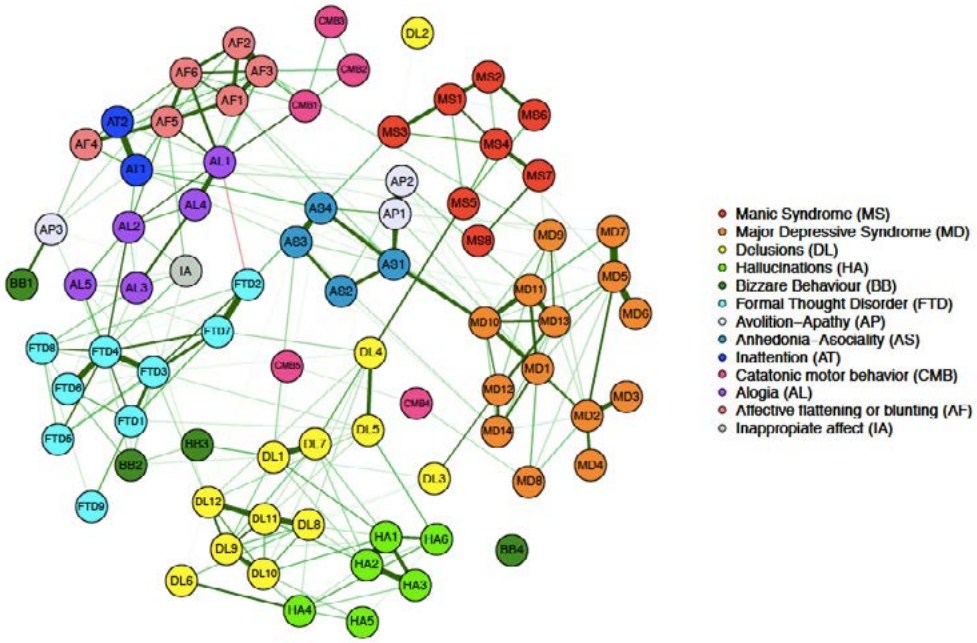

Figure 1. Network model of (male) participants (N=408). Network structure of 79 symptoms (based on symptomatology as assessed with the CASH) in male patients. Node colours refer to a priori symptom domains (see legend) and numbers refer to specific individual items (i.e. symptoms) (see Table 1). The associations are either positive (coloured green) or negative (coloured red), with thicker lines representing stronger associations.

Table 3. The number of connections within and between a-priori defined symptom domains

	Manic Syndrome (MS)	Major depressive syndrome (MD)	Delusions (DL)	Hallu-cinations (HA)	Bizarre Behavior (BB)	Formal Thought Disorder (FTD)	Avolition (AP)	Anhedonia (AS)	Inattention (AT)	Catatonic Motor behaviour (CMB)	Alogia (AL)	Affective flattening or blunting (AF)	Inappropiate affect (IA)
Manic Syndrome (MS) (%)	**14/28 (50)**												
Major depressive syndrome (MD) (%)	2/112 (1.8)	**38/91 (41.8)**											
Delusions (DL) (%)	1/96 (1)	1/168 (0.6)	**29/66 (43.9)**										
Hallucinations (HA) (%)	0/48 (0)	0/84 (0)	17/72 (23.6)	**10/15 (66.7)**									
Bizarre Behavior (BB) (%)	0/32 (0)	0/56 (0)	2/48 (4.2)	0/24 (0)	**1/6 (16.7)**								
Formal Thought Disorder (FTD) (%)	1/72 (1.4)	0/126 (0)	5/108 (4.6)	0/54 (0)	4/36 (11.1)	**24/36 (66.7)**							
Avolition (AP) (%)	0/24 (0)	7/42 (16.7)	1/36 (2.8)	0/18 (0)	1/12 (8.3)	1/27 (3.7)	**1/3 (33.3)**						
Anhedonia (AS) (%)	0/32 (0)	7/56 (12.5)	3/48 (6.2)	0/24 (0)	0/16 (0)	0/36 (0)	5/12 (41.7)	**5/6 (83.3)**					
Inattention (AT) (%)	0/16 (0)	1/28 (3.6)	0/24 (0)	0/12 (0)	0/8 (0)	1/18 (5.6)	2/6 (33.3)	2/8 (25)	**1/1 (100)**				
Catatonic motor behaviour (CMB) (%)	1/40 (0)	1/70 (1.4)	0/60 (0)	0/30 (0)	0/20 (0)	0/45 (0)	0/15 (0)	0/20 (0)	0/10 (0)	**4/10 (40)**			
Alogia (AL) (%)	0/40 (0)	1/70 (1.4)	1/60 (1.7)	0/30 (0)	0/20 (0)	8/45 (17.8)	2/15 (13.3)	1/20 (5)	5/10 (50)	3/25 (12)	**7/10 (70)**		
Affective flattening or blunting (AF) (%)	0/48 (0)	2/84 (2.4)	0/72 (0)	0/36 (0)	0/24 (0)	0/54 (0)	3/18 (16.7)	2/24 (8.3)	3/12 (25)	8/30 (26.7)	8/30 (26.7)	**14/15 (93.3)**	
Inappro-piate affect (IA) (%)	0/8 (0)	0/14 (0)	0/12 (0)	0/6 (0)	1/4 (25)	1/9 (11.1)	1/3 (33.3)	0/4 (0)	0/2 (0)	0/5 (0)	3/5 (60)	1/6 (16.7)	**0/0 (-)**

Overview of the number of connections between and within a priori defined symptom domains relative to the maximum number of possible connections. The maximum number of connections *within* domains can be computed as follows: suppose domain x has *Sx* number of symptoms, then the maximum number of connections within this domain equals *Sx* (*Sx*–1)/2. The maximum number of connections *between* domains can be calculated by multiplying the number of symptoms from one domain to the number of symptoms of the other domain. In bold the within-domain associations.

Interestingly, symptoms of the Schneider's First Rank Symptoms (FRS)[40,41] were strongly associated, namely DL9 (delusions of mind reading), DL10 (thought broadcasting), DL11 (thought insertion), DL12 (thought withdrawal), and DL8 (delusions of being controlled). Other notable connections were between symptom MD14 (recurrent thoughts of dead / suicide) and MD12 (feelings of worthlessness) and between MD14 and MD1 (depressive mood), namely since connections from suicidal thoughts to other symptoms were missing.

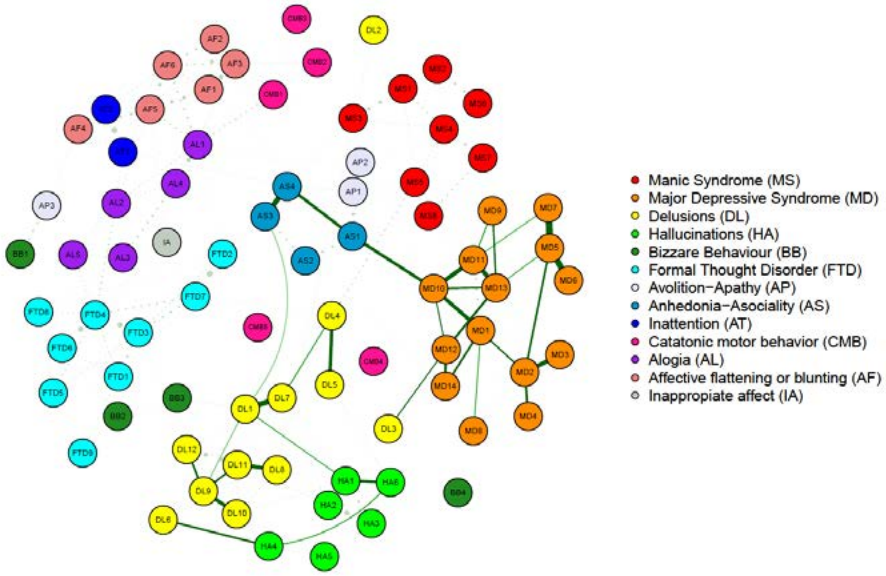

Figure 2. Shortest pathways between depression and delusional symptoms. Network illustrating shortest pathways between the depressive domain and delusional symptoms. Thicker lines represent stronger connections.

3.2.3. Associations of symptoms between a priori defined symptom domains

Table 3 further presents the percentage of connections between the domains. This was highest for alogia (AL) and inappropriate affect (IA) (i.e., 60% of all possible connections), followed by anhedonia (AS) and avolition (AP) (i.e., 41.7% of all possible connections), meaning that symptoms of these domains tend to co-occur (or might influence each other). Besides the number of possible connections, the domain hallucinations (HA) was only connected to the domain delusions (DL) and not to other domains, while the domain delusion was connected to 8 other a priori defined domains (among others: formal thought disorder and anhedonia).

Several specific symptoms connected the different domains with each other. For example: DL3 (delusions of sin or guilt) was related with depressive symptom MD12 (feelings of worthlessness). Moreover, node MS5 (inflated self-esteem) was related to DL4 (grandiose delusions). DL2 (delusions of jealousy) was weakly associated with MS3 (increased talkativeness), but not with other delusion symptoms. In addition, there were several dense connections between items of the domains avolition (AP) and anhedonia (AS) and the depressive domain, suggesting that these domains cluster together more closely.

3.2.4 Centrality measures

MD10 (loss of interest and pleasure), FTD4 (chaotic speech), AS1 (inability to enjoy recreational interest in activities), AS4 (inability to form or maintain relationships with friends) and AL2 (poverty of content of speech) showed high centrality (Supplementary Material Figure S4), indicating that these symptoms were central symptoms within the network.

3.2.5 Shortest Pathways: delusional and depressive symptoms

We further constructed a network showing the shortest pathways between the depressive and delusional domains (Figure 2). The shortest pathways from all delusional symptoms to depressive symptoms went through DL1 (persecutory delusions) and all passed through the domain anhedonia (AS) or vice versa. Notable, the shortest path from DL6 (somatic delusions) to depressive symptoms first went through symptoms of hallucinations.

4. DISCUSSION

The purpose of the current study was to determine the network structure of a broad range of symptoms within the psychosis spectrum (i.e., positive, negative, catatonia and affective symptom domains) based on the CASH, in a large sample of male patients with non–affective psychosis. To the best of our knowledge, this is the first report investigating a wide variety of symptoms in such a sample. Overall, the findings of this study lend support for the existence of the symptom domains as identified with the CASH, but also present evidence of multiple symptom-level associations not previously accounted for by factor analytical studies. Moreover, we identified specific symptoms with high centrality and specific associations both within-domains as well as between-domains, indicating that these symptoms may play an important role in the development and/or persistence of psychopathology. This report therefore is corroborative and additive to the existing literature.[15] In addition to knowledge about the clustering of symptoms, we add information on meaningful associations between individual symptoms, importance of certain symptoms to the network, as well as potential symptom pathways between-cluster domains. We herewith emphasize that important information might be lost when using only factor analytic methods.

4.1. Network clustering

The finding that, in general, network clusters correspond to results of factor analytic studies is in line with a previous study which compared principal component analysis with a network approach in 192 patients with 'unselected mental disorders'.[2] They showed an 89% overlap between network clusters and components. In addition, an earlier factor-analytic study, which also included the present sample[6] found that the thirteen a priori defined symptom domains of the CASH in this study were reduced to the existence of five factors (mania, positive, depression, disorganization, and negative symptoms) to describe the psychosis spectrum. Especially the first three factors are also distinguished in our network model, within different symptom clusters.

4.2. Research relevance and implications

Thus, when these different psychometric approaches show overlap in findings, such as the findings described above, what is the added value of network analysis when investigating psychopathology? First, we consider the overlap in findings as a proof of stable and replicable

research, which is relevant especially from the perspective of the recent replicability crisis.[42] Second, despite certain overlap in findings, we argue that our network approach highlights novel results that could not have been identified otherwise when using a factor analytic approach. For instance, it is not possible within a factor analytic approach to investigate associations between individual symptoms of a disorder and to distil symptoms that connect distinct domains with each other while these symptoms might play an important role in the maintenance of psychopathology. Furthermore, the network approach allows for the identification of central (i.e., important) symptoms within a network, which could ultimately prove to be important targets for clinical intervention. Below we discuss in detail both findings also identified in previous literature, as well as novel findings and hypothesis generating results relevant for further research.

4.3. Within- and between-domains associations

We will first address the *within*-domain association identified in our study. We regard the clustering between the symptoms 'recurrent thoughts of death/suicide' and 'feelings of worthlessness' and 'depressive mood' relevant. As most important finding we found no other connections from 'recurrent thoughts of death/suicide' to other symptoms (and domains). This is particularly interesting since – although most studies revealed the contribution of depressive symptoms on suicidality[43,44] – previous research has also described a correlation between positive symptoms and suicidality (i.e., command auditory hallucinations leading to suicidality).[45] Recently, a study using Structural Equation Modeling (SEM) to investigate the influence of depressive and positive symptoms on suicidal ideation,[46] reported that symptoms of depression predicted suicidal ideation. In addition, positive symptoms were found to moderate the relationship between depression and suicidality (i.e., an increase in positive symptoms was leading to 'an increase in the estimated effect of symptoms of depression on suicidal ideation').[46] Our results support the important role of depressive symptoms on suicidal ideation, since there were no connections from 'recurrent thoughts of death/suicide' to other non-depressive symptoms. Furthermore, we showed that there was no direct relationship between delusional symptoms and 'recurrent thoughts of death/suicide', but instead, delusional symptoms seem to activate depressive symptoms and via this pathway influenced suicidal thoughts. Of note, based on our cross-sectional design, no clear causal relationship can be inferred (see limitations). Nevertheless, our findings underline the importance of interconnectedness between symptoms, which as hypothesis generating results can guide future research (e.g., interventions in these hypothesized pathways).

Regarding *between* domains associations, we found several symptoms connecting different domains. These associations are important as 'bridge symptoms'[10] and are assumed to play an important role in maintaining and linking psychopathology. Of note, such bridge symptoms cannot be identified by studies using factor analytic approaches. Specifically, bridge symptoms connect different domains within a network and thus, the activation of these bridge symptom might spread the activation towards other domains. For instance, in our network 'grandiose delusion' was associated with 'inflated self esteem', indicating that manic patients suffering from 'grandiose delusion' may be more likely to develop other delusional symptoms or vise versa (a patient who has 'grandiose delusions' may be 'at risk' to develop manic symptoms).

Furthermore, our centrality analyses revealed symptoms, which had more *within* and *between* connections compared to other symptoms and are therefore more important to the network. Central symptoms are for instance 'loss of interest and pleasure', 'inability to enjoy recreational interest in activities' and 'inability to form or maintain relationships with friends'. From a clinical perspective, these are recognizable, important symptoms since they determine the active social participation of patients. Symptoms with high centrality measures are known as 'hubs' and could be important for guiding treatment interventions. In the way that these symptoms are well connected to other symptoms, intervening on these hubs might have more "downstream consequences" in the network, e.g., reducing the co-occurrence of other symptoms. Nevertheless, we would like to stress that these findings are hypotheses generating, and the application of these ideas in clinical practice need to be demonstrated in well-designed trials.

4.4. From depressive to delusional symptoms

A recent developed technique of the network approach is the use of shortest pathway analysis. Shortest pathway analysis is a hypothesis generating technique that allows for the investigation of potential pathways and mediating items accounting for the associations between symptoms.[16] Here we investigated pathways between the depressive and delusional symptom domains, as previous research identified that depressive symptoms are a central part of a psychotic episode[17,18] and argued this association should be more thoroughly investigated. Our results indicate that the cluster 'anhedonia-asociality', together with the symptom 'persecutory delusions' plays a central role in this association between depressive and delusional symptoms. This might indicate that patients suffering from persecutory delusions are more likely to develop symptoms of anhedonia and as a result develop depressive symptoms or vice versa (i.e., depressed patients, probably those more vulnerable to psychosis, may first develop symptoms of anhedonia, which may then lead to persecutory delusions and trigger the activation of other delusional symptoms). Of note, the fact that the domain anhedonia is involved within the shortest paths from delusion to depressive symptoms might be due to a conceptual overlap between depression and anhedonia. Given the cross-sectional design of our study, which does not allow for causal inferences, these pathways are – as previously emphasized – hypothesis-generating pathways that should be investigated in future confirmatory research studies.

4.5. In light of previous (network) studies

We believe our study adds on to a recent network study, which was conducted within a more narrow perspective, with a focus on the negative symptoms domain rather than on a wider spectrum of symptoms.[15] The authors grouped symptoms assessed with the Scale for the Assessment of Negative Symptoms (SANS), in four 'symptom groups' namely: lack of interest, poor responsiveness, apathy-inattentiveness and affect. Of note, the negative items of the SANS are incorporated in the CASH. Broadly, the symptom groups 'affect' (including items 'inability to enjoy recreational interest and activities', 'loss of sexual interest and activity', 'ability to feel intimacy and closeness' and 'inability to form or maintain relationships with friends') and 'lack of interest' (including items 'monotone facial expression', 'paucity of expressive gestures', 'poor eye contact', 'affective non-responsivity' and 'lack of intonation') are also 'recognizable' in our network, but not the other two domains. We therefore argue that taking into consideration a wider range of symptoms may yield results otherwise not

identified, as it allows for the interaction of between-domains items, which may themselves form new domain clusters. It may thus be beneficial to evaluate associations between domains rather than only at a single construct. Corroborative with this idea, Isvoranu and colleagues[16] recently showed that there is no direct relation between childhood trauma and positive or negative psychotic symptoms, but that this relation is only mediated by general psychopathology symptoms when these are included within a network.

Our findings can also be interpreted within the earlier proposed concept of the 'transdiagnostic dimension of psychosis'.[47] Van Os and colleagues[47] stated that an absolute focus on distinguishing illness (i.e., between 'psychotic' versus 'non-psychotic') hinders clinical practice and research, since co-occurring symptoms are not taken into account. For example, a delusional patient might suffer from depressive symptoms while not meeting criteria for a depressive episode. However these co-occurring symptoms (e.g., depressive symptoms) might have important implications for treatment interventions and the persistence of psychopathology. Moreover, our findings also underline the results of the Bipolar and Schizophrenia Network for Intermediate Phenotypes (B-SNIP) study: a large cohort study that investigated patients with psychosis, family members of these patients and healthy controls.[48] Three distinct 'biotypes' of psychosis were identified that did not respect traditional clinical diagnosis boundaries.[49] Thus, although in different domains, our findings are in line with this report, suggesting that new approaches towards diagnostic categories should be embraced and might be contributing to our understanding of schizophrenia. By using unconventional statistical approaches, we might be able to find more (data–driven) etiological models of mental disorders.

4.6 Limitations

With the relatively recent development and introduction of network analyses in psychiatry, many points of discussion remain, which are also applicable to this study. At first, a general criticism of networks concerns their replicability.[39] The first approach needed to improve network reproducibility is by estimating and publishing the stability of the networks. Although future studies are needed to prove generalizability of network models, the stability check of our network showed a relatively stable network (Supplementary material, figure S1-S3).[22] Second, we cannot rule out any bias due to the proportion of subjects who were excluded from analyses due to missing items. Nevertheless, imputation strategies are considered inappropriate for network analysis, since they are presumed to rely on associations between different symptoms. Therefore, imputation techniques will unquestionably bias the generated network model. Third, the naturalistic cross–sectional design does not permit to elucidate the possible effects of different pharmacological or other treatments on the symptomatology. Since 86% of the patients used different psychopharmacological agents, with highly variable duration and dosage the stratification of network-topology for treatment versus no treatment of different drugs was not feasible. Fourth, given the relatively low number of included female patients we were not able to construct a network for female patients, which would allow for gender comparison, as gender differences in symptomatology are now well established.[8,9,50] In line with this limitation we were unable to construct different subnetworks to assess the influence of important clinical characteristics (e.g., (extrapyramidal) side effects, age at onset of psychosis and /or total illness duration). Further network studies in larger groups should evaluate potential interactions of symptoms

networks with relevant clinical variables. Fifth, based on the included symptoms of the CASH we generated the present symptom network, however including different items from other assessment instruments may generate a different network.[39] Although the CASH is a widely used questionnaire including a wide variety of symptoms and validated in patients with psychotic disorders, the results should be interpreted with caution. Finally, as mentioned before, the cross-sectional design of the current study makes it impossible to investigate causal interactions between symptoms. Measuring symptoms within short time intervals as in Experience Sampling Method (ESM) studies are promising.[51] Future studies may add to our findings by investigating the individualized networks of symptoms and their (causal) changes over time within the psychosis spectrum.

5. CONCLUSION

In summary, the network structure we identified in the current study shows that individual psychotic symptoms are meaningfully related to each other. Our results support the overall structure indicated by previous factor-analysis based symptom domains, while in addition we described relations and interactions between the symptoms themselves. Investigating the network-topology may inform further research of etiology, course of illness and ultimately treatment selection.

ACKNOWLEDGMENTS

We are grateful for the generosity of time and effort by the patients, their families and healthy subjects. Furthermore we would like to thank all research personnel involved in the GROUP project, in particular: Joyce van Baaren, Erwin Veermans, Ger Driessen, Truda Driesen, Karin Pos, Erna van 't Hag, Jessica de Nijs, Atiqul Islam, Wendy Beuken and Debora Op 't Eijnde. Dr. H.G. Ruhé is supported by a NWO/ZonMW VENI-Grant #016.126.059.

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SUPPLEMENTARY MATERIAL

1. SUPPLEMENTARY METHODS

1.1. Network stability

The details of network stability checks were described earlier.[S1] In short, although several studies applied network models to psychopathology, fewer studies described possible statistical methods to test the stability of generated networks. 'Stability' refers to the degree of certainty at which the structure of a network and its interpretation would be comparable when estimating the same network in another (comparable) sample. Epskamp et al.[S1] described statistical methods to further explore this issue in networks. Applying such stability checks is needed to improve reproducibility of networks. With respect to the current study, given the wide variety of the symptoms, we wanted to test the robustness of our network. Therefore, we estimated the accuracy of edge-weights, by drawing bootstrapped confidence intervals (CIs) and performed the 'bootstrapped difference test' for edge-weights and centrality measure 'node strength'.

1.2. Bootstrapped confidence intervals

For both stability checks the R package 'bootnet' was used.[S1,S2]In a generated network an edge between two symptoms has a given weight. However, we want to know whether an edge-weight has the same value when constructing the same network in another sample. We therefore utilized bootstrapping methods to construct a 95% CI around the regularized edge weight (termed as bootstrapped CI).[S1]A wide interval indicates that the stability is low and a narrow interval indicates that the stability is high.

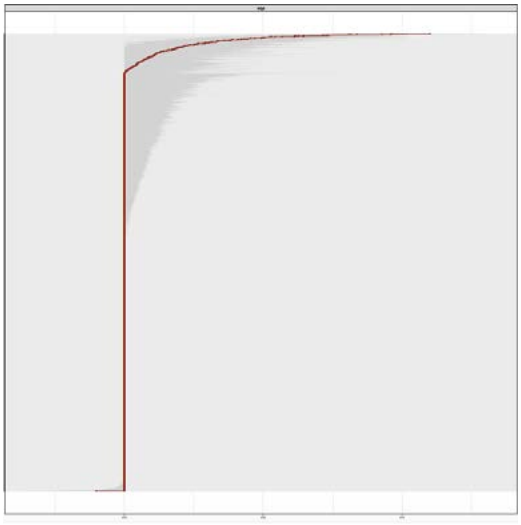
When 'bootstrapping',[S3] a new dataset is constructed by multiplying (here 1000 iterations) the sample to population size and sample from this bootstrapped population. Then this population is sampled again; called resampling. These new samples will show a certain variation with a normal distribution. The 95% - bootstrapped CI is the variation that covers 95% of the cases. Of note, the results of the bootstrapped CIs should not be interpreted as a significance tests, but only as a method to estimate the accuracy of the network, generated from this specific sample.

1.3. Bootstrapped difference test

We also applied bootstrapping to investigate whether edge-weights or centrality measures differ significantly from each other. A difference score between the bootstrap values of a certain edge-weight and bootstrap values of another edge-weight is calculated. When constructing a bootstrapped CI around this difference score, a null-hypothesis test can be performed. Moreover, when the constructed CI includes 'zero', the edge-weights do not differ significantly from each other. In the same way, we applied the bootstrapped difference test to the centrality measure 'node strength' (i.e., the sum of the weighted number and strength of all connections of a specific node to all other nodes).

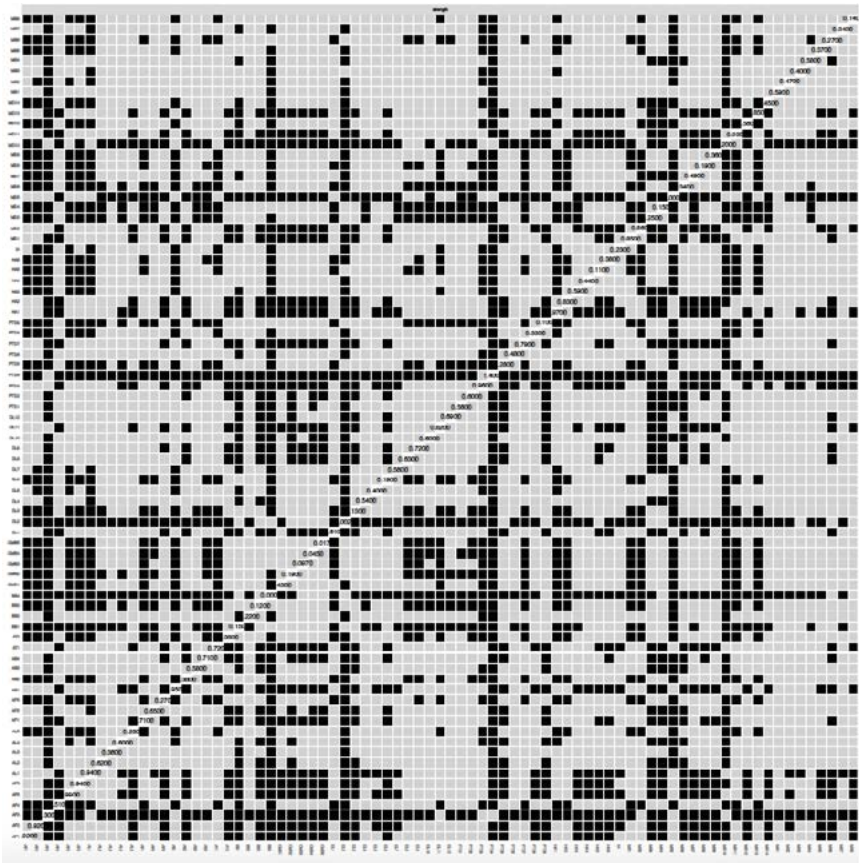
Of note, when performing multiple significant tests, the problem of 'multiple testing' exists (i.e., due to performing many significance tests, significant results could be find purely by chance). To correct for these Type I Errors, the 'Bonferroni corrections' [S4] are frequently applied. However, applying Bonferroni corrections to the network approach will be too conservative and result in very low significance levels, which appears unfavourable. [S1] However, there are currently no other methods of correcting for the 'multiple testing problem' or other stability checks. Therefore, the results of the bootstrapped difference test should be interpreted with caution.

2. SUPPLEMENTARY FIGURES

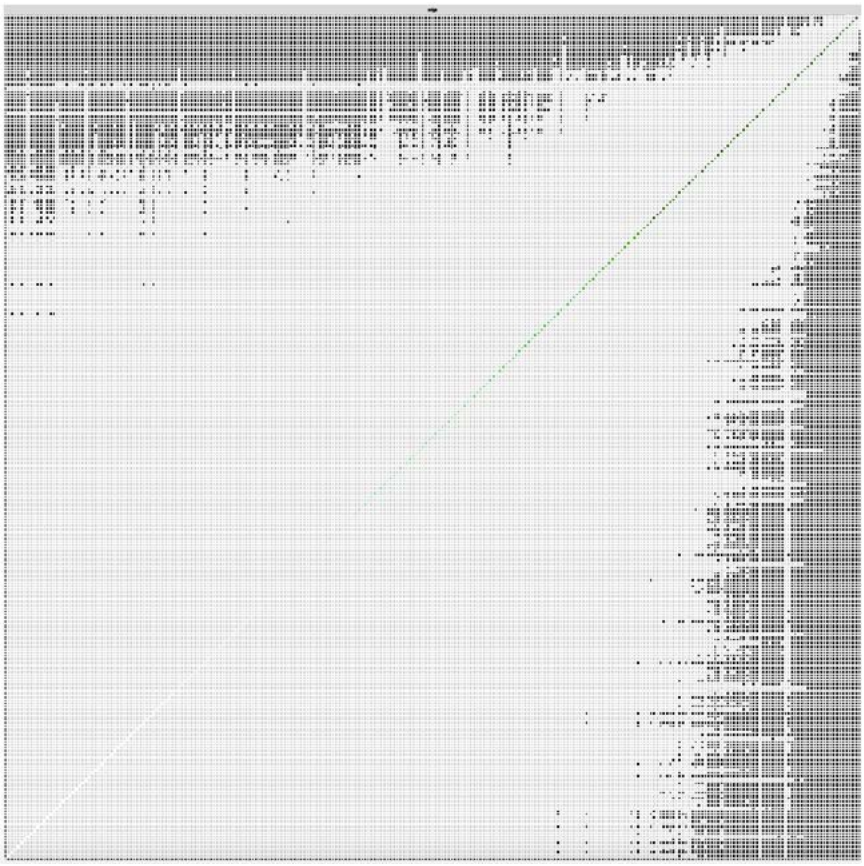


2.1. Figure S1: Stability of the network: bootstrapped confidence intervals. Figure showing the bootstrapped confidence intervals (CIs) of estimated edge-weights of all 79 symptoms (as assessed with the CASH), in grey. On the x-axis we show the distribution of the bootstrapped estimations of the CIs; on the y-axis all edges are shown, however, the labels of the edges were deleted to prevent cluttering. The edges are arranged such that the one with the highest edge-weight is at the top and the lowest edge-weight at the bottom. The red line shows the calculated edge-weight in our network, while the grey area – surrounding the red line – indicates the width of the bootstrapped CIs. Of note, overlapping CIs means that edge-weights likely do not significantly differ from one-another, in that case the order of the edges (i.e., the applied top-down ordering) should be interpreted with caution.

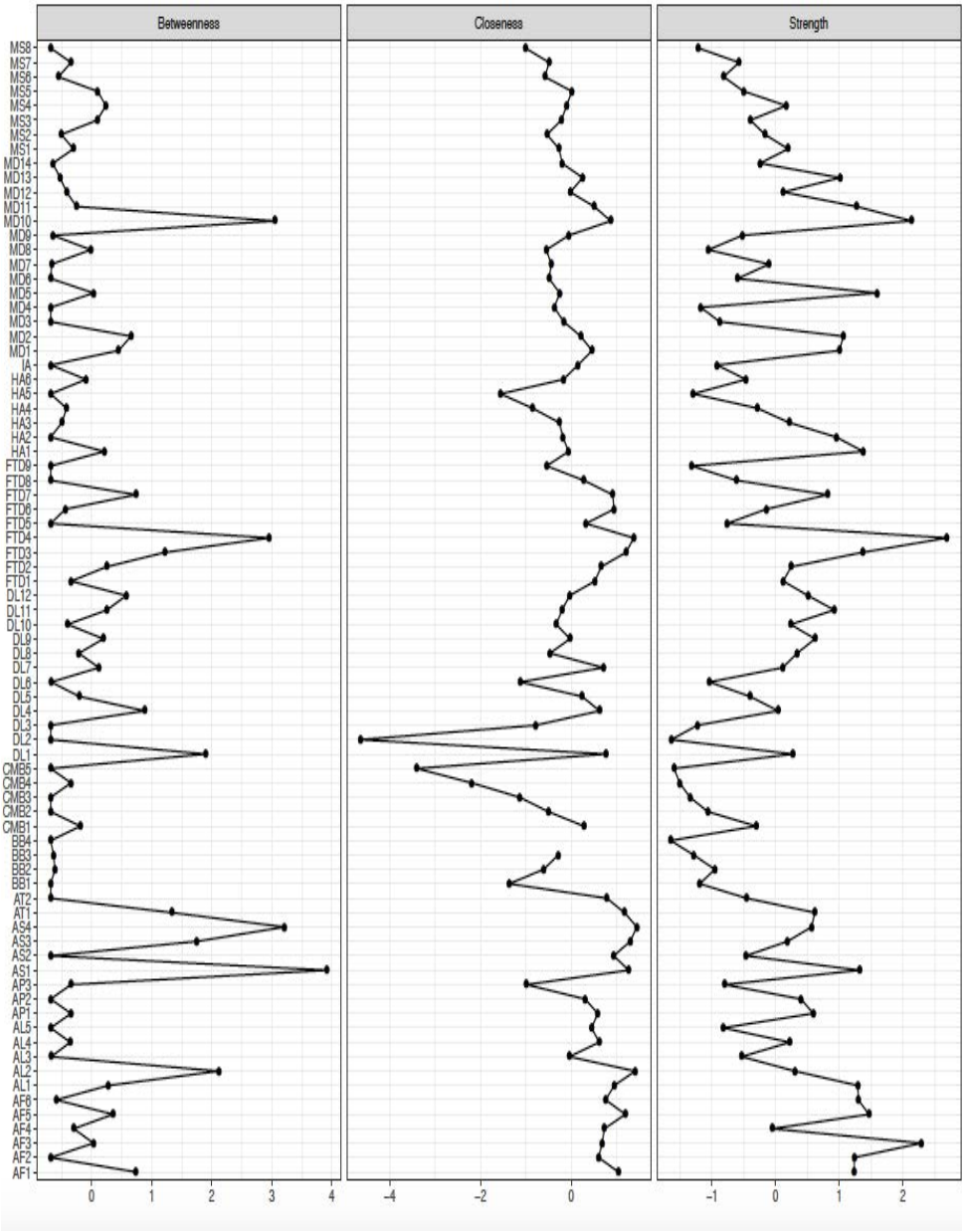
When interpreting this figure please note: i) many edges are consistently estimated as zero, ii) some edges are larger then zero, but the bootstrapped CIs contain zero and iii) some edges are larger than 0 with CIs not including zero. The fact that a large number of edges with a weight larger than zero have large CIs with zero in them means that we should interpret the network with caution (i.e., the figure suggest that bootstrapped edge-weights might differ from each other, but this might not be significant).



2.2 Figure S2: Stability of the network: bootstrapped stability tests for node strength. Figure showing bootstrapped stability difference tests (α = 0.05) of the centrality measure 'node strength' (i.e., the sum of the weighted number and strength of all connections of a specific node to all other nodes) in order to show whether the centrality measure node strength of the symptoms differs significantly between nodes. Both axes list all 79 nodes. The grey boxes represent node strengths that do not differ significantly from each other, while black boxes indicate node strengths that do differ significantly. The numbers in the white boxes (i.e., the diagonal line) represent the value of the centrality measure 'node strength' of the specific node. Here, a high number of black boxes can be observed, suggesting significant differences between the centrality measures of 'node strength' within our network.



2.3 Figure S3: Stability of the network: bootstrapped stability tests for edge-weights. Figure showing bootstrapped stability difference tests (α = 0.05) for edge-weights to investigate whether edge-weights differ significantly from each other. At both axes are all edges (i.e., n*(n-1)/2= 3081) between all 79 symptoms, listed. The grey boxes represent edge weights that do not differ significantly from each other, while black boxes indicate edge-weights that do differ significantly. The diagonal represents the strength of the edge weights, changing from white (i.e., weaker edges) to dark green (i.e., stronger weight).



2.4 Figure S4: Centrality measures of all symptoms. Figure showing three centrality measures: betweenness, node strength and closeness of all symptoms as assessed with the CASH. [S5-7] 'Betweenness' is measured by calculating how often a particular symptom lies on the shortest path between any combination of two nodes. 'Node strength' is calculated as the sum of the weighted number and strength of all connections of a specific node in relation to all other nodes. 'Closeness' is the average distance from the node of interest to all other nodes. Centrality indices are shown as standardized z-scores. For abbreviations of symptoms see Table 1.

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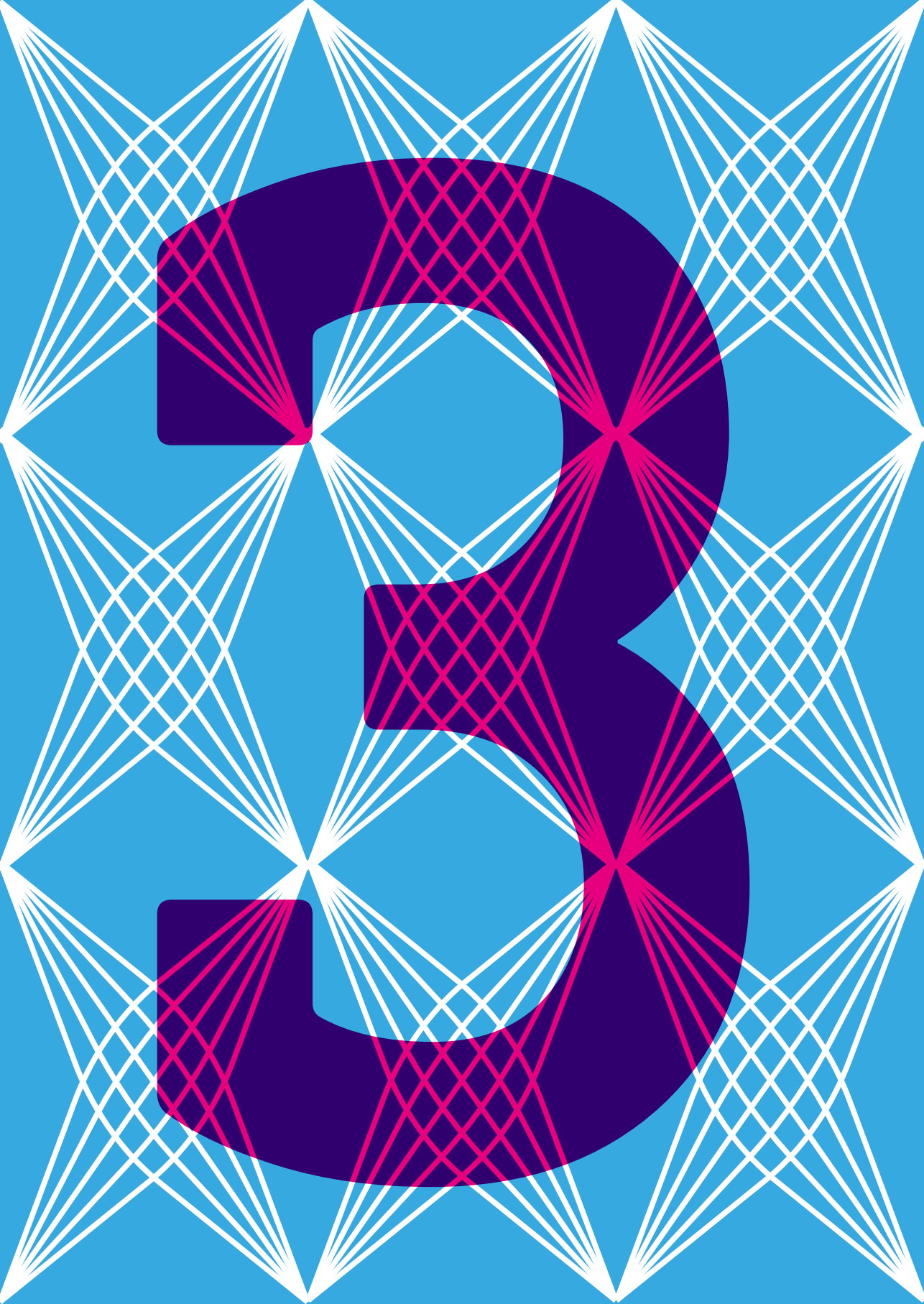

A STATE-INDEPENDENT NETWORK OF DEPRESSIVE, NEGATIVE AND POSITIVE SYMPTOMS IN MALE PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Schizophrenia Research 2018; 193: 232-239

ABSTRACT

Depressive symptoms occur frequently in patients with schizophrenia. Several factor analytical studies investigated the associations between positive, negative and depressive symptoms and reported difficulties differentiating between these symptom domains. Here, we argue that a network approach may offer insights into these associations, by exploring interrelations between symptoms. The aims of current study were to I) construct a network of positive, negative and depressive symptoms in male patients with schizophrenia to investigate interactions between individual symptoms; II) identify the most central symptoms within this network and III) examine group-level differences in network connectivity between remitted and non–remitted patients.

We computed a network of depressive, positive and negative symptoms in a sample of 470 male patients diagnosed with a psychotic disorder. Depressive symptoms were assessed with the Calgary Depression Rating Scale for Schizophrenia, while psychotic symptoms were assessed with the Positive and Negative Syndrome Scale. Networks of male patients who fulfilled remission criteria (Andreasen et al., 2005) and non–remitters for psychosis were compared.

Our results indicate that depressive symptoms are mostly associated with suicidality and may act as moderator between psychotic symptoms and suicidality. In addition, 'depressed mood', 'observed depression', 'poor rapport', 'stereotyped thinking' and 'delusions' were central symptoms within the network. Finally, although remitted male patients had a similar network structure compared to non-remitters the networks differed significantly in terms of global strength. In conclusion, clinical symptoms of schizophrenia were linked in a stable way, independent of symptomatic remission while the number of connections appears to be dependent on remission status.

1 INTRODUCTION

Patients with schizophrenia may present with a wide variety of symptoms: positive and negative symptoms are considered core features of schizophrenia, but depressive symptoms are also common, with a modal prevalence rate of 25%.[1,2] In order to study the associations between symptoms, a network approach might be advantageous - in comparison to traditional factor-analytic approaches, network models offer the possibility to study potential interactions between individual symptoms.[3,4] Specifically, within a network perspective, it is presumed that mental health problems result from complex interactions between individual symptoms, which influence and reinforce each other, instead of originating from an underlying latent disorder.[4]

In the past years the network approach has been increasingly applied to study psychopathology (for a review see Fried et al.).[5–8] For instance, Wigman and colleagues[9] showed that the networks of individuals with a psychiatric diagnosis contained positive feedback loops, which may explain a 'downward spiral of negative mental states', which are clinically recognizable in the way symptoms of psychosis can enhance each other. Isvoranu and colleagues[5] have moved beyond symptom-symptom associations, integrating environmental risk factors into network models; they found that childhood trauma was associated with symptoms of general psychopathology and not directly to positive or negative symptoms. The network approach is therefore not bound to 'traditional' diagnostic categories – psychopathology is conceptualized as a complex system and the 'overlap' between symptoms and risk factors of different disorders is a source of valuable information rather than a problem to overcome.

Notably, a recent network paper using the baseline symptoms of the 'Genetic Risk and Outcome of Psychosis' (GROUP) study[10] showed that in male patients with schizophrenia the symptoms assessed by the Comprehensive Assessment of Symptoms and History (CASH)[11] displayed strong within-and between- cluster interactions and formed a network with central symptoms such as 'loss of interest', 'chaotic speech', 'inability to enjoy recreational interest in activities', 'inability to form or maintain relationships with friends' and 'poverty of content of speech'.[8] Central symptoms have been argued to be relevant as targets for treatment interventions, as these symptoms are most likely to influence the other symptoms in the network. In addition, relations between suicidality, depressive and positive symptoms were investigated and based on the strong associations between depressive symptoms and suicidality and between delusional and depressive symptoms, but in the absence of a direct relationship between delusional symptoms and suicidality, it was hypothesized that delusional symptoms may activate depressive symptoms and influence suicidal thoughts via this pathway.

However, the CASH is limited in addressing current depressive symptoms, since within the CASH the DSM-IV criteria are investigated; these are known to show overlap with other symptoms in patients with schizophrenia (i.e., negative and extrapyramidal side effects).[2] We therefore aimed to expand on the previous study and investigate the association between positive, negative and depressive symptoms further by constructing a network model that includes the Calgary Depression Rating Scale for Schizophrenia (CDSS),[12] which is a validated instrument for assessing depression in patients diagnosed with schizophrenia.[13]

The CDSS was administered at first follow-up. We combined data from the CDSS and the Positive and Negative Syndrome Scale (PANSS)[14] assessed at follow-up. In addition, the latter questionnaire was used to assess psychotic remission status. A previous study in depression showed that different severity symptom networks in depressed patients (at baseline) were associated with varying illness courses.[15] In order to apply this type of profiling, first the stability (i.e., state-independence) of a network structure is required. However, this has not been investigated in patients with schizophrenia and was therefore the secondary aim of this study.

In summary, network analysis has been shown to help disentangle the interactions between individual symptoms of a disorder and as such we have employed this methodology in the current study in order to investigate the association between psychosis and depressive symptoms. The aims of current study were as follows: I) to construct a network of symptoms in male patients with a schizophrenia spectrum disorder in order to investigate how negative, positive and depressive symptoms interact, by using a validated questionnaires to asses depressive symptoms; II) to identify the most central symptoms within this network and III) to examine potential group-level differences in network connectivity between remitted and non–remitted patients. This might reveal important profiling information for prognosis.

2 METHODS

2.1 Subjects

Data was collected as part of the longitudinal multicentre GROUP study, described in detail elsewhere.[10] Here we used data from a GROUP subsample, consisting of male patients with non-affective psychotic disorders, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[16] Of note, we chose to include *only* male patients, given the known gender differences in symptomatology and the relatively small number of included female patients in GROUP.[17,18] Measurements of the GROUP study were collected at baseline, at 3 and 6-year follow-up. Because the CDSS was obtained in a large subsample at 3-year follow-up, we used data from this wave only.

2.2 Symptom assessment

The CDSS[12] was used to assess depressive symptoms. The CDSS is a nine-item structured interview, in which every item is rated on a scale ranging from 0 (absent) to 3 (severe) (Supplementary Table S1). The PANSS[14] was used to measure the severity of positive and negative symptoms. The PANSS consists of 30 items (Supplementary Table S1) in which each item is scored on a scale ranging from 1 (absent) to 7 (extreme) and it is divided into three subscales: positive, negative and general psychopathology (e.g., depression, anxiety and somatic concern) symptoms. The general psychopathology subscale was not included in our network, since inclusion of this subscale would have created a substantial overlap between with the items of the CDSS. In addition, we used the Andreasen remission criteria[19] to assess whether a patient was in symptomatic remission at the time of assessment (i.e., during the second assessment of the GROUP-cohort). The Andreasen criteria constitute a symptom severity and a time criterion. The symptom severity criterion was determined by a score of 3 or lower on all of the following items: P1 (delusions), P2 (disorganization),

P3 (hallucinatory behavior), G5 (mannerisms/posturing), G9 (unusual thought content), N1 (blunted affect), N4 (passive social withdrawal), and N6 (lack of spontaneity). For the time criterion we assessed whether a symptomatic remission had been maintained for 6 months or longer prior to the time of assessment (i.e., 6 months before the assessment).

2.3 Statistical analysis

2.3.1 Network construction

We constructed a symptom network as previously described[4,8,20] of positive, negative and depressive symptoms. In the generated network model, individual items (i.e., symptoms) were represented as *nodes* and associations between them as *edges*.

A non-paranormal transformation (i.e., a tool for relaxing the normality assumption) was performed prior to the analysis, since current data were not normally distributed [21]. For constructing the generated network, the *R* package *qgraph* was used.[22,23] The network structure was based on *L1-regularized* partial correlations.[24,25] For estimating the relations between symptoms, partial correlations are chosen over zero-order correlation (i.e., correlation between two variables), since zero-order correlations can be spurious (i.e., resulting from indirect interactions). Moreover, L1-regularization guarantees an optimal balance between parsimony and goodness of fit of the network model. A specific form of L1-regularization, LASSO regularization, encompasses model selection with the Extended Bayesian Information Criterion (EBIC), which uses a so-called hyperparameter γ.[26–29] The details of the influence of γ on the network have been published earlier.[15] In the generated network the hyperparameter was set to 0.5, which showed an optimal balance between a network with many connections (γ=0) and a network with minimal connections (γ=1). The layout used when computing the networks was derived from the Fruchterman-Reingold algorithm, which computes the optimal layout so that nodes with stronger and/or more connections are placed closer and more central to each other.[30] We primarily displayed the correlation results in a figure as the applied Fruchterman-Reingold algorithm simultaneously shows the strength of associations between different symptoms (thickness of the connections) as well as the direction of these associations (i.e., positive or negative association) in the network.

2.3.2 Network analysis

Based on earlier network studies, we expected that some symptoms would cluster strongly. Therefore, in our results we will use the term *'communities'* (i.e., a part of the total network that contains strongly connected items). At first, a symptom network was constructed for the total sample of male subjects. Communities and important symptom interactions were described, with a specific focus on the relations between delusional and depressive symptoms (including suicidality). Moreover, we analysed the importance of each node by investigating the following centrality measures: 'node strength', 'closeness' and 'betweenness'.[31–33] For a description on centrality measures see Supplementary Methods. In the second step of the analyses, the symptom network of male patients who were in remission (based on the PANSS-remission tool) was compared to the network of male patients who were not in remission. In order to compare networks of remitted and non-remitted male patients, we used a network comparison test (NCT),[34] which is a permutation test (1000 iterations) in which the difference between networks of two groups (i.e., remitters

and non–remitters) is calculated repeatedly for randomly regrouped individuals. The NCT is implemented in the *R* package 'NetworkComparisonTest'.[23,35] By using the NCT it is possible to compare two (independent) networks based on i) network structure and ii) overall global strength. For details on the NCT see Supplementary Methods.

2.3.3 Additional analyses

We performed a stability check to investigate the stability of the generated networks.[20] Moreover we used Exploratory Graph Analyses (EGA) to detect highly connected clusters of symptoms (i.e., *communities*).[36] For a detailed description of both analyses see the Supplementary Methods.

3 RESULTS

3.1 Study sample

After removing missing data, 470 male patients were included in the analyses (from which 32% were in remission; see Table1). Mean and median scores of positive, negative and depressive symptoms are presented in Supplementary Table S1. Moreover, the derived correlation matrix between the different items is presented in Supplementary Table S2. The (overall) mean score of the CDSS was 1.07 (SD=2.04) for patients in symptomatic remission from psychosis and 2.5 (SD=3.1) for patients not in remission, respectively. A commonly used cut–off value of the CDSS of ≥ 6 was used,[37] 17.1% of the patients in the psychotic group suffered from depression. In the non-psychotic (remission) group this was 5.3% (Table1). The *time criterion* of the psychotic remission criteria was lacking in 4 patients (of whom 3 were in symptomatic remission). We therefore excluded these patients from the comparisons between remission and non–remission.

Table 1. Demographics and Clinical Characteristicsc

	Male participants (n = 470)	**Males Remission[a] (n = 150)**	**Males Non – Remission[a] (n = 316)**
Age at inclusion, years (Mean ± SD)	26.9 (6.6)	25.99 (6.60)	27.2 (6.59)
Number of episodes (Mean ± SD)	2.21 (1.41)	1.94 (1.33)	2.36 (1.44)
CDSS total (Mean ± SD)	2.1 ± 2.9	1.07 (2.04)[b]	2.5 (3.1)[b]
CDSS (%), no depression (score ≤ 5)	407 (86.6)	142 (94.7)[b]	262 (82.91)[b]
PANSS (Mean, SD)			
Positive symptoms	1.68 (0.70)	1.87 (0.75)	1.27 (0.31)
Negative symptoms	1.75 (0.76)	1.93 (0.83)	1.37 (0.39)
Diagnosis			
Schizophrenia (%)	371 (78.9)	110 (73.33)	259 (81.96)
Schizoaffective disorder (%)	83 (17.7)	27 (18.0)	54 (17.09)
Schizophreniform disorder (%)	16 (3.4	13 (8.67)	3 (0.95)
Use of antipsychotic medication, n (% yes)[c]	366 (77.9)	110 (73.3)	254 (80.4)

[a] Remission criteria based on the PANSS remission tool.[19]
[b] Mean differences between remission and non – remission was significant ($p < 0.001$) for both CDSS score and percentage of depressed patients.
[c] Data were missing for 52 patients.

3.2 Network including all patients (Figure 1)

The network of negative, positive and depressive symptoms is presented in Figure 1; symptoms from the original subscales (depressive, positive and negative symptoms) are shown in different colours. In general, all symptoms within the network were connected. Of note, the stability check showed considerable overlap between bootstrapped confidence intervals (CIs), indicating that the generated network should be interpreted with caution regarding the differences between edge-weights (see Supplementary Material Figures S1-S3). Of note, fit indices (e.g., RMSEA/BIC indices) to contrast for parsimony can be extracted from the *qgraph* package 'ggmFit'. However, there are currently several problems with such fit indices in network models and this method has not been validated. Consequently, we decided to not report these fit indices.

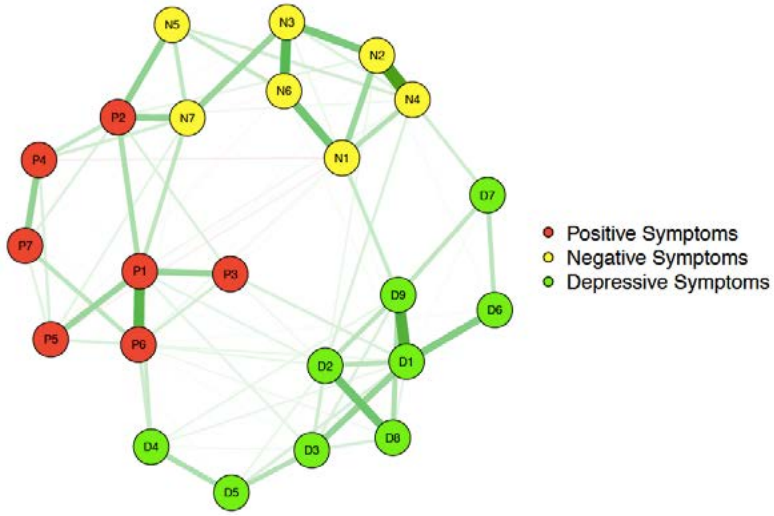

Figure 1. Network structure of psychotic symptoms and depressive symptoms male participants (n=470). The partial correlations are either positive (colored green) or negative (colored red), with thicker lines representing stronger correlations. D1 indicates depressed mood; D2, hopelessness; D3, self-deprecation; D4, guilt ideas of reference; D5, pathological guilt: D6, morning depression; D7, early wakening; D8, suicide; D9, observed depression; N1, blunted affect; N2, emotional withdrawal; N3, poor rapport; N4, passive social withdrawal; N5, difficulty in abstract thinking; N6, lack of spontaneity; N7, stereotyped thinking; P1, delusions; P2, disorganization; P3, hallucinatory behavior; P4, excitement; P5, grandiosity; P6, suspiciousness; P7, hostility.

3.2.1 Communities

We used EGA to identify 3 highly connected clusters of symptoms (i.e., *communities*) within the original three subscales (i.e., positive and negative subscales of the PANSS and the depressive symptoms as derived from the CDSS; see Supplementary Figure S4). The depressive symptoms formed 1 community; within this community strong connections between D2 (hopelessness) and D8 (suicide), as well as between D9 (observed depression) and D1 (depressed mood) were prominent. The second community was formed of all positive symptoms, including the negative symptoms N5 (difficulty in abstract thinking) and N7

(stereotyped thinking). Within this community, clustering between P1 (delusions) and P6 (suspiciousness), and P3 (hallucinatory behavior) and P5 (grandiosity) were the strongest. The last community was formed by the remaining negative symptoms: N1 (blunted affect), N2 (emotional withdrawal), N3 (poor rapport), N4 (passive social withdrawal) and N6 (lack of spontaneity).

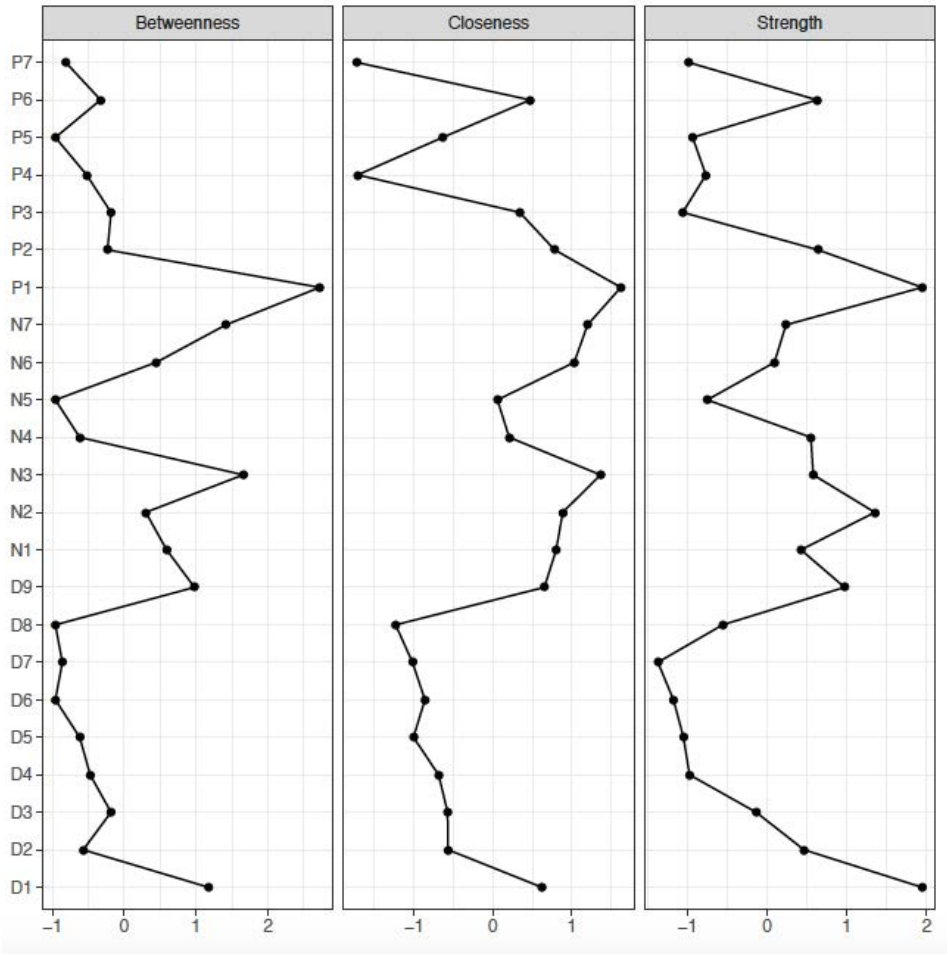

Figure 2. Centrality measures of all symptoms within the network (n=470). Figure showing the centrality measures (i.e., betweenness, node strength and closeness) of all symptoms within the network. The highest betweenness index (i.e., P1) reflects the node, that is the most involved in the information flow through the network, since it is calculated by counting how often a symptom is passed on the shortest path between any combinations of two nodes. The nodes with the highest 'node strength' (i.e., P1 and D1) reflect the nodes with the most and strongest connections, since node strength is calculated as the sum of the weighted number of all connections that are incident in a specific node. Lastly, the highest closeness index (i.e., P1) reflects the node that is most easy to reach, since it is calculated as the inverse of the mean shortest distance to all other nodes. For the abbreviations of the items, see Figure 1.

3.2.2 Interrelatedness between depressive and delusional symptoms

There was one association between depressive and positive symptoms, namely between D8 (suicide) with P6 (suspiciousness). Of note, between suicide (D8) and delusions (P1) was no direct connection. However, P1 (delusions) was connected with (other) depressive symptoms, including D2 (hopelessness), D3 (self-deprecation) and D4 (guilt ideas of reference).

3.3 Centrality measures

D1 (depressed mood), D9 (observed depression), N3 (poor rapport), N7 (stereotyped thinking) and P1 (delusions) showed highest centrality measures (Figure 2), indicating that these symptoms may be important symptoms within this network.

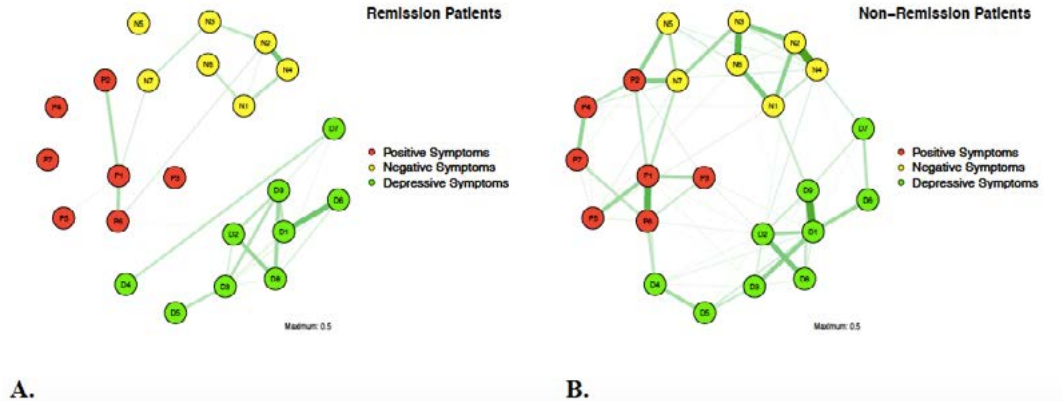

Figure 3. Network model of remitted (n=150) (A.) and non-remitted (n=316) (B.) male participants. Network structure of positive, negative and depressive symptoms in remission (A) and non-remission (B) male patients. The difference between the two networks was statistically significant (P=0.04) for global strength, but not in terms of edge-weight (P=0.39) or individual edges (all P=1). The green colored edges indicate positive partial correlations, with thicker lines represent stronger partial correlations. D1 indicates depressed mood; D2, hopelessness; D3, self – deprecation; D4, guilt ideas of reference; D5, pathological guilt: D6, morning depression; D7, early wakening; D8, suicide; D9, observed depression; N1, blunted affect; N2, emotional withdrawal; N3, poor rapport; N4, passive social withdrawal; N5, difficulty in abstract thinking; N6, lack of spontaneity; N7, stereotyped thinking; P1, delusions; P2, disorganization; P3, hallucinatory behavior; P4, excitement; P5, grandiosity; P6, suspiciousness; P7, hostility.

3.4 Differences between remitters and non-remitters (Figure 3A + B)

The NCT analysis comparing the symptom network of male patients in remission of psychosis (based on the PANSS remission tool) versus the network of male patients not in remission of psychosis showed significant differences in global strength (P=0.04), but not in terms of network structure (P=0.39). The fact that the test about network structure invariance yielded no significant differences indicates that the null hypothesis cannot be rejected because there are no edges that differ more than can be expected. The fact that the overall global strength did differ significantly might be due to more and/or stronger edges. Combining both findings (i.e., no significant difference between network structure indicating no difference in edges, but significant differences regarding global strength), it is more plausible that the significant difference regarding the overall global strength is driven by more edges, rather than a few strong edges. Since there were no significant differences

between the networks regarding network structure, we did not pursue with further testing of specific edges (i.e., further testing could lead to Type I errors).[34] These results of the NCT may be explained by the fact that in the network of the *remitted* patients less edges were present compared to the network of the *non-remitted* patients (of note, this may be, in part, due to sample size differences). For example, a community (i.e., highly connected cluster of symptoms) was no longer present within the symptoms of the positive subscale of the remitters. The association between P1 (delusions) and other depressive symptoms disappeared in the network of the remitted patients. Interestingly, in the network of the remitted psychotic patients, no associations existed between symptoms originating from the positive and depressive subscales. This was also the seen between the negative and depressive subscales.

4 DISCUSSION

This study investigated the interrelatedness of positive, negative and depressive symptoms in male patients with non-affective psychosis, using a network approach. As a first main finding, we identified the symptoms 'depressed mood', 'observed depression', 'poor rapport', 'stereotyped thinking', 'delusions' and 'suspiciousness' as being important central symptoms with strong associations with other symptoms. The second main finding is that the networks of remitters and non-remitters are comparable regarding network structure, although the networks differed regarding overall global strength. Symptoms with high centrality measures may be important symptoms as potential targets for treatment interventions, while the differences in global strength indicate that the number of connections between symptoms seems to be dependent on illness state. Furthermore, we identified important interactions between individual symptoms, for example, between depressive symptoms and delusions. Based on these associations we hypothesize that depressive symptoms might be able to activate suicidality, while positive symptoms may trigger depressive symptoms and hereby influencing suicidality. This interrelatedness of symptoms may further increase our understanding of psychopathology and provides important information for profiling.

4.1 Symptoms networks and remission of psychotic symptoms

Remission status of psychosis influenced only the overall global strength between symptoms; the remitted patients showed a network that was not significantly different in structure, but had fewer connections than the network in non-remitted psychotic patients. To the best of our knowledge, no earlier study investigated the influence of state on networks in patients with non-affective psychosis. Of note, our results are based on group-level data and it is important to acknowledge that group-level results may not be generalizable to individual networks (earlier discussed by Bos and Wanders[38,39] It is currently unknown to what degree networks of an individual match the network at group level.[7]

If we assume that our group-level results are representative for individuals, our finding that non-remitted patients showed a stronger connected network supports the *hysteresis* principal of the network theory.[3] This idea posits that mental disorders should be interpreted as complex dynamical systems in which symptoms are able to influence each other, ultimately creating self-reinforcing feedback loops. The hysteresis principal implies that the

self-reinforcing nature of symptom activation is more likely to take place in more strongly connected networks (i.e., networks with more and/or stronger edges).[3] Therefore, the observed difference in global strength but not in structure between the remitted psychosis and non-remitted psychosis, may be explained by the presence of a more strongly connected network during an active psychosis, possibly due to self-reinforcing loops of symptom activation, which might play an important role in the maintenance of psychopathology.

Interestingly, both groups suffered from depressive symptoms (although the remitted patients showed significantly less depression i.e., 5.3% versus 17.1% respectively). In the network of the remitted psychotic group no associations existed between depressive symptoms and symptoms of the other subscales, while in the non-remitted group several edges connected the depressive symptoms with symptoms of the other subscales. This suggests that especially in the non-remitted group symptoms of different subscales co-occur and might activate each other. However, future longitudinal studies are required to investigate how symptom networks change, first to a different state (e.g. from absence of symptoms towards manifest psychosis or vice versa), and second in relation to external stimuli (e.g., after stressful events and/or discontinuation of treatment) and third whether patterns of network connectivity are also related to the course of illness, as shown in depressed patients.[38] This is also important to pursue given the differences in sample size between our two groups, which make it difficult to disentangle whether edge absence is dependent on the sample size or remission criterion.

4.2 Centrality measures

The symptoms 'depressed mood', 'observed depression', 'poor rapport', 'stereotyped thinking' and 'delusions' showed to have high centrality within our network. This implies that these symptoms might be relevant as targets for treatment interventions, as these symptoms are most likely to influence several other symptoms. Although comparing between different network studies is challenging, due to the use of different questionnaires measuring different constructs of symptoms, current results are in concordance with results from previous studies [7,8,40,41]. In our earlier performed network analysis in the same sample using different questionnaires and at a different time point, central symptoms included, among others, items reflecting the social participation of patients (i.e., loss of interest, inability to enjoy recreational activities and inability to maintain relationship with friends).[8] In the current study, centrality of the symptom 'poor rapport' underlines the importance of symptoms reflecting the social participation of patients. Although measured by a different questionnaire, Levine and Leucht[40] constructed a network of only negative symptoms and showed in their baseline network that 'poverty of content speech' had, among others, one of the highest closeness indexes from which there is overlap with the central symptom 'stereotyped thinking' in current study. Additionally, in depressed patients the most frequently reported centrality symptoms are 'depressed and loss of interest/pleasure' and 'energy/fatigue',[7,41] from which the first symptom is also in line with our results, suggesting that depressive symptoms have an important role in maintaining symptoms across different psychiatric disorders; these may be important transdiagnostic targets for treatment interventions across different psychiatric disorders. Future research should elaborate on these findings by investigating whether targeting these central symptoms might indeed lead to better outcomes, as the importance of central symptoms is currently only theoretically based.[42]

4.3 The relations between suicide, depressive and delusional symptoms

As highlighted above, in our previous network study in the same sample but with different symptom scales and a different point of time[8] we found no direct connection between delusional symptoms and 'recurrent thoughts of suicide' but instead several connections between delusional and depressive symptoms. Based on these findings we suggested that delusional symptoms seem to activate depressive symptoms and via this pathway influenced suicidal thoughts. In the current study, which including a validated questionnaire to measure depressive symptoms in psychotic-patients, we found similar results since 'suicide' was connected to several depressive symptoms, however, only one association was present with the positive symptom 'suspiciousness'. Moreover, the symptom 'delusions' was connected with several (other) depressive symptoms. This finding is also in line with an earlier study, where Bornheimer and colleagues[43] showed that depressive symptoms were moderated by positive symptoms in predicting suicidal ideation. Thus, it could be hypothesized that depressive symptoms are linked to suicidality, while positive symptoms especially trigger depressive symptoms and hereby influence suicidality. Of note, this hypothesis is based on the assumption that our resulting network displays potential causal relationships and that it is representative for the network structure within individual patients.

4.4 Limitations

As the network approach is developing there are several issues of debate. Some limitations are also applicable to current study; firstly, results of the performed stability check indicated that the generated network should be interpreted with caution due to the overlapping confidence intervals, especially when investigating differences in edge-weights of the network. As a result further studies with larger datasets are needed to replicate our findings. Secondly, as discussed in-depth in comments on earlier published network studies we should be careful with generalizing results to individuals since the generated networks are based on group-level analysis.[7,39] This is especially important in the interpretation of centrality measures for treatment interventions: ideally, within-person network should be investigating to help determine the central symptoms within these networks; this may help guide personalized treatment interventions. Thirdly, the naturalistic study design does not allow a control for the effect of differences in current treatment; for example the differences in overall global strength between remitters and non-remitters could be due to differences in medication use or compliance. Fourthly, it could be hypothesized that the difference in global strength is a result of reduced severity of symptoms in those who are in remission, represented by decreased mean sum-scores of positive, negative and to a lesser extent depressive symptoms in remitted patients. However, van Borkulo and colleagues[15] argued that the level of mean scores does not necessarily influence the generated network. Likewise, a lower score of items does not automatically lead to weaker associations between these items. Nevertheless, factors that are related to severity, such as variance in symptom scores (i.e., due to a floor/ceiling effect) in one of the groups might still lead to different levels of network connectivity. A fifth limitation is that due to a low number of female participants, there was insufficient data to perform separate analyses in female participants and compare male-female networks. Given known differences between men and women in terms of onset, course and nature of psychotic symptomatology,[44] extrapolation of our results to women should be done with caution. Lastly, based on the cross-sectional design of our study we are unable to establish causality, which makes our conclusions regarding

interactions between individual symptoms hypothesis driven. In line with this limitation, remission status was assessed at 3-years of follow-up after baseline and the 6-months time criterion was assessed retrospectively. Consequently, a recall bias could have taken place with patients having difficulties with remembering symptom severity up to 6 months prior to assessment. Moreover, the items G5 (mannerisms/posturing) and G9 (unusual thought content) are both part of the Andreasen remission criteria,[19] however, we did not include all symptoms of the general psychopathology scale in our network analyses. Given the wide application of the Andreasen criteria[19] in current literature we chose to apply the original and complete criteria.

In *conclusion*, in the current study we constructed a network to highlight interrelations between psychotic and depressive symptoms and identified symptoms with high centrality measures, indicating that these symptoms are important within the network and might be potential targets for treatment interventions. In addition, we replicated in part that depressive symptoms may moderate the relation between psychotic symptoms and suicidality, and in addition we showed that the number of connections between symptoms differed between remitted versus non-remitted psychotic male patients. These findings on symptom level may be informative to generate hypotheses regarding the maintenance and development of psychopathology.

ACKNOWLEDGEMENT

We are grateful for the generosity of time and effort by the patients, their families and healthy subjects. Furthermore we would like to thank all research personnel involved in the GROUP project, in particular: Joyce van Baaren, Erwin Veermans, Ger Driessen, Truda Driesen, Karin Pos, Erna van 't Hag, Jessica de Nijs, Atiqul Islam, Wendy Beuken and Debora Op 't Eijnde. JTWW is supported by NWO VENI grant (no 016.156.019). HGR is supported by a ZonMW/NWO VENI grant (no 016.126.059).

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SUPPLEMENTARY MATERIAL

1.0 SUPPLEMENTARY METHODS

1.1 Centrality measures

To investigate the importance of individual symptoms we calculated the following three centrality measures: node strength, closeness and betweenness.[S1,S2,S3] 'Node strength' reflects the involvement of a node within the network and is calculated as the sum of the number and strength of all connections of one node to all other nodes. 'Closeness' is calculated as the inverse of the sum of all the shortest paths between the index symptom and all other symptoms and thereby gives an indication of how easy it is to reach all other nodes from the node of interest. The last centrality measure ('betweenness') is determined by counting how often a symptom of interest is placed on the shortest path between any combination of two nodes. Thus, a high betweenness indicates that a specific node is highly connected with other nodes in a network. Of note, centrality measures are highly correlated, however, for the completeness we calculated all three measures.

1.2 Network Comparison Test

In order to compare networks of psychotic remitted and non-remitted male patients we used a network comparison test (NCT).[S4] The NCT is a permutation test (1000 iterations) in which the difference between networks of two groups (i.e., remitters and non–remitters) is calculated repeatedly for randomly regrouped individuals and is implemented in the *R* package 'NetworkComparisonTest'.[S5,S6] By using the NCT it is possible to compare two (independent) networks based on i) network structure and ii) overall global strength. In the situation that the network structure shows a significant difference it is possible to test which specific edges differ significantly.

The NCT includes three steps: in the first step the networks of both groups are estimated. In the following steps, different networks are estimated based on randomly regrouped individuals (i.e., random permutation of group membership across cases)[S4] from these different networks. Thirdly, the test statistic of interest is calculated which generates a reference distribution and a *p*-value (which we determined to be significant at a threshold of p=. 05).

1.3 Stability check

The stability check was designed by Epskamp and colleagues and details of this test are published elsewhere[S7] and also applied to our earlier performed network study.[S8]Overall the results of the stability check give an indication of the robustness of the network, by investigating how likely it is to find a comparable network when constructing the same network in another sample. More robust findings indicate that the degree of certainty of finding a comparable network in another sample is increased, which suggest generalizability of the generated network.

In order to apply stability tests, we make use of a technique known as 'bootstrapping resampling'.[S9] By using this procedure, a new cohort is created by multiplying the existing

sample. From this cohort, a new sample is taken and analysed: this process is repeated several times (i.e., 1000 iterations). The characteristics of the bootstrapped samples are plotted and analyzed (providing a sample with a normal distribution). The statistic measures of interest of the bootstrapped sample can be compared with the true values within the original data. For the stability checks the *R* package *'bootnet'* was used.[S5,7]The applied stability check consists of three parts: i) estimating bootstrapped confidence intervals (referred throughout the text below as CIs) on edge-weights for testing the accuracy of edge-weights and ii) a 'bootstrapped difference test' for edge-weights and iii) centrality measure 'node strength'.

1.3.1 Bootstrapped confidence intervals of edge-weights

In the generated network there are many edges connecting different symptoms with each other. Our network is an undirected, weighted network indicating that the edges connect different symptoms but, it is unclear whether symptom *x* influence symptom *y, y* influence symptom *x,* or causality goes both ways. Additionally, thicker lines represent stronger partial correlations between symptoms.

In this first part of the stability check, it is tested what the chance is of finding comparable strengths of the partial correlations between symptoms (i.e., edge-weights) when constructing the network in a different (but comparable) sample. For this, 95% bootstrapped CIs for edge-weights are constructed based on the normal variance in the bootstrapped sample. Based on the range of these CIs something can be said about the stability of the edge-weights (i.e., a wide interval represents low stability and a narrow interval represents high stability). Moreover, when a bootstrapped CI around a specific edge-weight contains 'zero' in it, this indicates that the weight of this edge does not differ significantly from other edge-weights. As a result, the applied ordering in the figure (indicating that the strength of the partial correlations between symptoms differ) might, however, not be the case. Hence, the stability check should not be interpreted as a significance test, but rather as a way to investigate the robustness of findings of a generated network.

1.3.2. Bootstrapped difference test for node strength and edge-weights

In this part of stability check, we investigate whether edge-weights and the centrality measure 'node strength' differ significantly from other edge-weights respectively other node strengths within the generated network. As mentioned earlier, node strength is a centrality measure, which is calculated by the sum of the weighted numbers of all associations of a specific node. As a result, a high node strength index indicates that a specific node is highly connected with other symptoms within the network.

For both counts (i.e., node strength and edge-weights), we calculated bootstrapped values of these measures for every symptom within the network. Next, difference scores between the bootstrapped values of every combination of two symptoms are calculated. Additionally, a difference score between the bootstrapped values of two symptoms is estimated and a CI around this difference score is constructed. Lastly, a null-hypothesis test is performed on the range of the CI. In the situation that the range of the constructed CIs contains 'zero' in it, the edge-weights (or node strength) of two different symptoms do not differ significantly from each other.

Of note, in the situation of performing multiple significant tests as done in the stability check described above, the problem of 'multiple testing' arises. This means that purely based on chance, a number of tests will test significantly while this might not be true. To get around this problem, one may use 'Bonferroni corrections'.[S10] Using Bonferroni corrections in the network approach will lead to very low significance levels, because when using Bonferroni correction one needs to divide α by the number of tests. Thus, as outlined by Epskamp and colleagues, applying the Bonferroni correction to a "20-node network requires 17.955 tests, leading to a corrected significance level of 0.000003".[S7] Testing on this Bonferroni corrected significance level is not considered feasible. In other words, we recognize the limitations of the current stability tests, however, there are currently no other statistical techniques to investigate the stability of a network, nor methods to correct for multiple testing problem.

1.4 Exploratory Graph Analyses (EGA)

There are several methods to detect for the number of underlying dimensions in data. Here, we considered the Exploratory Graph Analysis (EGA) the most appropriate; as this technique allows not only to detect the number of underlying dimensions but also to assess which items belong to the same dimension. For the details of this approach we refer to Golino and Epskamp[S11] who in depth discusses the pros and cons of this approach. In short, the first steps of EGA resemble our approach of constructing a symptom network. At first, the correlation matrix of all variables is constructed, which is followed by LASSO regularization, which encompasses model selection with the Extended Bayesian Information Criterion (EBIC). This is followed by the 'walktrap' algorithm, which defines the number of underlying communities within the partial correlation matrix. Based on random walks, this algorithm generates a "measure of similarities between vertices" [S11] that determine the number of clusters within the symptom network.

2.0 SUPPLEMENTARY TABLES

Table S1. An overview of the items of the CDSS and the PANNS, their abbreviations, median and mean scores per item

Item description		Total sample (n=470)			Males Remission (n = 150)			Males Non – Remission (n = 316)		
Item[a] Label	Depressive symptoms (CDSS, range 0 to 3)	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR	Mean	Median	IQR
D1	Depressed mood	0.46 (0.70)	0	1	0.21 (0.44)	0	0	0.57 (0.77)	0	1
D2	Hopelessness	0.27 (0.60)	0	0	0.11 (0.35)	0	0	0.34 (0.67)	0	1
D3	Self – deprecation	0.33 (0.62)	0	1	0.19 (0.50)	0	0	0.48 (0.73)	0	1
D4	Guilt ideas of reference	0.15 (0.47)	0	0	0.08 (0.30)	0	0	0.19 (0.53)	0	0
D5	Pathological guilt	0.17 (0.49)	0	0	0.13 (0.41)	0	0	0.20 (0.53)	0	0
D6	Morning depression	0.19 (0.53)	0	0	0.13 (0.43)	0	0	0.22 (0.58)	0	0
D7	Early wakening	0.11 (0.41)	0	0	0.07 (0.30)	0	0	0.13 (0.46)	0	0
D8	Suicide	0.12 (0.41)	0	0	0.06 (0.24)	0	0	0.14 (0.44)	0	0
D9	Observed depression	0.25 (0.48)	0	1	0.11 (0.35)	0	0	0.31 (0.52)	0	1
	Negative symptoms (PANSS. range 1 to 7)									
N1	Blunted affect	2.12 (1.24)	2	2	1.61 (0.77)	1	1	2.37 (1.34)	3	3
N2	Emotional withdrawal	1.72 (1.00)	1	1	1.33 (0.60)	1	1	1.91 (1.09)	2	2
N3	Poor rapport	1.54 (0.96)	1	1	1.20 (0.52)	1	0	1.71 (1.07)	1	1
N4	Passive social withdrawal	2.00 (1.28)	1	2	1.42 (0.74)	1	1	2.27 (1.40)	2	2
N5	Difficulty in abstract thinking	1.73 (1.15)	1	1	1.47 (0.92)	1	0	1.86 (1.23)	1	2
N6	Lack of spontaneity	1.68 (1.10)	1	1	1.35 (0.65)	1	1	1.85 (1.23)	1	2
N7	Stereotyped thinking	1.45 (0.90)	1	1	1.22 (0.54)	1	0	1.56 (1.01)	1	1
	Positive symptoms (PANSS. range 1 to 7)									
P1	Delusions	2.29 (1.48)	2	2	1.51 (0.81)	1	1	2.66 (1.58)	3	3
P2	Disorganization	1.60 (1.05)	1	1	1.23 (0.55)	1	0	1.77 (1.19)	1	1
P3	Hallucinatory behavior	1.92 (1.48)	1	2	1.22 (0.61)	1	0	2.27 (1.65)	1	3
P4	Excitement	1.32 (0.76)	1	0	1.19 (0.59)	1	0	1.38 (0.82)	1	0
P5	Grandiosity	1.44 (1.00)	1	0	1.22 (0.62)	1	0	1.56 (1.13)	1	1
P6	Suspiciousness	1.99 (1.30)	1	2	1.49 (0.84)	1	1	2.22 (1.42)	2	2
P7	Hostility	1.20 (0.58)	1	0	1.07 (0.35)	1	0	1.27 (0.65)	1	0

[a] Item label corresponds to individual items (i.e., symptoms) as questioned in the Calgary Depression Scale for Schizophrenia (CDSS) and Positive and Negative Syndrome Scale (PANSS), IQR = interquartile range.

Table S2. Correlation matrix of the items of the CDSS and the PANSS

[a]	P1	P2	P3	P4	P5	P6	P7	N1	N2	N3	N4	N5	N6	N7	D1	D2	D3	D4	D5	D6	D7	D8	D9
P1		0.41	0.42	0.21	0.39	0.59	0.20	0.21	0.23	0.18	0.25	0.18	0.08	0.38	0.26	0.28	0.25	0.31	0.16	0.08	0.05	0.17	0.22
P2	0.41		0.27	0.29	0.20	0.27	0.24	0.17	0.29	0.28	0.28	0.41	0.17	0.46	0.14	0.15	0.12	0.11	0.08	0.03	0.03	0.05	0.15
P3	0.42	0.27		0.08	0.18	0.33	0.15	0.15	0.14	0.13	0.18	0.16	0.07	0.15	0.25	0.22	0.17	0.18	0.08	0.05	-0.04	0.12	0.18
P4	0.21	0.29	0.08		0.22	0.19	0.34	-0.10	0.02	0.12	0.0.	0.15	-0.08	0.25	-0.01	0.0.	0.02	0.08	-0.04	0.08	0.10	0.03	0.04
P5	0.39	0.20	0.18	0.22		0.31	0.22	-0.09	0.03	0.06	0.02	0.01	-0.08	0.24	0.05	0.08	-0.02	0.17	0.02	0.03	-0.06	0.08	0.04
P6	0.59	0.27	0.33	0.19	0.31		0.28	0.21	0.22	0.20	0.22	0.14	0.08	0.27	0.27	0.27	0.23	0.29	0.14	0.17	0.02	0.22	0.21
P7	0.20	0.24	0.15	0.34	0.22	0.28		0.01	0.02	0.12	0.02	0.12	0.06	0.13	0.07	0.14	0.09	0.03	-0.08	0.09	0.03	0.10	0.10
N1	0.21	0.17		-0.10	-0.09	0.21	0.01		0.54	0.43	0.49	0.23	0.51	0.20	0.26	0.20	0.20	0.13	0.12	0.08	0.15	0.09	0.31
N2	0.23	0.29	0.15	0.02	0.03	0.22	0.02	0.54		0.57	0.71	0.21	0.41	0.27	0.23	0.16	0.22	0.13	0.08	0.18	0.25	0.15	0.22
N3	0.18	0.28	0.14 0.13	0.12	0.06	0.20	0.12	0.43	0.57		0.46	0.22	0.57	0.40	0.15	0.10	0.12	0.14	0.01	0.13	0.16	0.10	0.14
N4	0.25	0.28	0.18	0.0.	0.02	0.22	0.02	0.49	0.71	0.46		0.29	0.36	0.25	0.22	0.26	0.19	0.12	0.05	0.12	0.15	0.10	0.20
N5	0.18	0.41	0.16	0.15	0.01	0.14	0.12	0.23	0.21	0.22	0.29		0.29	0.34	0.02	0.11	0.03	0.04	-0.05	-0.03	0.03	0.03	0.01
N6	0.08	0.17	0.07	-0.08	-0.08	0.08	0.06	0.51	0.41	0.57	0.36	0.29		0.20	0.20	0.14	0.15	0.11	0.03	0.08	0.09	0.13	0.18
N7	0.38	0.46	0.15	0.25	0.24	0.27	0.13	0.20	0.27	0.40	0.25	0.34	0.20		0.11	0.07	0.15	0.17	0.11	0.01	0.03	0.09	0.07
D1	0.26	0.14	0.25	-0.01	0.05	0.27	0.07	0.26	0.23	0.15	0.22	0.02	0.20	0.11		0.48	0.48	0.26	0.30	0.42	0.26	0.39	0.64
D2	0.28	0.15	0.22	0.0.	0.08	0.27	0.14	0.20	0.16	0.10	0.26	0.11	0.14	0.07	0.48		0.38	0.20	0.24	0.18	0.18	0.50	0.47
D3	0.25	0.12	0.17	0.02	-0.02	0.23	0.09	0.20	0.22	0.12	0.19	0.03	0.15	0.15	0.48	0.38		0.23	0.33	0.22	0.16	0.33	0.40
D4	0.31	0.11	0.18	0.08	0.17	0.29	0.03	0.13	0.13	0.14	0.12	0.04	0.11	0.17	0.26	0.20	0.23		0.30	0.14	0.13	0.14	0.24
D5	0.16	0.08	0.08	-0.04	0.02	0.14	-0.08	0.12	0.08	0.01	0.05	-0.05	0.03	0.11	0.30	0.24	0.33	0.30		0.18	0.08	0.16	0.24
D6	0.08	0.03	0.05	0.08	0.03	0.17	0.09	0.08	0.18	0.13	0.12	-0.03	0.08	0.01	0.42	0.18	0.22	0.14	0.18		0.27	0.17	0.27
D7	0.05	0.03	-0.04	0.10	-0.06	0.02	0.03	0.15	0.25	0.16	0.15	0.03	0.09	0.03	0.26	0.18	0.16	0.13	0.08	0.27		0.13	0.30
D8	0.17	0.05	0.12	0.03	0.08	0.22	0.10	0.09	0.15	0.10	0.10	0.03	0.13	0.09	0.39	0.50	0.33	0.14	0.16	0.17	0.13		0.43
D9	0.22	0.15	0.18	0.04	0.04	0.21	0.10	0.31	0.22	0.14	0.20	0.01	0.18	0.07	0.64	0.47	0.40	0.24	0.24	0.27	0.30	0.43	

[a] Item label corresponds to individual items (i0.e0., symptoms) as questioned in the Calgary Depression Scale for Schizophrenia (CDSS) and the Positive and Negative Syndrome Scale (PANSS)0.

3.0 SUPPLEMENTARY FIGURES

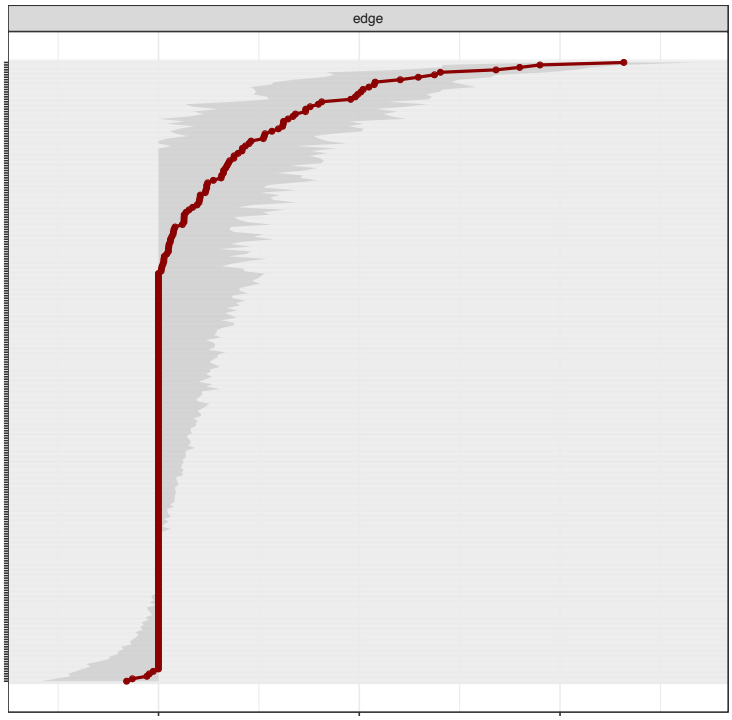

Figure S1. Bootstrapped Confidence intervals of all edges. Figure showing the bootstrapped 95% CIs around edge-weights. The X-axis represents the strength of the edge-weights. The y-axis lists all possible edges (i.e., (n*(n-1))/2) = 253) between all 23 symptoms. Every horizontal line represents a certain edge-weights between two symptoms. But for the sake of clarity the labels are deleted. A top-down ordering is applied, so that the highest edge-weight is at the top (of the Y-axis) and the lowest edge-weights (i.e., negative correlations) are at the bottom. The red line indicates the value of the edge-weights in our network (Figure 1). The grey area around the red line indicates the bootstrapped 95% CIs. When CIs of different edge-weights show considerable overlap, the ordering of the edges could also be otherwise and the edge-weight might not significantly differ from each other (and the top-down ordering could indeed be different). Likewise, when the range of the CIs contains zero, the edge-weights may also not differ from each other.

Based on this figure the following can be noticed: i) many CIs are larger then zero, for some of those there is considerable overlap with other CIs; ii) some edges are estimated as zero; iii) some CI are larger or smaller than zero but the bootstrapped CIs contain zero. The combination of overlap between CIs and the fact that many CIs include zero in their range implies that we should interpreted the network with caution regarding the differences between edge-weights. In other words, this figure indicates that differences edge-weights may not be significant, limiting us in the generalizability of the findings to other populations.

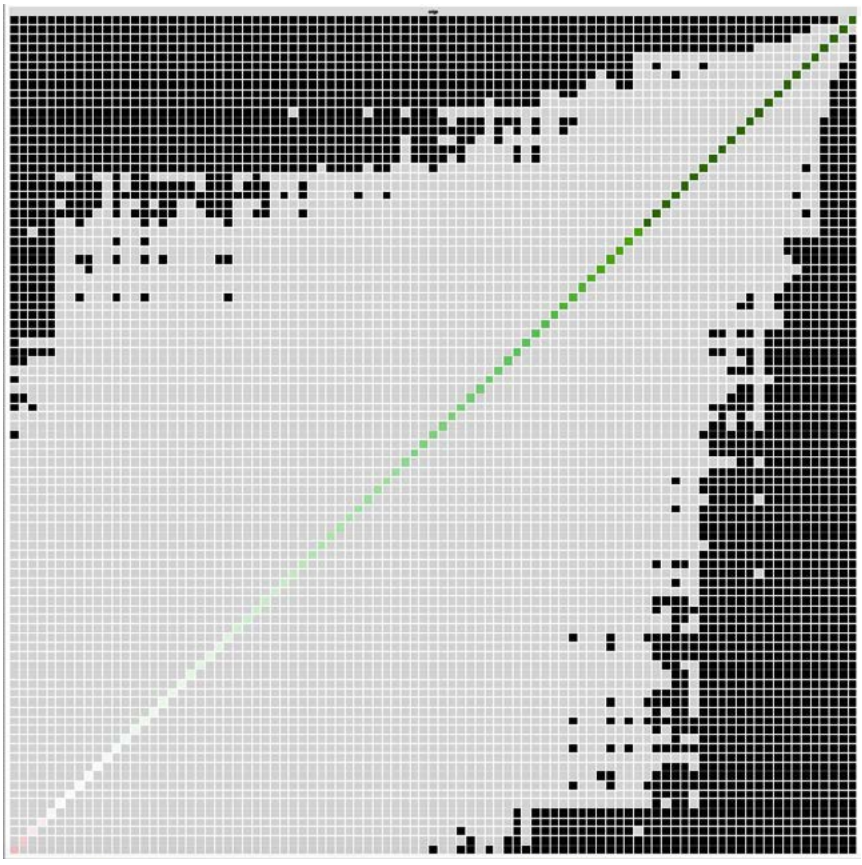

Figure S2: Bootstrapped stability test for edge-weight. Figure showing the results of the bootstrapped difference tests (α=0.05) for edge-weights. All possible edges (i.e., (n*(n-1))/2) = 253) between all 23 symptoms are shown at both axes. For the sake of clarity, the labels of the edges are deleted. The color of the boxes indicates whether edge-weights differ significantly from each other (i.e., black) or do not differ significantly (i.e., grey). The diagonal line indicates the strength of edge-weights, shifting from red (negative associations), to white (representing weaker edges) and ultimately dark green (representing stronger edge-weights).

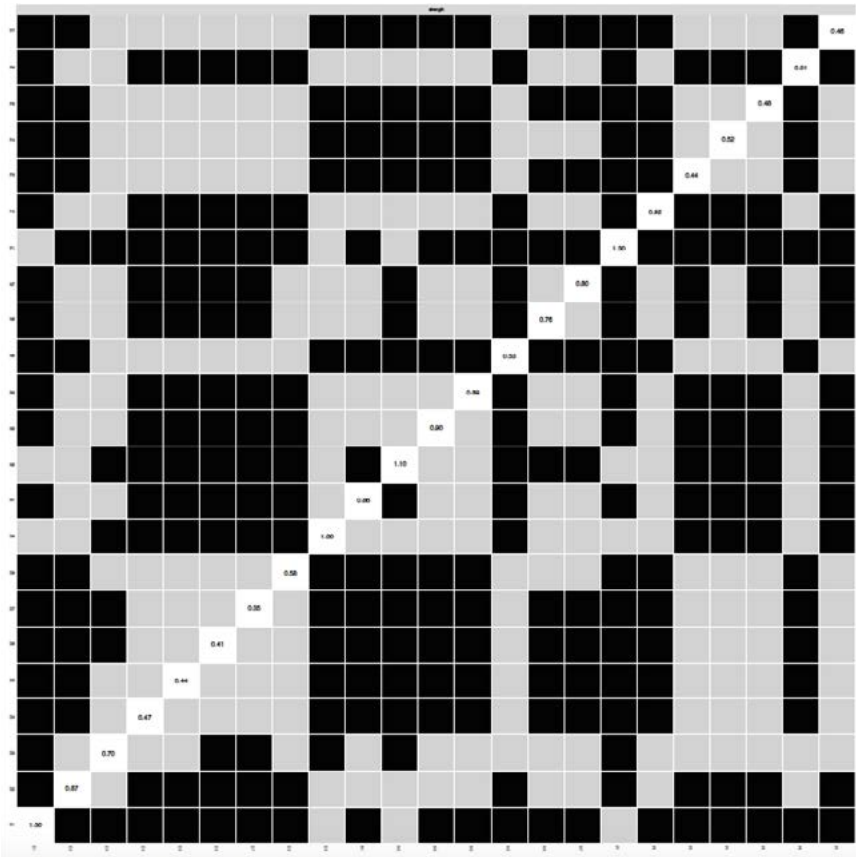

Figure S3: Bootstrapped stability test for centrality measure 'node strength'. Figure showing the results of the stability difference tests (α=0.05) for the centrality measure 'node strength'. Node strength reflects the involvement of a node within the network and is calculated as the sum of the weighted number of all associations of a specific node. The applied stability test investigates whether node strengths of symptoms differ significantly from each other. For the sake of clarity, the labels of the symptoms (listed at both axes) are deleted. The colour of the boxes indicates whether there is a significant difference between symptoms (i.e., grey boxes reflect no significant differences and black boxes reflect significant differences). The number in the white boxes (i.e., the diagonal line) denotes the value of node strength of a specific node. In this figure several black boxes can be noticed, indicating significant differences between symptoms regarding the centrality measure node strength.

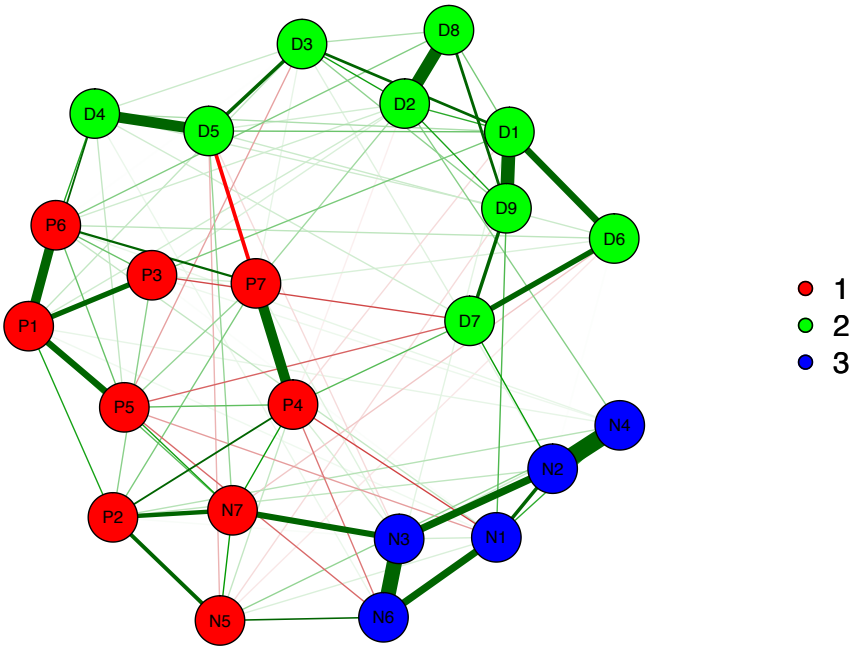

Figure S4: Network figure depicting the layout of the different dimensions derived from EGA.

4.0 SUPPLEMENTARY R – CODES

```
################################ AMC Analysis PANSS & CDSS
############################

##Required libraries
library(qgraph)
library(huge)
library(NetworkComparisonTest)
library(bootnet)
library(EGA)

##Data Manipulation

#Total Sample - Men only
data_men <- read.csv("data.csv") ## Only men data

names(data_men) <- c("P1", "P2", "P3", "P4", "P5", "P6", "P7",
                     "N1", "N2", "N3", "N4", "N5", "N6", "N7",
                     "D1", "D2", "D3", "D4", "D5", "D6", "D7", "D8", "D9")

#Conduct nonparanormal transformation on the data & directly get back a correlation matrix
datanpn_men <- huge.npn(data_men, npn.func='skeptic') # n = 470

#Compute network
network1 <- qgraph(datanpn_men, graph='glasso', sampleSize=nrow(data_men),
          layout='spring', color = c("red", "yellow", "green"),
          groups = list("Positive Symptoms" = 1:7,
                        "Negative Symptoms" = 8:14,
                        "Depressive Symptoms" = 15:23),
          vsize=3.5, legend.cex=.4, details=TRUE, cut=0, maximum=.5)

#Compute centrality indices
centralityPlot(network1)

# Save figures as pdf
# pdf("CDSS_men.pdf", width=(3.5/2.5)*5, height=5)
# network1 <- qgraph(datanpn_men, graph='glasso', sampleSize=nrow(data_men),
#                    layout='spring', color = c("red", "yellow", "green"),
#                    groups = list("Positive Symptoms" = 1:7,
#                                  "Negative Symptoms" = 8:14,
#                                  "Depressive Symptoms" = 15:23),
#                    vsize=4.5, legend.cex=.5, details=FALSE, cut=0, maximum=.5)
# dev.off()
#
# pdf("centralityCDSS_men.pdf")
```

```
# centralityPlot(network1)
# dev.off()



################## Analysis PANSS Remission versus no remission men only ###############

##Data Manipulation
datarem_long <- read.csv2("data2.remmission.csv", sep=",", header = TRUE) ## Data patients in remission (n=150)
datanorem_long <- read.csv("data2.nonremission.csv", sep=",", header = TRUE) ## Data patients not in remission (n=316)

names(datarem_long) <- c("P1", "P2", "P3", "P4", "P5", "P6", "P7",
                         "N1", "N2", "N3", "N4", "N5", "N6", "N7",
                         "D1", "D2", "D3", "D4", "D5", "D6", "D7", "D8", "D9")
names(datanorem_long) <- c("P1", "P2", "P3", "P4", "P5", "P6", "P7",
                           "N1", "N2", "N3", "N4", "N5", "N6", "N7",
                           "D1", "D2", "D3", "D4", "D5", "D6", "D7", "D8", "D9")

#Conduct nonparanormal transformation on the data & directly get back a correlation matrix
dataremlong_npn <- huge.npn(datarem_long, npn.func='skeptic')
datanoremlong_npn <-huge.npn(datanorem_long, npn.func='skeptic')

#Compute networks
r <- qgraph(dataremlong_npn, graph='glasso', sampleSize=nrow(datarem_long),
        layout=network1$layout, groups = list("Positive Symptoms" = 1:7,
                                              "Negative Symptoms" = 8:14,
                                              "Depressive Symptoms" = 15:23),
        color=c("red", "yellow", "green"), vsize=4.5, legend.cex=.5,
        details=TRUE, cut=0, maximum=.5)
title("Remission Patients", line=1.4, adj=1)

nr <- qgraph(datanoremlong_npn, graph='glasso', sampleSize=nrow(datanorem_long),
          layout=network1$layout, groups = list("Positive Symptoms" = 1:7,
                                                "Negative Symptoms" = 8:14,
                                                "Depressive Symptoms" = 15:23),
          color=c("red", "yellow", "green"), vsize=4.5, legend.cex=.5,
          details=TRUE, cut=0, maximum=.5)
title("Non-Remission Patients", line=1.4, adj=1)

# Save Figures as pdf
# pdf("RemissionNoRemission_longitudinal.pdf", width=(3.5/2.5)*10, height=5)
# layout(t(1:2))
```

```
# r <- qgraph(dataremlong_npn, graph='glasso', sampleSize=nrow(datarem_long),
#           layout=network1$layout, groups = list("Positive Symptoms" = 1:7,
#                                                 "Negative Symptoms" = 8:14,
#                                                 "Depressive Symptoms" = 15:23),
#           color=c("red", "yellow", "green"), vsize=4.5, legend.cex=.5,
#           details=TRUE, cut=0, maximum=.5)
# title("Remission Patients", line=1.4, adj=1)
#
# nr <- qgraph(datanoremlong_npn, graph='glasso', sampleSize=nrow(datanorem_long),
#            layout=network1$layout, groups = list("Positive Symptoms" = 1:7,
#                                                  "Negative Symptoms" = 8:14,
#                                                  "Depressive Symptoms" = 15:23),
#           color=c("red", "yellow", "green"), vsize=4.5, legend.cex=.5,
#           details=TRUE, cut=0, maximum=.5)
# title("Non-Remission Patients", line=1.4, adj=1)
# dev.off()


##Network comparsion test to compare the network of patients in remission to
##the network of patients who were not in remission.

set.seed(1)
nct.res_long <- NCT(huge.npn(datarem_long), huge.npn(datanorem_long), gamma = 0, it =
1000,
                    weighted=TRUE, binary.data=FALSE, progressbar = TRUE, test.edges=TRUE,
edges='all')

nct.res_long$glstrinv.pval # 0.04 -> significant difference in global strength
nct.res_long$nwinv.pval # 0.4 -> no significant difference in terms of edge weights


############################### Bootnet Stability Check ########################
#######

##Write a function that uses the same estimation method as the one that has been used in
the
##analysis (i.e., using the nonparanormal transformation)

estimator <- function(Data){
  library("qgraph")
  library("huge")
  Network_cor <- huge.npn(Data, npn.func='skeptic')
  Network <- qgraph(Network_cor, graph='glasso', sampleSize=nrow(Data), layout='spring')
  return(getWmat(Network))
}
```

```
#Re-estimate Total sample network (men)
set.seed(1)
net_boot <- estimateNetwork(data_men, fun = estimator)

#Check whether networks computed are the same
networkEst <- qgraph(net_boot$graph, layout=network1$layout,
                vsize=3, groups = list("Positive Symptoms" = 1:7,
                                       "Negative Symptoms" = 8:14,
                                       "Depressive Symptoms" = 15:23),
                color=c("red", "yellow", "green"), vsize=4.5, legend.cex=.5,
                cut=0, maximum=.5)

###Run stabilitiy check for the network
stability_men <- bootnet(net_boot, nBoots = 1000, nCores = 8)

plot(stability_men, order = "sample", labels=FALSE) # confidence intervals
plot(stability_men, "edge", plot = "difference", onlyNonZero = TRUE, order = "sample") #
difference of edges
plot(stability_men, "strength", plot = "difference") # node strenght


# Save Figures as pdf
# pdf("StabilityCDSSsample.pdf")
# plot(stability_men, order = "sample", labels=FALSE)
# dev.off()

# pdf("StabilityCDSSdiff.pdf", height=20, width=20)
# plot(stability_men, "edge", plot = "difference", onlyNonZero = TRUE, order = "sample")
# plot(stability_men, "strength", plot = "difference")
# dev.off()


#################### Perform Exploratory Graph Analysis (EGA)
#########################

#Run EGA
EGA(data_men, plot.EGA = TRUE)

# Save Figure as pdf
# pdf("EGA.pdf", width=(3.5/2.5)*5, height=5)
# EGA(data_men, plot.EGA = TRUE)
# dev.off()
```

SUPPLEMENTARY REFERENCES

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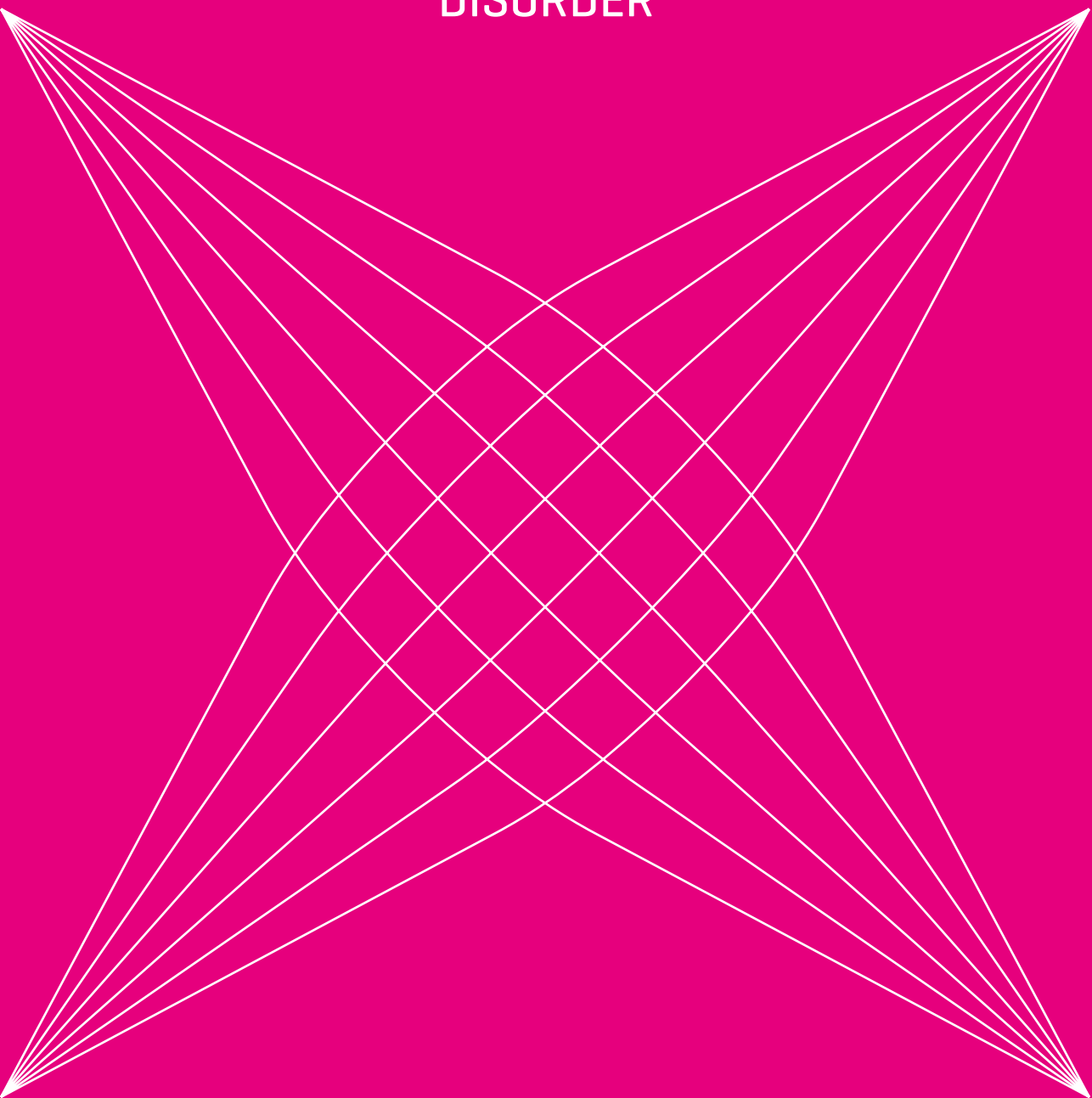
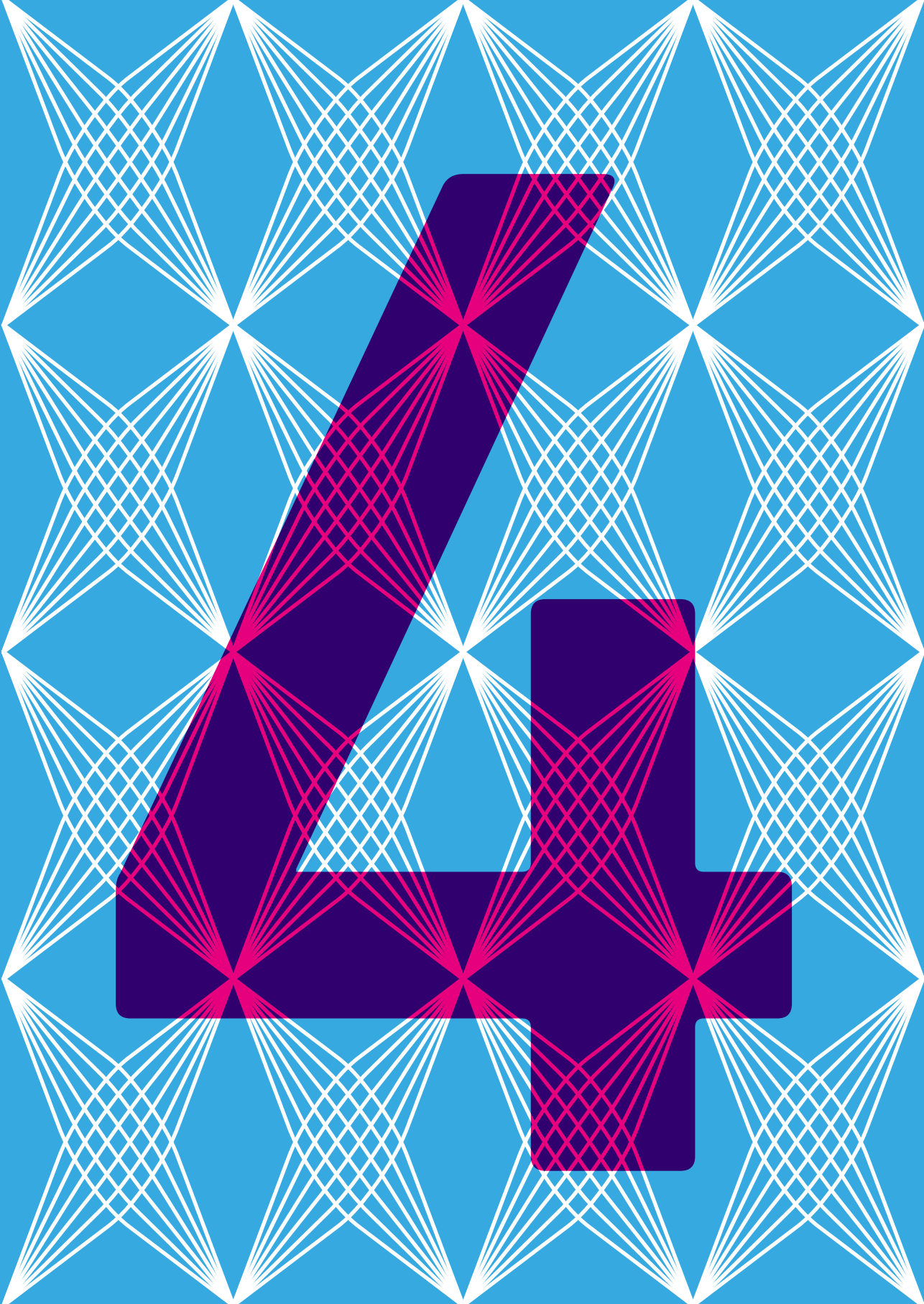
PART II

-

NEURAL CORRELATES OF DEPRESSIVE SYMPTOMS IN MAJOR DEPRESSIVE DISORDER





NEURAL CORRELATES OF DYSFUNCTIONAL EMOTION REGULATION IN MAJOR DEPRESSIVE DISORDER. A SYSTEMATIC REVIEW OF NEUROIMAGING STUDIES

Maria M. Rive, Geeske van Rooijen, Dick J. Veltman, Mary L. Phillips, Aart H. Schene, Henricus G. Ruhé

Neuroscience and Biobehavioral Reviews 2013; 37:2529-53

ABSTRACT

Abnormal emotion processing is a core feature of major depressive disorder (MDD). Since the emergence of functional neuroimaging techniques, many studies have been conducted in MDD subjects to elucidate the underlying abnormalities in the neural systems involved in emotion regulation. In this systematic review, we discuss this research in the context of the neural model of emotion regulation previously described by Phillips et al.[1] This model differentiates between automatic and voluntary emotion regulation subprocesses. Automatic regulation subprocesses were shown to involve predominantly medial prefrontal cortical structures, in addition to the hippocampus and parahippocampus, while voluntary regulation processes additionally recruited lateral prefrontal cortical regions. In conclusion, although the available data is limited, findings suggest that MDD subjects demonstrate abnormally reduced activity in lateral prefrontal cortices during explicit voluntary control of emotional experience. During early, automatic stages of emotion regulation, on the other hand, MDD subjects appear to achieve successful emotion regulation by recruiting additional lateral prefrontal neural regions, that may be mediated by medial prefrontal, especially rostral/dorsal anterior cingulate gyrus (ACG) functioning. Dysfunctional automatic regulation may impair successful voluntary emotion regulation, and may present a target for novel therapeutic approaches in MDD.

1. INTRODUCTION

Emotion dysregulation is one of the central features of major depressive disorder (MDD).[2;3] Insight in this process will aid to better understand the pathophysiology of MDD, which is vital to improve treatment and prevention strategies. In 2003, Phillips et al.[4;5] developed a neural model of emotion regulation to study abnormalities in MDD, bipolar disorder (BD) and schizophrenia. This model distinguished a ventral and a dorsal system: the *ventral* system comprising the amygdala, insula, ventral striatum, ventral anterior cingulate gyrus (vACG), the ventromedial prefrontal cortex (VMPFC) /medial orbitofrontal cortex (OFC); and the *dorsal* system consisting of the hippocampus, dorsal ACG (dACG) and dorsal prefrontal cortex (PFC). The ventral system is thought to be involved in recognizing emotionally salient stimuli and generating an emotional state (i.e., bottom- up emotional influences), the dorsal system in voluntary regulation of these states (i.e., voluntary top-down control of emotions).[4;5]

This model was updated in 2008 and used as a framework to further study neural circuitry supporting emotion regulation in BD.[1] A major adaptation was the integration with the Ochsner and Gross model, which distinguishes two different top-down cognitive control systems: the dorsomedial prefrontal cortex (DMPFC) and the dorsolateral prefrontal cortex (DLPFC) for reappraisal of emotional contexts, and the ventral PFC for learning of associations between emotionally relevant outcomes and prior choices and events.[6;7] Furthermore, it was recognized that emotion regulation can be effortful (voluntary) or proceed more or less automatically,[1] although it was acknowledged that voluntary and automatic regulatory subprocesses could operate simultaneously with appraisal and generation of emotion. Together, this led to the distinction of six psychological subprocesses of emotion regulation, defined by two factors: type of regulation strategy (behavioral, attentional and cognitive) and the manner in which the strategy is applied (automatically or voluntary).[1]

This conceptual framework allowed for the characterization of the various tasks used in neuroimaging studies on emotion regulation in healthy control subjects (HC) according to the various emotion regulation subprocesses under study. Processes are considered *automatic* when emotional aspects of a given task can be assumed to exert their influence in an implicit way, for example because subjects are not aware of the emotional value of stimuli, or because the emotional meaning of a stimulus is not the explicit focus of the task to be performed. The subject is thought to automatically engage in regulatory processes in order to be successful on the task. These automatic processes were shown to involve predominantly medial prefrontal cortical structures, including the ACG, the OFC and DMPFC, as well as the hippocampus and parahippocampus. *Voluntary* processes comprise effortful attempts to alter emotions of which the subject is consciously aware - for example because these are the focus of the task - and recruited lateral prefrontal cortical regions *in addition to* medial prefrontal cortical structures.

These two systems - automatic and voluntary - were conceptualized as operating in parallel and possibly simultaneously, regulating emotional responses emerging from the amygdala, ventral striatum and thalamus.[1] Specifically, in HC, *automatic behavioral control* strategies were found to be associated with medial prefrontal recruitment (subgenual ACG (sgACG) and VMPFC;[1;8;9] whereas *voluntary behavioral control* strategies involve ventrolateral PFC

(VLPFC) in addition to medial prefrontal structures (dACG, and DMPFC and rostral ACG (rACG)).[1] Additionally, distancing from aversive pictures was associated with an increase in activity in the DLPFC,[10;11] the frontal pole (BA 10),[12] the (inferior) parietal cortex,[10] and temporal regions.[10;12] *Automatic attentional control* strategies were found to recruit the (rostal) ACG,[1;13] in addition to the dACG, VMPFC, DMPFC, inferior parietal cortex, and insula;[10;14;15] *voluntary attentional control* strategies were found to recruit the DLPFC, dACG and probably the right parietal cortex.[1;16;17] For *automatic cognitive change s*trategies the hippocampus and parahippocampus were shown to be involved,[1] while *voluntary cognitive change* strategies recruited the right DLPFC and ventrolateral PFC (VLPFC), in addition to the ACG and DMPFC.[1;8;15;18;19] For the sake of consistency, we will further use the term cognitive *control* instead of cognitive change.

The above-described new dual model has been used as a framework for describing altered neural functioning during emotion regulation in bipolar disorder.[1] However, this model has not yet been applied to the study of emotion regulation circuitry in MDD. Therefore, in this systematic review we will integrate the existing neuroimaging literature on emotion regulation in MDD within the theoretical framework of the six emotion regulation subprocesses.[1] We aim to identify specific functional abnormalities in this circuitry that are associated with MDD.

2. MATERIALS AND METHODS

2.1. Search strategy and study selection

We searched PubMed, Embase and PsychInfo for fMRI studies on emotion regulation in MDD published since 1990 to January 16, 2013 with sensitive search terms for Major Depressive Disorder in combination with MRI-neuroimaging (for full search terms see Supplemental information). We used this sensitive search to avoid missing key papers on emotion regulation in MDD. We additionally performed an ancestry search from identified studies, earlier reviews and meta-analyses to retrieve remaining studies.

Inclusion criteria were:

1. Adults with a (DSM-III/IIIR/IV) diagnosis of MDD and having a current depressive episode.
2. Comparison with healthy controls (HC).
3. Functional MRI, or H_2O^{15}-PET as imaging methods.
4. Investigation of any top-down interaction between neurocognitive functioning and processing of emotional stimuli (including error-monitoring tasks, gambling tasks, tasks involving painful stimuli or feedback).

Exclusion criteria were:

1. Studies with more than 50% of depressed subjects with a diagnosis of BD, a comorbid psychiatric or neurological disease, or late onset depression (>55 years), in order to obtain homogeneous samples in our review, and e.g. exclude potential cognitive deficits in elderly subjects.
2. Use of tasks investigating emotional processing without any explicit neurocognitive or emotion regulation component (i.e., tasks assessing only the bottom-up effects of emotion processing, for example, on memory function or unconscious perception);

tasks investigating neurocognitive functioning without any emotional component; or tasks investigating self-referential emotional processing.

3. Studies investigating treatment effects only.

Identified studies were independently judged for the presence of these in- and exclusion criteria by two authors (MMR and GvR), based on title and abstract. In case of doubt, the full-text article was retrieved. Disagreement was resolved by a third author (HGR or MLP). Study paradigms were categorized by MMR and MLP according to the six emotion regulation subprocesses involved, as described in the original paper by Phillips et al.[1] and as summarized in the introduction. Finally, the categorization of all included papers was checked by MLP and HGR.

2.2. Data extraction and synthesis

Apart from study characteristics, we summarized methodological aspects (Supplemental Table S1), behavioural results and main conditions/contrasts of paradigms (Tables 1-3). Neuroimaging results from relevant contrasts and correlation analyses were obtained from text, tables, figures and supplementary data. For activation results, we focused on the following regions of interest identified as key regions in voluntary and automatic emotion regulation neural circuitry: DLPFC (lateral Brodmann area (BA) 9/44/46) ventrolateral PFC (VLPFC) (BA 45/47; previously partly referred to as lateral OFC), DMPFC (medial BA 9/32), VMPFC/medial OFC (BA 10/11), ACG including rostral and dorsal ACG subregions (BA 24 and 32, respectively), and subgenual ACG (sgACG) (BA 25), hippocampus and parahippocampus, amygdala, ventral striatum and thalamus.[1;20] If not specified in the study, BAs were obtained by entering coordinates of interest in the WFU pickatlas (ANSIR Laboratory, Department of Radiologic Sciences WFU School of Medicine, Medical Center Blvd. Winston-Salem, NC) and Munster T2T-Converter (3D version) (Olaf Steinsträter, supported by the NRW research group for hemispheric specialization, Prof. Knecht). We chose not to perform a formal meta-analysis, because even within our emotion regulation subprocess framework, we felt the identified studies were too heterogeneous regarding clinical characteristics of the subjects, task design and statistical approach.[21]

3. RESULTS

Our sensitive searches retrieved 9116 manuscripts, the majority of which were found to address different topics, like depression due to somatic disease, emotion regulation in other Axis I and/or Axis II psychiatric disorders, other imaging modalities than fMRI or PET or no imaging at all, or basic emotion processing without a regulatory component. Therefore, only forty-one studies were included, with a Cohen's K for inter-rater agreement of 0.89 (K values above .75 indicate 'almost perfect' agreement). Categorization yielded 1 study on automatic behavioural control, 2 studies on voluntary behavioural control, 10 on automatic attentional control, 13 on voluntary attentional control (3 also described automatic attentional control), 10 on automatic cognitive control, and 9 on voluntary cognitive control (1 also described automatic and voluntary attentional control). All studies used fMRI as imaging modality, except one study using ^{15}O-PET.[22]

Below, we will discuss these studies according to the subprocess involved. All reported results refer to differences between depressed MDD subjects and HC, unless stated otherwise. To organize the reporting of outcomes, results are grouped according to the various brain regions involved in the different subprocesses. We aimed to summarize all available results that are relevant for the emotion regulation model. However, for reasons of readability, results that we considered less important (e.g. isolated findings) are described in the supplemental information. A complete overview of results is provided in Tables 1-3 (results relevant to the model) and the Supplemental Tables S2-S4 (additional results, not applicable to the model).

Key methodological issues such as choice of statistical approach and medication use are discussed whenever appropriate. Each section ends with a summary, discussing the most important findings.

3.1. Behavioural Control

Behavioural control refers to the process of altering a single behavioural response or the behavioural expression of emotion.[1]

3.1.1. Automatic behavioural control (Table 1A)

Automatic behavioural control involves extinction of previously acquired behavior, learning by conditioning, and furthermore inhibition of the stress response.[1] It normally involves ventral medial regulatory structures, particularly the ventral/sgACG and VMPFC, which inhibit amygdala activity.[1;8;9]

One study investigated this process in MDD, using a Pavlovian *reward* learning paradigm, while modelling BOLD-responses associated with temporal difference (TD) signals (which encode reward-related learning).[23] In medicated MDD subjects the TD-signal was associated with a blunted sgACG deactivation relative to HC. Furthermore, blunted ventral striatum, dACG and hippocampus activity were found. These findings all may reflect an impaired evaluation or appraisal of positive stimuli, although these decreased non-brainstem activity was paralleled by VTA hyperactivity, the significance of which is unclear. Medication use (citalopram) could not be ruled out as a potential explanation: as the authors point out in their discussion, chronic use of citalopram may increase the number of spontaneously active VTA dopamine neurons, which might result in TD-reward-learning signal enhancement.[23;24] However, the VTA TD signal in MDD subjects positively correlated with depression severity, suggesting that this VTA hyperactivity is related to depression instead of medication.[23] There were no differences in task performance between MDD subjects and HC. Possibly, this increase in VTA activity may compensate for blunted reward-learning signals in the ventral striatum and other non-brainstem reward related regions. However, more studies on automatic behavioural control, also with regard to negative emotional stimuli, are needed before firm conclusions can be drawn regarding alterations of this emotion regulation process in MDD and the effects of medication.

3.1.2. Voluntary behavioural control (Table 1B)

Voluntary behavioural control involves the inhibition of ongoing emotive-expressive behavior, for example, by inhibiting facial emotional expressions, perceiving emotional stimuli as detached observers (i.e., distancing) and attempting to remain calm and diminish any emotional response.[1] In HC it involves the VLPFC, the dACG and probably the rostral ACG (rACG) and DMPFC, which influence the autonomic nervous system as well as the amygdala and insula via the OFC; and vice versa.[1] Additionally, especially distancing from aversive pictures is associated with increased activity of the DLPFC,[10;11] the frontal pole (BA 10),[12] the (inferior) parietal cortex,[10] and temporal regions.[10;12]

Two studies investigated voluntary behavioural control by distancing in MDD subjects.[25;26] In one study,[25] increased activity of the dACG in MDD subjects relative to HC was reported. This might reflect a stronger conflict between emotional distraction and cognitive attempts to distance in MDD subjects, or in other words, a stronger engagement with the negative stimuli presented.[25] Other findings supporting this hypothesis are defective lateral prefrontal (VLPFC and DLPFC) functioning in MDD and abnormally elevated amygdala and insula activity.[25;26] Furthermore, these abnormalities are paralleled by greater difficulty experienced while attempting to down-regulate sadness in MDD subjects, suggesting a lack of recruitment of the lateral PFC (VLPFC) in MDD subjects when emotional distancing becomes more difficult.[25]

A potential limitation is that most subjects in one of these studies used antidepressant medication.[26] Unfortunately, to our knowledge, there are no studies investigating the effect of medication on voluntary behavioural control strategies specifically. Nevertheless, medication is thought to diminish amygdala activity during passive exposure as well as during regulation of negative emotional stimuli.[27-35] Furthermore, with regard to DLPFC activity, there is evidence that medication increases activity during emotion regulation.[36;37] Therefore, it is likely that medication use if anything diminished the observed increased amygdala and decreased DLPFC activity in MDD subjects.

Also, Erk et al.[26] reported fewer differences between MDD subjects and HC as Beauregard et al.,[25] which may have been due to the more stringent statistical approach adopted by Erk et al.

Taken together, during voluntary behavioural control, there are some indications that in MDD subjects there is a primary top-down dysregulation of the amygdala during voluntary behavioural control, which during actual presentation of negative stimuli might be mediated by the VLPFC and by the right DLPFC. However, more studies concerning this subprocess are needed.

3.2. Attentional control

Attentional control refers to emotional regulation by engagement or disengagement of attention to emotional stimuli.[1]

Study	No. of MDD subjects Age (mean) HDRS score (mean)	Methodological aspects (Table S1)			Task	Key condition or contrast and statistical threshold	Task performance	Relevant brain regions	Recruitment in MDD vs HC
		Medication	Comorbidity	Statistics					
A. Automatic									
Kumar et al.[23]	15 (9F) Age:45.3 21HDRS:23.2	-	+	+	Pavlovian reward learning paradigm	Temporal difference error signal Whole brain: $p<0.05$ FDR C ROI: $p<0.05$ FDR SVC	=	VTA R r/sgACG L dACG PCG L hippocampus Ventral striatum	↑ Less deactivation ↓ Less deactivation Less deactivation ↓
B. Voluntary									
Beauregard et al.[25]	12 (9F) Age: 43 21HDRS: 25	+/-	+	+	Distancing from emotional film excerpts	Distancing > sadness ROI: $p<0.05$ C, k≥10	↓	R amygdala R dACG R ant temporal pole R insula VLPFC MOFC LPFC MPFC	↑ ↑ ↑ ↑ =[a] = = =
Erk et al.[26]	17 (8F) Age: 43.5 21HDRS: 18.5 BDI: 25.4	-	+	+	Distancing from emotional pictures during task 1; measurement of long-term effect during passive viewing in task 2	Distancing from negative pictures > passive viewing (task 1) Previously regulated negative > neutral (task 2) Whole brain: $p<0.05$ FWE C ROI: $p<0.05$ FWE C	=	Amygdala Ventral striatum DMPFC VLPFC R DLPFC Inf parietal cortex Hippocampus Inf parietal/temporal cortex	= (task 1); ↑ (task 2) = = = ↓(task 1); = (task 2) = = =

Abbreviations: ACG, anterior cingulate gyrus; ant, anterior; C, corrected; dACG, dorsal ACG; DLPFC, dorsolateral PFC; F, female; FDR, false discovery rate; FWE, family wise error; inf, inferior; k, number of contiguous voxels; L, left; LPFC, lateral PFC; MOFC, medial OFC; MPFC, medial PFC; OFC, orbitofrontal cortex; PCG, posterior cingulate gyrus; PFC, prefrontal cortex; R, right; rACG, rostral ACG; ROI, region of interest; sgACG, subgenual ACG; VLPFC, ventrolateral PFC; VTA, ventral tegmental area; 17-HDRS, 17-item Hamilton Depression Rating Scale; 21-HDRS, 21 item HDRS; BDI, Beck Depression Inventory; +, good (medication: none/washout ≥ 2 months: no ECT ≥ 2 months; comorbidity: no primary comorbid Axis I diagnosis; statistics: main effects and interactions corrected for multiple comparisons); +/-, moderate (medication: medication use in > 50% of sample/washout < 2 months; comorbidity: comorbid Axis I diagnosis in < 50% of sample; statistics: not good: not poor); -, poor (medication: medication use in ≥ 50% of sample/not mentioned; comorbidity: comorbid Axis I diagnosis in ≥ 50% of sample/not mentioned; statistics: uncorrected analysis).[a] left VLPFC: in contrast to HC: in MDD no correlation with regulatory difficulty; this indicates failure of recruitment

3.2.1. Automatic attentional control [Table 2A]

Automatic attentional control involves the automatic ability to overcome interference from emotional distracters that may more or less unconsciously divert attention away from cognitive task performance. It normally involves particularly the rACG (32/10).[1;13] Additionally, the dACG, VMPFC, DMPFC, inferior parietal cortex, and insula are reported to be involved.[10;14;15]

Studies comparing automatic attentional control in MDD subjects and HC have used paradigms examining attentional control in the presence of coincidental, but covert – i.e., not explicitly – presented, task-irrelevant, emotionally distracting information. These paradigms include: (1) Matching features of faces,[38;39] which features an implicit condition. During this implicit condition, participants match the gender of presented faces, such that the gender and not the emotional expression of the face is brought under attention, while the emotional expression serves to covertly distract the participant from actual task performance (i.e. performing gender matching). Therefore, an automatic redirection of attention away from the emotion towards the gender of the face is required.

(2) Matching houses in the presence of emotional facial expressions,[40] which requires participants to match pictures of houses, while trying not to be distracted by concurrently presented fearful faces (ignore condition). (3) Emotional Stroop (eStroop), during which participants have to name the colour of emotionally negative words[22;41] and Stroop-like tasks, during which participants are asked to decide whether letter strings are (emotionally valenced) words or non-words,[42] to categorize faces while ignoring overlaid affect labels,[43] or to indicate the fore-ground colour superimposed on a dynamically changing emotional background face.[44] (4) A negative affective priming task, during which participants have to respond to a target word while ignoring simultaneously shown emotional distracter words.[45] (5) An emotional n-back task, in which subjects have to perform a working memory task while being implicitly distracted by task-irrelevant emotional (happy or fearful) faces.[46]

Of medial regulatory regions, implicated in automatic attentional control in HC, the DMPFC, rACG and dACG have been studied in MDD subjects. Left DMPFC activity was found to be increased in MDD subjects relative to HC during distraction by negative emotional material.[42] Furthermore, the rACG showed an opposite pattern of activity in MDD subjects and HC: in MDD subjects, inhibition of response to *negative* words was associated with activity in the right rACG, whereas HC demonstrated rACG activity when inhibiting response to *positive* words.[45] Less activity in the rACG in MDD subjects versus HC during automatic attentional control of pooled negative and positive emotional stimuli was also demonstrated.[43] Two studies did not find any differences in rACG activity between HC and MDD subjects,[22;46] but these null findings might be explained by low power[22] or medication use.[46] Almeida et al.[44] focused on effective connectivity between the sgACG, VMPFC and amygdala. They found increased effective connectivity from the left sgACG to the amygdala in all MDD subjects relative to HC when automatically regulating fear. Furthermore, in female MDD subjects only, inverse effective connectivity from the left sgACG to the amygdala, as well as from the left VMPFC to the amygdala was also increased when regulating happiness.[44]

In short, most findings indicate increased medial prefrontal activity in MDD subjects during automatic attentional control, as well as increased effective connectivity between sgACG and amygdala. This medial prefrontal hyperactivity of regions may indicate the need for stronger automatic control in MDD subjects compared to HC, to achieve successful emotion regulation. Stronger effective connectivity between sgACG and amygdala[44] supports this hypothesis, since there is evidence that the sgACG is involved in regulation of limbic regions.[8] However, this finding of increased connectivity may partly be explained by medication use, because antidepressant medication has been shown to increase limbic-ACG functional coupling.[28;47;48]

Findings regarding dACG activity indicated hyperactivity in MDD subjects: in contrast to HC, MDD subjects needed dACG activity to an equivalent extent to overcome covert emotional distraction as they had to activate this region to overcome more overt emotional distraction;[38] furthermore left dACG activity was found to be increased in MDD subjects versus HC.[41] However, two studies did not find any differences in dACG activity between HC and MDD subjects.[22;46] These null results cannot be fully explained by sample size[22;38] or medication use,[38;46] or variability with regard to depression severity. Nevertheless, it should be noted that George et al.[22] used a sample with nearly 50% (5/11) BD patients, which may have influenced their results.

In sum, although findings are not wholly consistent, activity of the dACG in MDD subjects during automatic attentional control appears to be increased.

Lateral prefrontal regions were also investigated.[38;46] Most findings indicate additional recruitment of frontal regions in MDD subjects compared to HC. Left DLPFC activity was significantly greater in MDD subjects relative to HC, whereas amygdala activity was similar, suggesting that MDD subjects were capable of successful regulation of amygdala activity, probably due to additional DLPFC recruitment.[38] Another study[43] showed that MDD subjects also showed significantly greater activity in the bilateral DLPFC/frontal pole than HC, which was associated with intact emotion regulation on a behavioural level; however in this study MDD subjects failed to deactivate the amygdala, suggesting that this additional lateral prefrontal activity was *insufficient* to regulate amygdala activity. It should be noted that this elevated DLPFC activity was found in the MDD group only, and not in anxiety or comorbid depression-anxiety groups.[43] Confounding by anxiety was also demonstrated in the study by Fales et al.[40] MDD subjects showed less activity in the right DLPFC relative to HC, accompanied by increased left amygdala activity; however, most of these effects were abolished when adjusting for anxiety scores, again highlighting the importance of correcting for anxiety symptoms in major depression.[40] Two other studies showed no significant differences in DLPFC activity between MDD subjects and HC.[41;46]

Taken together, DLPFC findings in MDD subjects have been inconsistent, showing increased, decreased or similar activity compared to HC. Increased DLPFC activity was mostly associated with normal or decreased limbic activity and vice versa. Failure to increase DLPFC activity was also associated with anxiety, suggesting that at least a subgroup of (non-anxious) MDD subjects may successfully recruit DLPFC in addition to medial prefrontal regions in order to block emotional interference during automatic attentional control.

Table 2. Attentional control; results concern negative emotions unless otherwise stated

Study	No. of MDD subjects Age (mean) HDRS score (mean)	Methodological aspects (Table S1)			Task	Key condition or contrast and statistical threshold	Task performance	Relevant brain regions	Recruitment in MDD vs HC
		Medication	Comorbitiy	Statistics					
A. Automatic									
Frodl et al.[38]	12 (7F) Age:43.3 21HDRS:17.5	-	+	+/-	Matching faces on emotion or gender	Implicit processing (match gender) ROI: p<0.05 SVC Whole brain: p<0.001 UC, k≥10	=	L DLPFC DLPFC Amygdala R dACG (middle cingulum) L parietal cortex R gyrus angularis	↑ relatively ↑ (n.s.)[a] = relatively ↑ (n.s.)[a] relatively ↑ (n.s.)[a] relatively ↑ (n.s.)[a]
Frodl et al.[39]	25 (9F) Age:39.4 HDRS:20.6	+	+	+	Matching faces on emotion or gender	Implicit processing (match gender) Whole brain: p<0.05 FWE C	=	*Connectivity VLPFC and* R DLPFC R parietal cortex L dACG (middle cingulum) R thalamus	 ↑ ↑ ↓ ↓[b]
Fales et al.[40]	27 (17F) Age: 33.4 17HDRS: 20	+/-	+	+	Match or ignore fearful faces or neutral houses	Ignore fear> ignore neutral ROI: p<0.025, k≥9; post hoc p<0.006 Whole brain: p<0.001, k≥14	=	R DLPFC L amygdala	↓[c] ↑[c]
Mitterschiffthaler et al.[41]	17 (14F) Age: 39.3 17HDRS:20.8 BDI: 38	+/-	+	+	eStroop	Neg> neutral ROI: p<0.001+SVC Whole brain: p<0.05 FWE C	↓	DLPFC L dACG L thalamus	↓(n.s.) ↑ ↑(n.s.)[b]
George et al.[22]	11 (2F) Age: 36.6 21HDRS: 15	+/-	+/- BD:5	-	eStroop	Sad > control Whole brain: p<0.001	↓ (n.s.)	dACG vACG	=[d] =[d]
Canli et al.[42]	15 (12F) Age: 35.1 BDI:23.9	-	+	-	Lexicon decision task	Sad/fear/ happy > neutral words Whole brain: p<0.001 UC, k≥10	=	R VLPFC L VLPFC L DMPFC L inf parietal cortex Insula R amygdala	↓(pos) ↑ ↑ ↑ ↓(pos)[b] ↓(pos)

Etkin et al.[43]	14 (10F) Age: 32.2 BDI: 27.6	+/-	+/-	+	Emotional conflict task	Postincongruent incongruent >postcongruent incongruent ROI: p<0.05 FWE C	=	 R amygdala L rACG/L MOFC L frontal pole (BA 10) *Connectivity* rACG and amygdala	*(pos and neg pooled)* ↑ ↓ ↑ ↓
Almeida et al.[44]	19 (12F) Age: 30.3 25HDRS:28.1	-	-	+	Color naming task (overlaying dynamic faces)	Happy/sad/angy/ fearful > control ROI: p<0.05, k by MC	=	*Effective connectivity:* Amygdala *to* VMPFC L VMPFC *to* amygdala Amygdala *to* sgACG L sgACG *to* amygdala L VMPFC *to* sgACG sgACG *to* VMPFC	 = (all conditions) =[e] = (all conditions) ↑(fear)[e,f] =[g] = (all conditions)
Eugene et al.[45]	12 (6F) Age: 33.8 BDI-2:29	+/-	-	+	Negative affective priming task	Inhibition > no inhibition ROI: p<0.06, k≥13; MC Whole brain: p<0.001, k≥13; MC	=	R rACG	↑[h] ↓ (pos)[h]
Bertocci et al.[46]	23 (23F) Age: 29.7 25HDRS:26.3	-	+	+	Emotional n-back task	Happy/fearful/ >no distractors ROI: p<0.05, k by MC	=	Amygdala DLPFC r/dACG	= (pos, neg) = (pos, neg) = (pos, neg)
B. Voluntary									
Wang et al.[49]	19 (12F) Age:39.3 17HDRS:19.9	-	+/-	+/-	Emotional oddball task	Target after sad > target after neutral ROI: p<0.05 Whole brain: p<0.001 UC, k≥5	↓ (n.s.)	VLPFC dACG L DLPFC L insula	↑ ↓ Stronger deactivation ↓[b]
Dichter et al.[50]	14 (7F) Age: 34.8 BDI: 6.9	+/-	+	+	Emotional oddball task	Targets in sad blocks Cluster-based: p<0.05	=	R DLPFC R VLPFC R frontal pole L dACG R insula Thalamus	↑ ↑ ↑ ↑ ↑[b] ↑[b]
Siegle et al.[51]	7 (3F) Age:34.3	+/-	-	+/-	Cognitive task preceded by emotional task	Neg>pos/neutral Whole brain: p<0.01, C by k Identified ROIs: Bonferroni (3 comparisons)	=	L DLPFC Amygdala L amygdala /hippocampus	↓(n.s.) ↑ ↑

To be continued on the next page

Table 2. Continued

Lisiecka et al.[52]	50 (33F) Age:43 BDI II:32,5	-	+	+	Cognitive task preceded by emotional task	Neg+pos attention shifting >baseline Whole brain: p<0.05 FWE C	↓		*(pos and neg pooled)* R DMPFC ↓ R insula ↓[b,i] R rolandic operculum ↓ L inferior parietal cortex ↓[j] R parietal cortex ↓[b,i] L MCC/dACC ↓ (neg)[j]
Matthews et al.[53]	15 (12F) Age: 24.5 BDI-2: 27.8	+	+	+	Emotional face matching task	Angry+fearful+happy > neutral ROI: p<0.05, vol≥128 µl, k≥2; MC	=		*(pos and neg pooled)* Extended amygdala ↑ *Connectivity extended amygdala and* dACG ↓ sgACG ↑
Townsend et al.[54]	15(6F) Age:45.6 21HDRS:20.1	+/-	+	+/-	Emotional face matching task	Fear+sad> control condition ROI: p<0.05 UC Whole brain: Clusters (Z>2.3): p<0.05 FDR C	=		Amygdala = DLPFC ↑(n.s.) R VLPFC = L VLPFC =[k] R insula ↓[b] Hippocampus ↓[b] R thalamus ↑ (n.s.)[b]
Peluso et al.[55]	14 (9F) Age:37.9 21HDRS: 20.0	+/-	+/-	+/-	Emotional face matching task	Angry+fearful> neutral ROI: p<0.05 Whole brain: p<0.01 C, k≥9	-		Amygdala ↑
Carballedo et al.[56]	15(5F) Age:39.87 21HDRS:22.9	+	+	+/-	Emotional face matching task	Angry+sad> control condition Whole brain: p<0.01 UC→ identification of ROIs for FC	=		*Effective connectivity from* L amygdala *to* L VLPFC ↓ R amygdala *to* R VLPFC ↓ R amygdala *to* R dACG ↓ R dACG *to* R DLPFC ↓ R dACG *to* R amygdala ↑
Elliott et al.[57]	10 (7F) Age: 42.2 17HDRS:23.1	-	+	+/-	Emotional go/no go task	Happy/sad >neutral distractors Whole brain: p<0.05 C ROI: p<0.001 UC	=		VLPFC ↑
Berman et al.[58]	15 (?F) Age:24.4 (incl HC)	+/-	-	+/-	Forgetting encoded positive and negative words	Forget pos/neg versus control Whole brain: p<0.005, k≥20	↓		Area extending from L VLPFC to DLPFC (along entire L inf frontal gyrus) = (magnitude) but spatially more diffuse activation (neg) dACG = (pos and neg) parietal cortex = (pos and neg)

Frodl et al.[38]	12 (7F) Age:43.3 21HDRS:17.5	-	+	+/-	Matching faces on emotion or gender	Explicit processing (match emotion) ROI: P<0.05 SVC Whole brain: *p*<0.001 UC, *k*≥10	=	Amygdala Ventral striatum Pallidostriatum Putamen	= = = =
Frodl et al.[39]	25 (9F) Age:39.4 HDRS:20.6	+	+	+	Matching faces on emotion or gender	Explicit processing (match emotion) Whole brain: *p*<0.05 FWE C	=	*Connectivity VLPFC and* L parietal cortex, gyrus angularis L inferior parietal cortex Bi superior parietal cortex R thalamus Hippocampus L parahippocampus	 ↑ ↓ ↓ ↓[b] ↓ ↓
Fales et al.[40]	27 (17F) Age: 33.4 17HDRS: 20	+/-	+	+	Match or ignore fearful faces or neutral houses	match fear> match neutral ROI: *p*<0.025, *k*≥9; post hoc *p*<0.006 Whole brain: *p*<0.001, *k*≥14	=	R DLPFC R dACG L amygdala	= = ↑[c]; Neg correlation with R DLPFC

Abbreviations: ACG, anterior cingulate gyrus; BA, Brodmann area; Bi, bilateral; C, corrected; dACG, dorsal ACG; DLPFC, dorsolateral PFC; F, female; FC, functional connectivity; FDR, false discovery rate; FWE, family wise error; HC, healthy control; inf, inferior; k, number of contiguous voxels; L, left; LPFC, lateral PFC; MC, determined by Monte Carlo simulations; MDD, major depressive disorder; MOFC, medial OFC; MPFC, medial PFC; neg, negative; n.s., non-significant; OFC, orbitofrontal cortex; PFC, prefrontal cortex; pos, positive; R, right; rACG, rostral ACG; ROI, region of interest; sgACG, subgenual ACG; sup, superior; SVC, small volume corrected; UC, uncorrected; vACG, ventral ACG; VLPFC, ventrolateral PFC; VMPFC, ventromedial PFC; Vol, volume; 17HDRS, 17-item Hamilton Depression Rating Scale; 21HDRS, 21 item HDRS; BDI, Beck Depression Inventory; µl, microliter; +, good (medication: none/washout ≥ 2 months: no ECT ≥ 2 months; comorbidity: no primary comorbid Axis I diagnosis; statistics: main effects and interactions corrected for multiple comparisons); +/-, moderate (medication: medication use in > 50% of sample/washout < 2 months; comorbidity: comorbid Axis I diagnosis in < 50% of sample; statistics: not good: not poor); -, poor (medication: medication use in ≥ 50% of sample/not mentioned; comorbidity: comorbid Axis I diagnosis in ≥ 50% of sample/not mentioned; statistics: uncorrected analysis).

[a] i.e. equal activation during the implicit and explicit condition in MDD; in HC there is a decrease in activation during the implicit condition
[b] discussed in the supplemental information
[c] effects abolished when corrected for anxiety scores
[d] imaging method: PET
[e] females only: ↑ inverse connectivity (left-sided) in happy condition
[f] females only: MDD subjects: positive connectivity; HC: inverse connectivity in fear condition
[g] females only: ↓ connectivity in happy condition
[h] HC recruited the rACG inhibiting response to positive words
[i] HC without family history of MDD>MDD without family history of MDD
[j] HC with family history of MDD>MDD with family history of MDD
[k] less activation in anxious MDD subgroup vs non anxious MDD subgroup (preliminary result)

In addition to the DLPFC, other lateral prefrontal regions have been found to be differentially activated in MDD subjects relative to HC during automatic attentional control. Right VLPFC activity was decreased in MDD subjects relative to HC, but only while distracted by positive words, paralleled by *decreased* amygdala activity.[42] In contrast, the left VLPFC showed *elevated* activity with negatively valenced distraction.[42] Again, this could reflect a need for additional lateral prefrontal recruitment for automatic attentional control of negative emotions in MDD subjects. This conclusion receives some support from a functional connectivity study by Frodl et al.,[39] demonstrating increased connectivity of the VLPFC with the right DLPFC in MDD subjects relative to HC during the implicit condition, indicative of an overactive ventrolateral-dorsolateral system in order to overcome distraction by negative emotional, task- irrelevant stimuli.[39]

The right inferior parietal cortex also showed stronger connectivity with the VLPFC.[39] Furthermore, although only reported in two studies, increased parietal cortical *activity* in MDD subjects versus HC was reported as well.[38;42] This increased parietal activity in MDD subjects could reflect increased attention during processing of emotional stimuli. Alternatively, it may represent a compensatory mechanism, similar to increased DLPFC activity: a need to recruit additional lateral brain regions for successful attentional control during automatic emotion regulation. Since connectivity between the VLPFC with the DLPFC and parietal cortex is increased, the VLPFC may mediate this additional lateral cortical recruitment. Because these findings of increased lateral cortical activity mostly concern medicated MDD subjects, this increased lateral cortical activity might represent a medication effect. However, although there is evidence that antidepressant treatment may indeed increase DLPFC activity in MDD subjects, in this study by Fales et al.[36] this increase was associated with symptom remission, unlike in the studies reviewed in this section. Furthermore, studies in unmedicated subjects that failed to observe significant differences in lateral PFC activity between MDD subjects and HC,[22;41;43;45] used relatively stringent statistical thresholds, did not include lateral PFC regions as a priori ROIs, and/or suffered from low power. Therefore, the hypothesis that unmedicated MDD subjects are also able to recruit additional lateral prefrontal cortical regions during automatic attentional control is in need of further empirical testing.

In summary, for automatic attentional control, findings indicate abnormal activity in medial prefrontal regions (DMPFC and rACG) in MDD subjects relative to HC during automatic emotion regulation tasks, mostly increased when regulating negative emotions. Furthermore, effective connectivity from the sgACG - a medial regulatory structure - to the amygdala appears to be increased, supporting the hypothesis that MDD subjects need to recruit medial prefrontal regions to a greater extent than HC during automatic attentional control. In parallel, there are indications that in other tasks involving automatic attentional control components, MDD subjects demonstrate a compensatory recruitment of parietal and lateral prefrontal regions to automatically redirect attention away from interfering emotions. Since one study demonstrated stronger functional connectivity in MDD subjects relative to HC between the VLPFC and the parietal cortex as well as the DLPFC, we hypothesize that increased activity in parietal and dorsal prefrontal cortex in MDD subjects could be (partly) mediated by the VLPFC. Thus, MDD subjects seem to activate lateral as well as medial brain regions in these automatic processes, whereas in HC automatic regulation

is thought to involve mostly medial structures. This additional lateral prefrontal cortical activity and increase of medial prefrontal activity in MDD subjects might be necessary to overcome overengagement with distracting (negative) emotional stimuli. This recruitment of additional cortical resources may result in successful automatic attentional control, because activity in 'limbic' regions like the amygdala and insula did most often not differ in MDD subjects relative to HC (except Canli et al.[42] and Etkin and Schatzberg[43]). This conclusion is further supported by findings of normal task performance in MDD subjects (except Mitterschiffthaler et al.[41]). However, because medication use was allowed in several studies,[22;38-40;42;44-46] this ability may, again, also represent a medication effect.[36;47]

Identified studies also demonstrated that the level of comorbid anxiety may be an important factor to adjust for in neuroimaging research in MDD subjects, because correction abolished the finding of decreased DLPFC and increased amygdala activity in MDD patients, suggesting that these findings could be explained by anxiety rather than depression. Increased anxiety is a highly common feature during depression and may represent an important subdimension of MDD. Finally, gender may be important with regard to automatic attentional control of positive stimuli: abnormal connectivity between the sgACG, VMPFC and amygdala in females, but not in males, could reflect abnormal regulation of *positive* emotions in females due to reduced integration in this neural circuitry.[44]

3.2.2. Voluntary attentional control [Table 2B]

Voluntary attentional control involves effortful attempts to overcome emotional distraction, i.e., when the subject is aware of the emotional context by its explicit nature, and thus must use effortful strategies to overcome this distraction in order to perform the motor or cognitive task. It normally involves the DLPFC, VLPFC, dACG and parietal cortex, which are thought to reciprocally influence the amygdala, insula, ventral striatum, hippocampus and parahippocampus, as well as the autonomic nervous system.[1;16;17]

In MDD subjects, this has been studied using: (1) Emotional oddball tasks,[49;50] where participants have to respond to randomly presented target pictures amidst blocks of emotionally valenced distracter pictures, thereby requiring effortful disengagement from emotional distraction. (2) Alternating emotional and non-emotional tasks,[51;52] focusing on the impact of emotional verbal stimuli on subsequent performance during a cognitive task. (3) Matching of facial expressions,[38-40;53-56] which features an explicit condition. During this explicit condition, participants have to match the emotional expressions of the presented faces. Since in this condition the emotion is an overt focus of attention, it requires effortful control to overcome its influence in order to perform the matching task. (4) An emotional go/no-go task,[57] where participants either respond to emotional words by a button press or withhold this response; and (5) A directed forgetting task,[58] where participants are instructed to deliberately forget positively or negatively valenced words, a process that includes directing away one's attention from the words to be forgotten.

An alternative approach to investigate lateral prefrontal functioning in MDD subjects during voluntary attentional control was employed by Berman et al..[58] They focused not so much on the magnitude, but rather on the extent of the spatial variability of neural activity, assuming that more spatial variability (i.e., less spatially concentrated activity) indicates less effective

activity. In MDD subjects, spatial variability was indeed larger in the area extending from the left DLPFC to the VLPFC during voluntary attentional control of negative emotional stimuli, which could be indicative of VLPFC/DLPFC dysfunction in MDD subjects.[58] The findings of Siegle et al.[51] further support this result, demonstrating decreased regulation of amygdala activity by the left DLPFC. Findings regarding DLPFC activity by Wang et al.[49] are more difficult to interpret. They studied maladaptive engagement with emotional distracting stimuli by investigating regions involved in the default mode network (DMN). In MDD subjects, greater deactivation of components of the DMN indicated greater engagement with sad distracters than in HC. At the same time, MDD subjects and HC both *de*activated the left DLPFC when they had to voluntarily overcome distraction, but in MDD subjects, the DLPFC was deactivated to a greater extent than in HC, which may also indicate greater distraction in MDD subjects. These somewhat confusing findings might be due to the task design: a low level baseline for comparison with conditions of interest was lacking, which could have resulted in deactivation patterns when comparing these active conditions.[49] Other studies indicated DLPFC *hyper*activity in MDD subjects during voluntary attentional control over emotional distracters.[40;50;54]

Taken together, results indicate abnormal DLPFC functioning in MDD subjects, but findings are inconclusive regarding hyper- or hypoactivity. These conflicting findings could not be explained by medication status, depression severity, comorbidity, task performance, or power issues.

Whereas findings regarding DLPFC activity remain inconclusive, VLPFC activity was found to be increased in MDD subjects compared to HC.[50;57;49] While another study failed to observe differential VLPFC activity, these null results may have been due to anxiety levels, since VLPFC activity in non-anxious MDD subjects was stronger than in anxious MDD subjects.[54] Functional connectivity with the VLPFC was also investigated during voluntary attentional control.[39;56] Frodl et al.[39] demonstrated a stronger connectivity of the VLPFC with a part of the left parietal cortex, the gyrus angularis, in MDD subjects compared to HC. Connectivity between the VLPFC and the bilateral hippocampus, and left parahippocampal gyrus[39] as well as effective connectivity from the amygdala to the VLPFC appeared to be disturbed in MDD subjects.[56] Thus, whereas VLPFC activity appears to be increased in MDD subjects compared to HC during voluntary attentional control, (effective) connectivity with limbic regions is impaired, indicating decreased frontolimbic coupling in MDD subjects which may reduce emotion regulation effects of enhanced VLPFC activity.

Decreased frontolimbic coupling is also reflected by the findings of reduced effective connectivity from the amygdala to the dACG and furthermore from the dACG to the DLPFC.[56] However, effective connectivity in the opposite direction, i.e., from the right dACG to the right amygdala, was *enhanced* in MDD subjects.[56] As suggested by the authors, this may reflect enhanced processing of negative material, since the right hemisphere is suggested to be involved in negative affect.[59] Alternatively, it might be hypothesized that this increased dACG-amygdala effective connectivity underlies a compensatory mechanism for reduced functional frontolimbic coupling. However, Matthews et al.[53] demonstrated a weakened connectivity between the dACG with the bilateral amygdala in MDD subjects, which was associated with depression severity: the more depressed the subject, the lower the

connectivity. These different findings regarding dACG connectivity between Carballedo et al.[56] and Matthews et al.[53] could not be explained by medication status or depression severity, but might be due to differences in outcome measures and task design (effective versus functional connectivity, negative versus pooled negative and positive stimuli, respectively). Findings regarding dACG *activity* are also conflicting: normal dACG activity was found in MDD subjects,[40;58] but also increased[50] or decreased activity.[49;52] Decreased activity, however, was found only in medicated MDD subjects[49] and in medicated MDD subjects *with a family history of MDD* compared to HC with a family history of MDD.[52] The latter study also reported DMPFC hypoactivation in MDD subjects compared to HC, irrespective of emotional valence.[52]

In sum, dACG functioning during voluntary attentional control is likely to be abnormal in MDD subjects, given the findings of altered activity levels, as well as altered connectivity with limbic and dorsal prefrontal (regulatory) regions. Increased effective connectivity from the dACG to the amygdala when regulating negative emotions, and increased dACG activity in unmedicated MDD subjects suggest increased recruitment of dACG-amygdala circuitry. This increased recruitment may reflect an attempt to compensate for reduced frontolimbic coupling indicated by the findings of decreased dACG-DLPFC connectivity, decreased connectivity between the VLPFC and limbic regions, and DLPFC dysfunction in MDD subjects.

In summary, for voluntary attentional control, results suggest that MDD subjects engage VLPFC regions to a greater extent than HC when overt emotionally distracting stimuli are presented. Because (functional) connectivity between the VLPFC and limbic regions was disturbed, indicating reduced frontolimbic coupling, this hyperactivation might represent attempts of the VLPFC to actively regulate emotion. DLPFC functioning might also be abnormal in MDD subjects, but the precise nature of its dysfunction in MDD subjects remains unclear, since findings favour either hyperactivity or hypoactivity relative to HC. These heterogeneous results could not be explained by differences in medication use, depression severity, comorbidity or task performance: We could not detect a direct relationship between these factors and DLPFC activity patterns. Functional dACG connectivity with the amygdala has been reported as weakened in MDD subjects, and appears to be associated with depression severity. Therefore, we propose that functional lateral frontolimbic coupling is reduced in MDD subjects during voluntary attentional control. In contrast, effective connectivity *from* the right dACG *to* the right amygdala is enhanced in MDD subjects relative to HC, which may reflect increased processing of negative material despite regulation attempts. An alternative hypothesis is that the reduced functional lateral frontolimbic coupling during voluntary attentional control is (successfully) compensated for by recruitment of top-down dACG-amygdala circuitry. Although speculative, this hypothesis would be in line with findings of normal task performance (except Berman et al. [58] and Lisiecka et al.[52]) and the fact that limbic hyperactivity was reported in only a minority of studies (four[50;51;53;55] of thirteen). However, medication could have influenced these results, since during voluntary attentional control tasks in medicated subjects, decreased activity of the amygdala has been reported.[29;35;60]

Also, findings indicate that anxiety levels should be taken into account when interpreting neuroimaging results in MDD subjects.[54] Furthermore, MDD subjects with a family history of MDD might represent a specific MDD subgroup.[52]

3.3. Cognitive control

Cognitive control refers to altering the emotional meaning of originally salient stimuli by the process of reappraisal, and to cognitive processes involved in emotion regulation during expectancy of forthcoming events and outcomes.[1]

3.3.1. Automatic cognitive control (Tables 3A and S4A)

Automatic cognitive control in MDD subjects is studied by focusing on anticipation of emotional stimuli, during which subjects engage automatically in regulatory, cognitive control processes.* It normally involves the hippocampus and parahippocampus, the DMPFC and ACG.[1]

In MDD subjects, five studies involved the anticipation of emotional pictures,[62-66] and one the anticipation of pain.[67] Four studies reported on the anticipation of the outcome of the guess in gambling tasks.[68-71]

Of medial regulatory regions implicated in automatic cognitive control in HC, the DMPFC, VMPFC, rACG and dACG have been studied in MDD subjects. In contrast to HC, MDD subjects failed to activate left DMPFC during expectation of emotional pictures, and this effect was more pronounced during expectation of negative than during the expectation of positive pictures.[63] However, this single study is in need of replication, because decreased DMPFC activity in MDD subjects was found only at an uncorrected threshold. Right VMPFC activity was increased in MDD subjects compared to HC.[66] Five studies reported on dACG activity:[63;64;67;69;70] increased bilateral dACG activity was reported in MDD subjects versus HC during anticipation of negative as well as positive emotional stimuli;[63;67;69;70] however one study found decreased left sided activity in dACG during anticipation of negative or positive emotional pictures.[64] Furthermore, Smoski et al.[68] found that the right dACG was less active in MDD subjects during the anticipation of the outcome of a guess. Of note, in this study, subjects did not know whether they were to experience a positive emotion (winning) or a negative emotion (losing). Instead, subjects could calculate their chances to win, and therefore decreased dACG activity in MDD subjects could reflect an alternative strategy (less reliance on computational analysis) as well as regulation deficits.[68] Regarding the sgACG, activity was increased in MDD subjects during expectation of positive or negative emotions.[66;70]

Overall, findings from these studies indicate that medial brain structures, normally implicated in automatic cognitive emotion regulation, may function differently in MDD subjects and HC during automatic cognitive control. Most evidence is found for increased dACG and sgACG activity in MDD subjects during automatic cognitive control of expected positive as well as negative emotions.

* 1. Originally, these anticipatory tasks were categorized as voluntary cognitive change.[1] However, we reconsidered this classification. In anticipation, subjects are not instructed to regulate their feelings, but only to wait and see. So during the expectation of a (negative) stimulus, one will automatically engage in a cognitive regulatory process. We therefore decided that these tasks investigate automatic cognitive change. For references, see also Abler et al.[61]

The above studies also reported on patterns of lateral prefrontal activity in MDD subjects versus HC. Regarding the VLPFC, most findings indicate increased activity in MDD subjects.[63;66;67;70] Smoski et al.[68] found lower right VLPFC activity in MDD subjects than in HC, but again this might be due to other processes than emotion regulation, because subjects did not know what kind of emotion they were about to experience.

The DLPFC was also examined during automatic cognitive control as emotion regulation strategy.[62-67;69;70] A right sided,[63-66] left sided[62;70] or bilateral[67] overactivity of the DLPFC in MDD subjects during the expectation of emotional stimuli was found in MDD subjects versus HC.

Together, these findings indicate DLPFC and VLPFC hyperactivity in MDD subjects during automatic cognitive control paradigms. Similar to automatic attentional control, VLPFC and DLPFC hyperactivity in MDD subjects may reflect the need for additional recruitment of lateral brain regions to exert automatic cognitive control when processing emotional stimuli. Of note, evidence for lateral prefrontal hyperactivity in MDD subjects has been consistently observed, also in low-power studies (for example, Rosenblau et al.[66]) Furthermore, although medication may also induce an increase in lateral prefrontal activity,[37] this effect has been observed in medicated as well as unmedicated patients and may thus be considered MDD-related.

Nevertheless, additional recruitment of lateral regions might not always be successful in terms of reducing limbic activation: studies reporting greater DLPFC activity also reported increased bilateral or right-sided amygdala activity in MDD subjects during expectation of emotional, particularly negative pictures or painful stimuli.[62;65-67] Also for the parietal cortex, results indicate increased activity in MDD subjects compared to HC[63;64;66;68;70] (but see Grimm et al.[64]). This additional parietal recruitment may serve the same goal as VLPFC and DLPFC recruitment (i.e., increased regulatory activity) but may alternatively reflect increased attention for emotional stimuli, and is therefore, in line with amygdala hyperactivity, an indication of a failure of automatic cognitive control.

Of note, two studies failed to find any differences in ventral striatal activity during gain anticipation in MDD subjects compared to HC, implying similar capability of MDD subjects and HC to respond when expecting a positive outcome.[69;70] One study, however, did observe blunted ventral striatal activity in MDD subjects during the anticipation of gain as well as loss, correlating with depression severity and anhedonia in particular.[71] This discrepancy could be a result of differences in task design, but is likely not attributable to differences in medication status, statistical approach, or power issues.

In summary, for automatic cognitive control, findings from the above studies suggest differential medial cortical functioning in MDD subjects, as reflected by predominantly increased dAGG and sgACG activity. Similar to findings regarding automatic attentional control paradigms, it appears that MDD subjects recruit at least the DLPFC/VLPFC in addition to medial prefrontal regions for regulation by automatic cognitive control, possibly in an attempt to overcome emotional interference. However, in contrast to automatic attentional control, this attempt is not always successful, as reflected by residual limbic hyperactivity[62-67;70] as well as some behavioural evidence, as five studies found differences between MDD subjects and HC. A (non-significant) negative correlation between regulation

Table 3. Cognitive control: results concern negative emotions unless otherwise stated

Study	No. of MDD subjects Age (mean) HDRS score (mean)	Methodological aspects (Table S1)			Task	Key condition or contrast and statistical threshold	Task performance	Relevant brain regions	Recruitment in MDD vs HC
		Medication	Comorbidity	Statistics					
A. Automatic									
Abler et al.[62]	12 (12F) Age: 41.2 HDRS:18.5	-	+	+	Cued emotional pictures	Expectation of neg pictures ROI: $p<0.05$ SVC Whole brain: $p<0.001$, C by k	=	L DLPFC Amygdala	↑ ↑
Bermpohl et al.[63]	15 (10F) Age: 43.3 HDRS:24.7	-	+/- BD:2	-	Cued emotional pictures	Expectation of pos+neg pictures ROI: $p<0.001$ UC Whole brain: $p<0.001$ UC	=	L DMPFC L dACG L VLPFC R DLPFC L insula parietal cortex L parahippocampus	*(pos and neg pooled)* ↓ ↑ ↑ ↑ ↑[a] ↑ ↑[a]
Rosenblau et al.[66]	12 (5F) Age: 43.5 17HDRS: 21.2	+	+	+	Cued emotional pictures	Expectation of neg pictures ROI: $p<0.005$, $k\geq10$ (amygdala: $p<0.05$, $k\geq5$) Whole brain: $p<0.05$ FDR C	NA	R amygdala L VLPFC R VMPFC R DLPFC L sgACG R inferior parietal cortex	↑ ↑ ↑ ↑ ↑ ↑
Grimm et al.[64]	19 (11F) Age: 40.0 21HDRS: 33.1	+/-	+	-	Judgment and perception of emotional pictures in an unexpected and expected mode	Expectation of pos+neg pictures Whole brain: $p<0.001$ UC, $k\geq5$	Less pos ratings of pos pictures	L dACG L DLPFC R insula L parietal cortex	*(pos and neg pooled)* ↓ ↓ ↑[a] ↓
Grimm et al.[65]	19 (11F) Age: 40.0 21HDRS: 33.1	+/-	-	-	Judgment and perception of emotional pictures in an unexpected and expected mode	Expectation of pos+neg pictures Whole brain: $p<0.001$ UC, $k\geq5$	Less pos ratings of pos pictures	R DLPFC Amygdala	*(pos and neg pooled)* ↑[b] ↑

Strigo et al.[67]	15 (12F) Age:25.5 BDI-2:27.8	-	+	+	Cued noxious hot or non-noxious warm stimuli	Expectation of painful hot > warm stimuli Whole brain: $p<0.05$, vol≥ 512 □l; MC ROI: $p<0.05$, vol≥ 128 □l; MC	More neg ratings	dACG L VLPFC DLPFC Amygdala Insula	↑ ↑ ↑ ↑ ↑[a]
Smoski et al.[68]	14 (7F) Age:30.8 HDRS: 23.5	+/-	+	+	Wheel of fortune task	Anticipation of outcome Whole brain: Z=2.6 C,[137] k≥5	=	 R dACG R VLPFC L parietal operculum R hippocampus Thalamus	*(unexpected valence)* ↓ ↓ ↑ ↓[a] ↓[a]
Knutson et al.[69]	14 (9F) Age:30.7 BDI:25.4	+	+	+	Monetary incentive delay task	Expectation of gain/loss ROI: $p<0.167$ Bonferroni (3 comparisons) Whole brain: $p<0.05$ C, k≥4	=	dACG NAcc	↑(pos) = (pos)
Pizzagalli et al.[70]	30 Age:43.2 17HDRS: 18	+/-	+/-	+	Monetary incentive delay task	Expectation of gain/loss Whole brain: $p<0.005$, k≥12; MC Findings outside basal ganglia preliminary	↓ RT modula-tion (n.s. for loss) ↓ pos affect	R sgACC R VLPFC L DLPFC R uncus/parahippocampal gyrus NAcc L inferior parietal lobule L insula dACC	↑(pos) ↑(pos) ↑(pos) ↑(pos)[a] = (pos) ↑(pos) ↑(neg)[a] ↑(neg)
Stoy et al.[71]	15 (5F) Age:41.9 HDRS:19.7	+/-	+	+	Monetary incentive delay task	Expectation of gain/loss ROI: $p<0.05$ FWE C Whole brain: $p<0.05$ FWE C	=	Ventral striatum R ventral striatum	↓(neg)[c] ↑(pos)

To be continued on the next page

Table 3. Continued

B. Voluntary									
Taylor Tavares et al.[73]	13 (10F) Age: 38.3 MADRS: 23	+/-	+/-	+	Reversal learning task	Erroneous adjustment of response after misleading negative feedback ROI Whole brain: $p \leq 0.05$ C[138]	↓	R DMPFC VLPFC	↓ ↓
Steele et al.[72]	15 (11F) Age:45.9 HDRS:27.3	-	+	+	Receiving feedback during a gambling task	Temporal difference error signal ROI: 10 mm SVC Whole brain: $p<0.05$ FWE C	=	R rACG L ant parahippocampal gyrus *Connectivity between* VLPFC ↔ R ventral striatum VLPFC ↔L thalamus	↑ ↑ ↑ ↑
Gradin et al.[75]	15 (9F) Age:45.3 21HDRS: 23.2	-	+	+	Instrumental (decision making) reward learning paradigm	Prediction error signal Whole brain: $p<0.05$ C, $k \geq 141$ Only a priori ROIs reported	=	L putamen Nacc Caudate R hippocampus Midbrain R thalamus	↓ ↓[d] (R NAcc) ↓[d] ↓ ↓[d] ↓[a]
Remijnse et al.[74]	20(8F) Age:35 17HDRS:19.1 MADRS:29.7	+/-	+/-	+/-	Reversal learning task	Affective switching Whole brain: $p<0.05$ FDR C (main effects) $p<0.001$ UC (interactions) ROI: $p<0.005$ UC (interactions)	=	R DLPFC Ant PFC L rACG Insula R inf parietal cortex L inf parietal cortex L sup parietal cortex R thalamus	↓ ↓ ↓ ↓[a] ↑[a] ↓[a] ↑[a] ↓[a]
Fales et al.[40]	27 (17F) Age: 33.4 17HDRS: 20	+/-	+	+	Match or ignore fearful faces or neutral houses	Post error > post correct ROI: $p<0.025$, $k \geq 9$; post hoc $p<0.006$ Whole brain: $p<0.001$, $k \geq 14$	↓(n.s.) (speed –up)	r/dACG pregenual ACG DLPFC	= ↑ ↓[e]

Johnstone et al.[76]	21 (13F) Age: 33 HDRS: 21	+/-	+	+	Reappraisal of negative pictures	Reappraise negative> attend negative Whole brain: $p<0.01$, k by MC	=	R VLPFC L VMPFC-inhibition of amygdala Amygdala Parietal cortex Insula Thalamus	↑[f](n.s.) ↓ = =[a] =[a] =[a]
Heller et al.[78]	27 (15F) Age: 31.5 HDRS: 21.2	+/-	+	+	Reappraisal of positive pictures	Enhance positive> suppress positive Whole brain: $p<0.05$, $k\geq50$; MC connectivity maps: ROI: $p<0.05$ SVC, $k\geq15$	=	L NAcc L insula *Connectivity between* L NAcc ↔ PFC (BA 8)	↓sustained activity (pos) ↓sustained activity (pos)[a] ↓sustained connectivity (pos)
Sheline et al.[77]	24 (12F) Age: 34 HDRS: 21	+/-	+	+	Reappraisal of negative pictures[g]	Reappraise negative> attend negative ROI: $p<0.001$, $k\geq14$; post hoc $p<0.01$ Whole brain: $p<0.05$ C, $k\geq14$	=	DMN[h] L parahippocampal gyrus L DMPFC	Less deactivation ↑ ↑
Light et al.[79]	27 (25F) Age: 31.5 HDRS: 21.2	+/-	+/-	+	Reappraisal of positive pictures	Suppress positive > maintain positive Whole brain: $p<0.05$, $k\geq50$; MC	=	*Relation to anhedonia* R VLPFC DMPFC	*No comparison with HC* Higher baseline activity predicted higher anhedonia scores after treatment

Abbreviations: ACG, anterior cingulate gyrus; ant, anterior; C, corrected; dACG, dorsal ACG; DLPFC, dorsolateral PFC; DMN, default mode network; DMPFC, dorsomedial PFC; F, female; FC, functional connectivity; FDR, false discovery rate; FWE, family wise error; inf, inferior; k, number of contiguous voxels; L, left; LPFC, lateral PFC; MC, determined by Monte Carlo simulations; MPFC, medial PFC; NA, not applicable; NAcc, nucleus accumbens; neg, negative; n.s., non-significant; PFC, prefrontal cortex; pos, positive; R, right; rACG, rostral ACG; ROI, region of interest; RT, reaction time; sgACG, subgenual ACG; sup, superior; SVC, small volume corrected; UC, uncorrected; VLPFC, ventrolateral PFC; VMPFC, ventromedial PFC; Vol, volume; 17HDRS, 17-item Hamilton Depression Rating Scale; 21HDRS, 21 item HDRS; BDI, Beck Depression Inventory; µl, microliter; +, good (medication: none/washout ≥ 2 months: no ECT ≥ 2 months; comorbidity: no primary comorbid Axis I diagnosis; statistics: main effects and interactions corrected for multiple comparisons); +/-: moderate (medication: medication use in > 50% of sample/washout < 2 months; comorbidity: comorbid Axis I diagnosis in < 50% of sample; statistics: not good: not poor); -, poor (medication: medication use in ≥ 50% of sample/not mentioned; comorbidity: comorbid Axis I diagnosis in ≥ 50% of sample/not mentioned; statistics: uncorrected analysis).

[a] discussed in the supplemental information
[b] MDD: R DLPFC>L DLPFC; HC: R DLPFC = L DLPFC
[c] negative correlation with anhedonia symptom severity
[d] negative correlation with anhedonia symptom severity (i.e. decreased signal corresponded with increased anhedonia)
[e] MDD: posterror=postcorrect (deactivation in both cases); HC: activate DLPFC after receiving feedback on error
[f] MDD: activation L+R VLPFC; HC: activation L VLPFC only
[g] in fact, a mixture of distancing and reinterpretation was used
[h] L dACG, R rACG, VMPFC, cerebellum, L temporal cortex, R parietal cortex

success scores and amygdala activity was found in MDD subjects,[62] MDD subjects rated non-noxious heat as slightly more unpleasant[67] and positive pictures as less positive[64;65] than HC, and there were behavioural reward deficits in MDD.[70] The role of medication use is incompletely clear, but since lateral cortical recruitment and limbic hyperactivity during automatic cognitive control was found in medicated as well as unmedicated subjects, these findings are most likely related to MDD.

3.3.2. Voluntary cognitive control [Tables 3B]

Voluntary cognitive control (Table 3B) during emotion regulation normally involves the DLPFC, VLPFC, DMPFC, rACG and dACG to reciprocally influence the limbic system.[1;8;15;18;19]

This has been studied in MDD subjects using: (1) Tasks involving learning from overt positive and/or negative feedback, which can elicit either positive or negative emotions that have to be regulated in order to perform adequately during the remainder of the task. Gambling tasks,[72] cognitive tasks[40;73;74] or an instrumental reward learning paradigm[75] were used; and (2) Tasks involving reappraisal of emotional stimuli, requiring subjects to cognitively reframe the meaning of an emotional stimulus in order to diminish any evoked emotion.[76-79]

Regarding lateral regulatory structures, studies about learning from feedback reported a prefrontal hypofunction in MDD subjects: after (negative) feedback, MDD subjects showed reduced activity relative to HC in the bilateral or right DLPFC[40;74] and reduced activity in bilateral VLPFC relative to HC.[73] This hypoactivity of lateral prefrontal brain regions while learning from feedback may indicate a failure to recruit neural resources normally involved in voluntary cognitive control.

Feedback studies also compared medial prefrontal functioning in MDD subjects versus HC during voluntary cognitive control, with inconclusive results. DMPFC activity was found to be decreased in MDD subjects versus HC.[73] Reduced left rACG activity,[74] but also equal rACG/dACG activity was found after negative feedback between MDD subjects and HC, although in one study pregenual ACG activity was increased (suggested to be involved in more explicit emotional processes).[40] Steele et al.[72] examined differences in error signals when receiving feedback during a gambling task, regardless of valence (positive or negative). MDD subjects had increased error signals in the right rACG and left anterior parahippocampal gyrus, positively correlating with depression severity.[72] Overall, these findings regarding medial prefrontal activity during learning from feedback in MDD subjects are conflicting, so that definite conclusions cannot yet be drawn.

While learning from feedback appeared to be characterized by hypofunction of the lateral PFC in MDD subjects, voluntary cognitive control by reappraisal of negative emotional stimuli yielded opposite results. Results from the study by Johnstone et al.[76] indicated a relative overrecruitment of VLPFC in MDD subjects relative to HC: whereas HC activated only the left VLPFC during cognitive reappraisal, MDD subjects activated both left and right VLPFC. Furthermore, in MDD subjects, a positive association existed between activity in the right VMPFC and the amygdala. In HC, on the other hand, VMPFC activity mediated *inhibition* of amygdala activity.[76] These results may indicate an attempt to compensate for

compromised VMPFC inhibition of the amygdala by recruitment of the right VLPFC in MDD subjects. However, this additional right VLPFC recruitment might be counterproductive, since effortful attempts to regulate negative emotions were associated with increased amygdala and insula activity in MDD patients, whereas in HC this activity decreased. Indeed, relatively greater right prefrontal activity has been associated with negative affect.[76]

Reappraisal as a voluntary cognitive emotion regulation strategy was also examined in the context of DMN function.[77] Failure to *reduce* activity in DMN components (i.e. the left dACG and right rACG, the VMPFC, amongst others) in MDD subjects was found during reappraisal of negative pictures. This might reflect an inability to deactivate the DMN, possibly interfering with recruitment of cognitive resources for voluntary control of emotional stimuli. This pattern of abnormal activity was accompanied by overactivity in the left parahippocampus,[77] supporting the hypothesis of increased engagement with emotional stimuli in MDD subjects.

Finally, voluntary cognitive control was also used in the context of processing positive emotions.[78;79] One study examined the capacity to *enhance* positive emotions.[78] In contrast to HC, MDD subjects could not maintain activity in the left nucleus accumbens (NAcc) during the course of the task, which may have been mediated by a failure to maintain connectivity between the PFC and left NAcc.[78] In line with this finding, during an instrumental reward learning task blunted error signals in the dorsal as well as ventral striatum were found, correlating with severity of anhedonia.[75] Light et al.[79] examined downregulation of positive emotions in MDD. Baseline activity of the right VLPFC and to a lesser extent the DMPFC predicted decrease in anhedonia scores after antidepressant treatment in MDD subjects: the higher baseline right VLPFC and DMPFC activity while suppressing positive emotions, the higher anhedonia scores remained after treatment. As the authors suggest, this indicates an overactive right-sided prefrontal system in the context of downregulation of positive emotions, which might result in overactive suppression of positive emotions and, consequently, disrupt the capacity to experience positive emotions in MDD subjects.[79]

In summary, during voluntary cognitive control, lateral and medial prefrontal functioning appears to be compromised in MDD subjects. During learning from feedback, focusing on voluntary control of negative emotions, lateral prefrontal cortices are hypoactive in MDD subjects, which is a fairly consistent finding even in low-powered studies (for example, Taylor Tavares et al.[73]). Lateral prefrontal hypoactivity might reflect a failure to recruit regulatory brain regions for voluntary cognitive control of emotions resulting from feedback, although limbic hyperactivity or performance deficits were not found (except Taylor Tavares et al.[73]). Results from the reappraisal studies indicate medial prefrontal hypofunction in MDD subjects, although different methodological approaches were used. When activations of these medial regions were compared, the role of the VMPFC inhibiting the amygdala appeared to be compromised, but when the VMPFC (and the rACG) was considered to be part of the DMN, less deactivation in MDD subjects relative to HC was found, indicating a failure to deactivate the DMN. This could reflect a failure to disengage from self-referential processing,[80;81] required for *voluntary* regulation of elicited negative emotions. Because of the aberrant rACG activity in MDD subjects, we suggest that this failure of voluntary

cognitive emotion regulation is mediated by rACG dysfunction. Indeed, rACG functioning has been associated with the ability to switch from a state of DMN activity to a state of task positive network (TPN) activity. This TPN is normally also recruited during cognitive and attentionally demanding tasks.[82]

With regard to the voluntary cognitive control of positive emotions, striatal functioning seems impaired in MDD subjects when trying to *enhance,* or learn from, positive emotions, which appears to be associated with severity of anhedonia. This incapacity to maintain striatal activity may be due to failing connectivity with prefrontal regions. However, there are also indications that an *overactive* (right-sided) prefrontal system might result in a disruption of the capacity to experience positive emotions in MDD subjects.[79]

To our knowledge, there are no studies which (in)directly compared patients with or without medication during voluntary cognitive control, so the effect of medication on these results is unclear. Nevertheless, the main findings of hypoactivity of lateral prefrontal regions in general and striatal dysfunction in the context of positive emotions, were obtained in studies in unmedicated MDD subjects.

4. DISCUSSION

With this systematic review, we aimed to elucidate functional abnormalities in the emotion regulation neural circuitry in adult MDD subjects and identify how these abnormalities in neural circuitry relate to the different emotion regulation subprocesses. We therefore classified identified studies according to a theoretical framework of regulatory subprocesses (automatic and voluntary behavioural, attentional and cognitive control[1]) and summarized which differences have been observed in the neural underpinnings of emotion regulation between MDD subjects and HC. Here we first integrate the results and comments to provide a general outline of abnormalities during automatic and voluntary emotion regulation in MDD (Figure 1). Next, we compare our results with those of emotion regulation in BD subjects, and finally we discuss several methodological issues and implications for further research.

4.1. Abnormalities in MDD during automatic and voluntary emotion regulation

Taken together, most differences in activity of regulatory brain regions between MDD subjects and HC are found using automatic regulation paradigms. Based on twenty-one studies,[22;23;38-46;62-71] we conclude that additional neuronal resources are recruited by (medicated) MDD subjects, i.e. the VTA[23] during automatic behavioural control of rewarding stimuli, the parietal[38;42] and lateral prefrontal[38;42;43] cortex during automatic attentional control of emotional information, and the DLPFC/VLPFC[62;63;65-67;70] during automatic cognitive control. These additional resources may be necessary to override strong bottom-up emotional influences, as reflected by reports of limbic hyperactivity,[83;84] which may especially occur during automatic cognitive control.[62-67;70] Evidence for this hypothesis is strongest for automatic cognitive control, as effects of medication seem to be minor, and effect sizes are substantial.

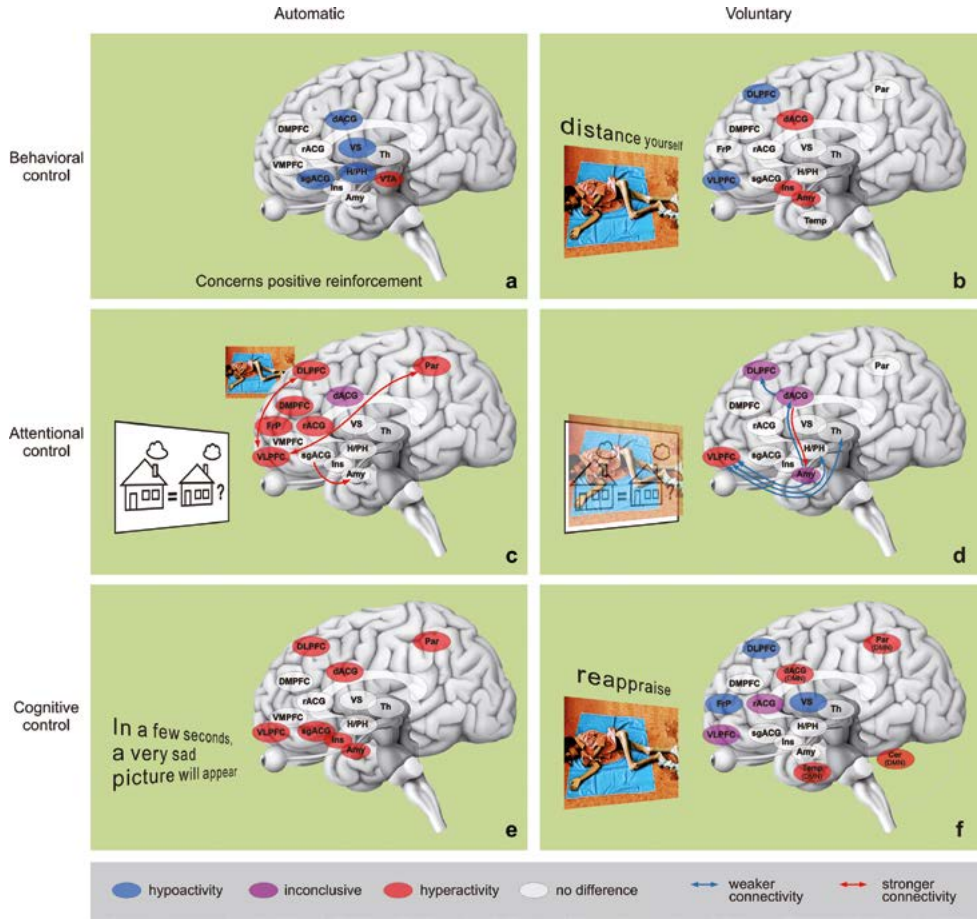


Figure 1 (picture b,d,f: from the International Affective Picture System). Differences in activity and connectivity of neural regions implicated in automatic and voluntary emotion regulation subprocesses in MDD subjects compared to HC. Most differences in activity of regulatory brain regions between MDD subjects and HC are found using automatic regulation paradigms. Additional neuronal resources appear to be recruited by (medicated) MDD subjects, i.e. the VTA[23] during automatic behavioral control of rewarding stimuli, the parietal[38;42] and lateral prefrontal[38;42;43] cortex during automatic attentional control of emotional information, and the DLPFC/VLPFC[62;63;65-67;70] during automatic cognitive control. These additional resources may be necessary to override strong bottom up emotional influences, as reflected by reports of limbic hyperactivity,[83;84] which might especially occur during automatic cognitive control.[62-67;70] Findings of differential neuronal activity in MDD subjects during voluntary regulation paradigms are less conclusive. Nevertheless, MDD subjects seem incapable of compensatory prefrontal recruitment during voluntary behavioral control and voluntary cognitive control, since here, activity is mostly equal[25;26] or decreased in MDD subjects relative to HC.[26;40;73;74] This might also be true for voluntary attentional control. Finally, there are indications of differential rACG, dACG and/or sgACG functioning in MDD subjects during most regulatory processes,[23;25;41;43;45;49;50;63;66-70;72;74] with indications for a relative overrecruitment of the rACG/dACG especially during automatic control .[38;41;45;63;67;69;70]

Abbreviations: Amy, amygdala; dACG dorsal anterior cingulate gyrus; rACG, rostral anterior cingulate gyrus; sgACG, subgenual anterior cingulate gyrus; Cer, cerebellum; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; FrP, frontal pole; H/PH, hippocampus/parahippocampus; Ins, insula; Par, parietal cortex; Temp, temporal cortex; Th, thalamus; VLPFC, ventrolateral prefrontal cortex;

Findings of differential neuronal activity in MDD subjects during voluntary regulation paradigms are not unequivocally conclusive, despite twenty-three studies.[25;26;38-40;49-58;72-79] Nevertheless, we tentatively conclude that MDD subjects are insufficiently capable of compensatory prefrontal recruitment during voluntary behavioural control and voluntary cognitive control, since activity of prefrontal regions is at most equal[25;26] but more often decreased in MDD subjects relative to HC.[26;40;73;74] This might also be true for voluntary attentional control, although here results are less consistent.

Finally, there are indications for differential rACG, dACG and/or sgACG functioning in MDD subjects during most regulatory processes,[23;25;41;43;45;49;50;63;66-70;72;74] with indications for a relative overrecruitment of the rACG/dACG especially during automatic control.[38;41;45;63;67;69;70]

To reconcile these findings, we speculate that during early, automatic stages of emotion regulation, MDD subjects may be capable of successful emotion regulation, but only by recruiting additional lateral prefrontal neuronal resources. This strategy might be mediated by medial prefrontal, especially rACG/dACG functioning. This hypothesis is in line with other neural models of emotion regulation, demonstrating that the rACG/dACG has a key modulatory function[82;85-87] - even with respect to MDD-specific emotional symptoms like self-blame[88] - and that higher rACG activity is associated with better treatment response.[82;89-93]

However, during explicit voluntary control, when the emotional experience is already ongoing, this strategy of additional recruitment of lateral prefrontal structures seems to fail, as reflected by abnormally reduced activity in lateral prefrontal cortices. This hypothesis corresponds with evidence from neurocognitive research, as summarized by Gotlib and Joorman.[2] These authors point out that MDD subjects have difficulty stopping or inhibiting the processing of negative material especially when this material has *already captured attention*, which addresses the above-described failure in voluntary regulation of already ongoing emotional processes.

Nevertheless, there appears to be a lack of consistency of positive findings and a relatively great amount of null findings from the identified studies. In addition, nearly all studies used (exploratory) whole-brain analyses at a relatively low significance threshold (except Beauregard et al.,[25] Etkin and Schatzberg[43] and Matthews et al.[53]), either when defining a priori ROI's or post hoc, to explore any differences between MDD subjects and HC. Therefore, most studies reported activation differences in separate brain regions, but these findings are neither consistent across studies, nor within the subprocess being studied. As stated before, due to this variety of heterogeneous paradigms we concluded that, unfortunately, these results cannot be aggregated by a formal meta-analysis, precluding definite conclusions.

4.2. Comparison with BD

In their review on emotion regulation in BD subjects, Phillips et al.[1] reported that during automatic emotion regulation, activity was *abnormally reduced in the left OFC and DMPFC*, whereas findings regarding voluntary emotion regulation were inconsistent.[1] It should be noted, however, that most of the included BD studies were done in euthymic or manic BD subjects, hampering a comparison with the current findings on emotion regulation in depressed MDD patients. Moreover, only few emotion regulation studies have been

conducted in depressed BD subjects since 2008: most studies concern passive emotion processing without regulation and/or were again conducted in manic or euthymic patients (for reviews, see Townsend and Altshuler,[94] Delvecchio et al.[95] and Almeida and Phillips[96]). Furthermore, emotion regulation studies in depressed BD subjects used only attentional control paradigms and these provided conflicting results (automatic[97;98] and voluntary[99-102]). Also, so far only two studies directly comparing emotion regulation in depressed MDD vs. BD patients were published, again investigating attentional control (automatic[46] and voluntary[73]).

Given this lack of emotion regulation studies in depressed BD subjects, it is not yet possible to extensively compare the results of our review in depressed MDD subjects with the results in BD subjects. Nevertheless, indications have been provided that MDD and BD subjects differ with regard to emotional *processing*. For example, a recent meta-analysis quantified passive emotion processing paradigms and demonstrated similar limbic reactivity to negative and positive stimuli in both groups, but differential subcortical and cortical reactivity.[95] MDD subjects revealed overall less emotional reactivity and/or reduced reactivity to positive stimuli, whereas in BD subjects reactivity to positive and negative stimuli was increased. Therefore, studies investigating differences in emotion *regulation* strategies between MDD and BD patients are warranted.

4.3. Methodological issues

Several methodological issues, that have also been mentioned before,[93;103] may be put forward to account for inconsistencies between studies.

4.3.1. Sample sizes

Modest sample sizes within studies (mean 17.6 (range 7-50) MDD subjects) limited the power and interpretability of null results (i.e., no difference between MDD subjects and HC with regard to a given brain region). However, less stringent statistic thresholds were applied for exploratory analyses in most studies, but this strategy, while increasing the risk of Type I error, did not yield consistent additional results. Furthermore, the use of modest sample sizes (<20 subjects) reduces reliability of the results, i.e. the chance of reproducing these results is small,[104] which might partly explain inconsistencies across studies regarding the same subprocess.

4.3.2. Clinical factors: medication use, comorbidity, depression severity and clinical heterogeneity

Studies included heterogeneous patient groups regarding medication use, comorbidity and depression severity. Antidepressant medication has been shown to affect regional brain activity in depressed[23;49] as well in (partially) remitted MDD subjects[105] and HC.[106] For example, during both automatic and voluntary emotion regulation paradigms as well as (passive) emotion processing, attenuation of regional limbic activity, especially the amygdala, is frequently found in medicated versus unmedicated subjects.[27-35;105;107] Therefore, it cannot be ruled out that the lateral prefrontal hyperactivity in MDD subjects reported during automatic regulatory processes is in fact a medication effect: in a number of studies demonstrating this finding, more than 50% of the subjects used antidepressants.[23;26;38;39;42;44;46;49;50;57;62;63;72;74] Moreover, it is not yet clear whether these effects are direct (i.e. by enhancing lateral prefrontal activity) or indirect (by reducing limbic activity and thereby (re-)enabling

cognitive control.[36;37;105] Therefore, the exact effects of medication on our results are difficult to establish, since few studies specifically investigated these effects during various emotion regulation processes, and a variety of medication types was used with different neural effects.[35;37;108;109] However, in *un*medicated MDD subjects lateral prefrontal hyperactivity was also found, especially during automatic cognitive control,[65-67] indicating that this finding is related to the pathophysiology of MDD rather than medication use.

Likewise, comorbidity could be an important confounder: in several studies, more than 50% of the MDD subjects had some form of Axis I comorbidity,[51;58;65] while various Axis I disorders are characterized by differential neuronal activity patterns (for example, bipolar disorder,[1;110] obsessive compulsive disorder,[111] anxiety disorders[112]). Another potential confounder is depression severity: whereas this correlates with neural activity in limbic as well as prefrontal regions[45;50;53;55;62;72] (but see Elliott et al.,[57] Mitterschiffthaler et al. [41] and Townsend et al.[54]), across studies the average depression severity varied from minimal to severe. Finally, apart from anxiety disorders, the level of state anxiety levels could be an additional factor responsible for the variation in neuronal activity,[113;114] and this was most often not taken into account (except Fales et al.[40] and Townsend et al.[54]).

Finally, as reflected by its operationalization, major depression itself is a heterogeneous clinical entity: according to the DSM-IV criteria, the presence of five of nine symptoms for at least two weeks are sufficient to fulfil the criteria of having a major depressive episode, provided that depressed mood and/or anhedonia are present. Therefore, major depression may present in a number of guises, each with different symptom combinations. As such, clinical heterogeneity within MDD samples is inherent to MDD research, unless specific clinical subsamples are investigated. Although there is currently a growing interest in symptom profiling, this was not usually done in the studies included in this review. Therefore, clinical heterogeneity within MDD samples may (partly) account for the heterogeneous results of included studies and limits our conclusions regarding a general underlying pathophysiology of MDD.

4.3.3. Task design

Task designs differed across studies with respect to several aspects, like stimulus type (pain, words, pictures of faces and pictures of scenes, outcome of gambling tasks), the valence of the used stimuli (positive, negative) or elicited emotions (happiness, sadness, fear) (Tables 1-3). These and factors like uncertainty about the valence of the upcoming stimulus, emotional conflict experienced, and self-referential quality of the stimuli, may all have influenced neuronal activity patterns and likely resulted in heterogeneous outcomes.[8;115-117] In fact, positively valenced stimuli[23;42;44;45;63;69;75;78;79;118] and self-relevant stimuli[2;119-121] might be most appropriate to detect differences between MDD subjects and HC. Therefore, the lack of significant differences in task performance between MDD subjects and HC in some studies might reflect a suboptimal task design to detect differential neuronal activity. The greater heterogeneity of results from voluntary control studies relative to those from automatic control studies might also be due to less experimental controllability of regulation strategies applied by the subjects during voluntary emotion regulation.

4.3.4. Data analysis

Data analysis strategies varied considerably with respect to signal type (activation, deactivation, temporal difference errors, spatial variance), signal contrasts (with/without a baseline or combining different emotional valences), statistical approach (ROI versus voxel-wise approach),[93] and multiple comparisons correction methods.

For example, having *a priori* ROIs increases sensitivity to detect differences between MDD subjects and HC, in particular in low-powered studies, but this strategy may lead to propagation of Type I as well as Type II error, when whole-brain multiple comparisons correction is used outside these ROIs. Finding an acceptable balance between Type I and Type II error is often difficult as experimental power depends not only on sample sizes but also on task paradigm used, including preprocessing methods, smoothing, filtering, choice of contrasts, signal to noise ratio etc.[104] For example, strong focal signals are more likely to be detected by voxel-wise statistical inference than by cluster-wise inference, so cluster-wise inference is not always more sensitive.[122] Therefore, data analytic approaches are a major source of heterogeneity between studies.

4.3.5. Limitations of the emotion regulation model

Automatic and voluntary regulation are not always strictly dichotomous and may not truly "carve nature at her joints". However, as initially stated by Phillips et al.,[1] this distinction of automatic versus voluntary is necessary to better understand the mechanisms of emotion regulation and their corresponding neural systems. Likewise, there is an overlap between behavioural, attentional and cognitive regulation processes (see e.g. the review by Ochsner and Gross[123]). For example, the process of distancing, a behavioural control strategy characterized by inhibition of ongoing emotive-expressive behavior by perceiving emotional stimuli as detached observers, and the process of reappraisal, a cognitive control strategy defined as reframing the meaning of an emotional stimulus in order to diminish any evoked emotion,[1] seem closely related. One can even use reappraisal to achieve distancing, e.g. by reframing an emotional picture as being unreal. These processes are indeed associated with involvement of both unique and shared neural regions, like the cingulate, parietal and temporal cortices and caudate nucleus.[124] In the same vein, reappraisal may be considered a form of distraction, i.e., an attentional regulation strategy.[15;124] Again, there are different as well as similar brain regions involved in these two strategies, like the DMPFC, DLPFC, precuneus and inferior parietal cortex.[10;15] The fact that the different subprocesses of the emotion regulation model show procedural as well as neural overlap limits the specificity of fMRI findings of each subprocess.

4.4. Limitations and future directions

Limitations of this review concern the modest number of studies per subprocess and the variability in paradigms within each subprocess, which precludes meta-analysis of the observed findings yet. A recent meta-analysis of Hamilton et al.[125] pooled studies with a broad range of negatively and positively valenced affective challenges and stimuli. The authors justified pooling because they reasoned that positive and negative valence are fundamental components of emotions, despite heterogeneity of task paradigms involved. Pooling was performed when at least three studies could contribute to the meta-analytical contrast, but this was in fact done over much more studies. Furthermore, the multilevel

kernel density analysis approach enabled comparisons between contrasts obtained across studies, thereby obtaining results that are typically impossible in a single study. For the current review, this technique would have yielded four pooled estimates (for automatic and voluntary attentional control, as well as automatic and voluntary cognitive control). We did not use this technique, however, for two reasons: (1) Differences between the various subprocesses and tasks are likely to be subtle instead of fundamentally different (as in emotional valence), which would make pooling more sensitive to noise; (2) Due to the low number of studies per subprocess, results would be highly vulnerable for effects of outliers. Therefore, such meta-analyses will be feasible only if a sufficient number of emotion-regulation studies are available in MDD.

Furthermore, categorization according to the different subprocesses was not always unambiguous. Unfortunately, the majority of studies reviewed in this paper still described activity patterns in distinct regions, instead of investigating networks by, for example, effective connectivity analyses. Thus, the way brain regions relate to and influence each other in MDD subjects is still insufficiently clear from these reports, precluding firm conclusions regarding the specific (causal) role of isolated abnormally activated brain region in the emotion regulation networks.

Another limitation is the exclusion of studies conducted in elderly subjects, preventing extrapolation of results to late-life depression. Although still a matter of debate, there are indications that late-onset depression is a separate entity.[126;127] Also, healthy elderly subjects are more likely to exhibit cognitive deficits,[128;129] which could interfere with (voluntary) emotion regulation strategies, and furthermore demonstrate positively biased emotion regulation strategies.[130]

More research is needed to test our hypothesis of the ability to recruit compensatory brain regions during automatic emotion regulation, but failure to do so during voluntary emotion regulation in MDD subjects. Future research should preferably be performed in unmedicated MDD subjects, use optimal fMRI paradigms, focus on specific regulatory subprocesses, and -if possible- sequentially in the same patients. Potentially confounding covariates like depression severity, rumination and anxiety levels should be taken into account. In addition, future studies should expand their focus to networks rather than distinct brain regions.

The emotion regulation model presented here has important implications for the understanding of the pathophysiology of MDD and might have therapeutic implications. Although this hypothesis needs further testing, it is conceivable that voluntary emotion regulation is facilitated when (or perhaps only if) one is capable of automatic emotion regulation. For example, one study demonstrated that MDD subjects do indeed vary in their capacity to voluntary regulate their emotions after receiving negative feedback.[131] MDD subjects who were used to habitually apply cognitive emotional control strategies, without explicit instructions to do so, performed similarly on the voluntary emotion regulation task as HC, indicating intact voluntary emotion regulation. In contrast, MDD subjects who did not habitually apply cognitive emotional control strategies performed worse on the voluntary emotion regulation task, indicating impaired voluntary emotion regulation. Therefore, it is possible that voluntary emotional control was facilitated by the capacity to habitually

apply cognitive control. It is unclear, however, whether this capacity to habitually apply cognitive emotional control reflects intact automatic emotional control, because no specific automatic emotion regulation paradigm was used in this study.

If indeed successful voluntary regulation of emotions is (partly) dependent on intact automatic regulation, therapeutic strategies that focus on more voluntary regulation of emotions, like cognitive behavioural therapy (CBT), should work more effectively if automatic emotion regulation functions adequately. Some support for this hypothesis comes from the cognitive neuropsychological model regarding the therapeutic action of medication:[132] normalization of neural activity during early, automatic emotional processing enables MDD subjects to adequately control negative and positive emotions in daily life, ultimately resulting in symptom remission. When optimal neuropsychological and/or neuroimaging tests to quantify the functioning of automatic and voluntary emotion regulation in MDD subjects are developed further, the hypothesis that e.g. CBT is more effective in subjects with intact automatic emotion regulation, can be investigated by stratification of MDD subjects for impairment of automatic emotion regulation capacities.

If our hypothesis is confirmed, it also implies that a first step in treating MDD will be to restore automatic emotion regulation when impaired. Possibly, biological therapeutic strategies are specifically useful to boost automatic regulation processes.[133] However, few studies specifically investigated medication effects during various emotion regulation processes, often conducted in HC only. For example, an effect was found in four studies during automatic regulation: an increase of lateral and medial prefrontal activity in HC (DLPFC, VLPFC, MPFC, with citalopram; DLPFC, MPFC with reboxetine[37] and DLPFC in MDD subjects treated with escitalopram, paroxetine or sertraline.[36] However, a *de*crease of medial prefrontal activity after escitalopram treatment was also observed in HC (MPFC, pgACG).[134] With regard to limbic regions like the amygdala, Fales et al.[36] as well as Rosenblau et al.[66] found normalization of amygdala activity in MDD subjects after SSRI treatment. Furthermore, Stoy et al.[71] found that escitalopram normalized blunted ventral striatum activity in MDD subjects. Although preliminary, these results may indicate that antidepressant medication enhances activity of prefrontal regulation areas (lateral as well as medial) during automatic emotion regulation processes, at least in HC. In MDD subjects, this mechanism may lead to recovery of control over limbic activity during automatic regulation processes, especially when treatment is successful.[135] Alternatively, greater prefrontal activity may be secondary to a primary attenuation of limbic responses by medication. Results regarding voluntary emotion regulation (in particular voluntary attentional control) also indicate an increase of prefrontal activity with antidepressant treatment: In MDD subjects, buproprion treatment induced an increase in lateral prefrontal activity (frontal pole and DLPFC).[60] Also, greater functional connectivity between the prefrontal lateral regions OFC/VLPFC and DLPFC was found in MDD subjects responsive to treatment with mirtazapine.[108] Furthermore, successful venlafaxine treatment led to an increase in connectivity between the OFC/VLPFC and the cerebellum, which is increasingly acknowledged to be involved in MDD. However, medial prefrontal activity in HC (sgACG) was *decreased* by (es)citalopram treatment in one study.[29] With regard to limbic regions, attenuation of amygdala[29;35] and insula[29] activity during (negative) emotion regulation with (es)citalopram treatment in HC and with bupropion in MDD subjects[60] and an increase of

amygdala activity during regulation of positive emotions[136] was reported. This pattern of medication effects on voluntary emotion regulation is broadly comparable to the effects on automatic regulation. It can be hypothesized that these effects on voluntary regulation are indirect, i.e. mediated by restored automatic regulation. However, this hypothesis needs further investigation by using automatic and voluntary paradigms sequentially in the same subjects, while stratifying for any impairments of automatic emotion regulation capacities.

It could furthermore be hypothesized that the ability of MDD subjects to regulate emotions automatically depends on several factors, e.g. symptom profile, depression severity, or capability to recruit additional regulatory resources (with or without medication or other therapeutic strategies). These relationships also need further investigation, preferably in relation to consecutive therapeutic interventions. Eventually, this model might be of use to predict which therapeutic strategy is indicated in an individual patient during the course of illness.

5. CONCLUSION

Findings from the currently available emotion regulation literature indicate that MDD subjects demonstrate abnormally reduced activity in lateral prefrontal cortices especially during explicit voluntary control, when the emotional experience is already ongoing. During early, automatic stages, on the other hand, (medicated) MDD subjects may be capable of successful emotion regulation by recruiting additional lateral prefrontal neuronal resources. This strategy might be mediated by medial prefrontal regions, especially the rACG/dACG. During voluntary control strategies MDD subjects demonstrate abnormally reduced activity in lateral prefrontal cortices. In combination with the preliminary impression that dysfunctional automatic regulation might preclude successful voluntary emotion regulation,[131] this model might be of use to develop diagnostic approaches for improved selection of therapeutic options in MDD patients. If a dysfunction of *automatic* emotion regulation could be determined beforehand, this could be indicative for a biological therapeutic strategy. If automatic emotion regulation is apparently intact, treatment of *voluntary* emotion regulation strategies (i.e. psychotherapy like CBT) could be indicated. This hypothesis needs to be confirmed by further studies.

ACKNOWLEDGMENTS

We thank Joost Daams for expert librarian assistance during the search and Inge Kos for the artwork. This work is supported by a grant from the Netherlands Organization for Health Research and Development (ZonMw), program Mental Health, education of investigators in mental health (OOG; #100-002-034) to Drs. M.M. Rive. Dr. H.G. Ruhé is supported by a NWO/ZonMW VENI-Grant #016.126.05

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SUPPLEMENTARY MATERIAL

1.0 MATERIALS AND METHODS

1.1. Search terms used

PubMed:
(Depressive Disorders OR Involutional Psychoses OR Involutional Psychosis OR Involutional Melancholia OR Involutional Depression OR affective disorder OR Melancholia OR unipolar depression) AND (dti[tiab] OR diffusion tensor imaging OR Diffusion Tractography OR diffusion fractography OR brain mapping OR Echo-Planar OR echoplanar OR tomography OR functional connectivity OR effective connectivity OR mr imaging OR nmr imaging OR Magnetization Transfer Contrast Imaging OR mri OR fmri OR neuroimaging OR neuro imaging[tiab])

Embase and PsychInfo:

1. exp nuclear magnetic resonance imaging/
2. diffusion tensor imaging.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. Diffusion Tractography.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
4. brain mapping.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

2.0 RESULTS

For reasons of completeness, we here describe additional results that have been reported as findings in separate studies.

2.1 Automatic attentional control

Other regions of interest for the emotion regulation model are the insula and the thalamus. The insula was activated less in MDD subjects than in HC in the context of positive emotional distraction.[42]The thalamus was activated more in MDD subjects relative to HC[41], and connectivity with the VLPFC was decreased.[39]

For other regions, not belonging to the original model, see Table S3A.

2.2 Voluntary attentional control

In addition to regions described in the main text, other areas of interest for voluntary attentional control were differentially activated in MDD subjects versus HC. These included the insula, showing either hypoactivity (left or right sided)[52;54] or hyperactivity (right sided)[50] in MDD subjects; the thalamus, demonstrating hyperactivity[50;54] and decreased connectivity with the VLPFC; [39] and right hippocampus, showing hypoactivity.[54] The parietal cortex, also involved in voluntary attentional control, did not show differential activity in MDD

subjects versus HC, except when MDD subjects with or without a family history of MDD were specifically compared to HC with or without a family history of MDD, in which case there was a hypoactivity of the left or right parietal cortex, respectively.[52]

For other regions, not belonging to the original model, see Table S3B.

2.3 Automatic cognitive control

In addition to regions described in the main text, MDD subjects showed left and/or right sided hyperactivity of the insula[63;63;64;64;67;67;70] and the parahippocampal gyrus[63;63;70] during emotional expectation. Another finding during automatic cognitive change was decreased activity of the right hippocampus and bilateral thalamus[68] in MDD subjects versus HC.

For other regions, not belonging to the original model, see Table S4A.

2.4 Voluntary cognitive control

In addition to regions described in the main text, other regions of interest were investigated in MDD subjects versus HC with regard to voluntary cognitive change. Johnstone et al.[76] found no difference in parietal activity between MDD subjects and HC during reappraisal. Nevertheless, when considered as part of the DMN, MDD subjects demonstrated a failure to deactivate right parietal cortex.[77] In feedback studies differential activity in parietal regions was also observed: affective switching after negative feedback was associated with enhanced activity in the right inferior parietal cortex, the left superior parietal cortex, and with decreased activity in the left inferior parietal cortex.[74] Affective switching was also associated with decreased activity in the right thalamus and insula;[74;78] furthermore, decreased activity of the right thalamus was found during the reward learning paradigm.[75] Down-regulation of negative emotions by reappraisal, in contrast, equally activated the insula and thalamus in MDD subjects and HC.[76]

For other regions, not belonging to the original model, see Table S4B.

Table S1. Legend for rating of methodological aspects

	Medication status	Level of comorbity	Statistics
Good (+)	no psychotropic medication or a washout for at least 2 months before scanning (except benzodiazepines) AND no electroconvulsive therapy in the last two months	no primary comorbid Axis I diagnoses	regions of interest/whole brain analysis + correction both main effects and interactions (if appropriate)
Moderate (+/-)	use of psychotropic medication in <50% of participants during scanning OR no medication during scanning, but washout < 2 months before scanning (except benzodiazepines)	comorbid Axis I diagnoses in <50% of population	not good, not poor
Poor (-)	not mentioned OR use of psychotropic medication during scanning for ≥50% of participants	comorbid Axis I diagnoses in ≥ 50% of population OR No information about Axis I disorders	uncorrected analysis

Table S2. Behavioural control; additional findings (results concern negative emotions unless otherwise stated)

Study	No. of MDD subjects Age (mean) HDRS score (mean)	Methodological aspects (Table S1)			Task	Key condition or contrast and statistical threshold	Task performance	Relevant brain regions	Recruitment in MDD vs HC
		Medication	Comorbidity	Statistics					
A. Automatic									
none									
B. Voluntary									
Erk et al.[26]	17(8F) Age: 43.5 21HDRS :18.5 BDI:25.4	-	+	+	Distancing from emotional pictures during task 1; measurement of long-term effect during passive viewing in task 2	Distancing from negative pictures > passive viewing (task 1) Previously regulated negative > neutral (task 2) Whole brain: $p<0.05$ FWE C ROI: $p<0.05$ FWE C	=	Inf parietal/temporal cortex Fusiform gyrus Lingual gyrus	= = =

Abbreviations: C, corrected; F, female; FWE, family wise error; inf, inferior; ROI, region of interest; 21HDRS, 21 item HDRS; BDI, Beck Depression Inventory; +, good (medication: none/washout ≥ 2 months: no ECT ≥ 2 months; comorbidity: no primary comorbid Axis I diagnosis; statistics: main effects and interactions corrected for multiple comparisons); -, poor (medication: medication use in ≥ 50% of sample/not mentioned; comorbidity: comorbid Axis I diagnosis in ≥ 50% of sample/not mentioned; statistics: uncorrected analysis).

Study	No. of MDD subjects Age (mean) HDRS score (mean)	Methodological aspects (Table S1)			Task	Key condition or contrast and statistical threshold	Task performance	Relevant brain regions	Recruitment in MDD vs HC
		Medication	Comorbitiy	Statistics					
A. Automatic									
Frodl et al.[38]	12 (7F) Age:43.3 21HDRS:17.5	-	+	+/-	Matching faces on emotion or gender	Implicit processing (match gender) ROI: $p<0.05$ SVC Whole brain: $p<0.001$ UC, $k\geq10$	=	Temporal cortex Sup temporal gyrus Visual cortex L primary motor cortex R lingual gyrus Ventral striatum Pallidostriatum Putamen	relatively ↑ (n.s.) [a] Stronger deactivation relatively ↑ (n.s.) [a] relatively ↑ (n.s.) [a] relatively ↑ (n.s.) [a] = = =
Frodl et al.[39]	25 (9F) Age:39.4 HDRS:20.6	+	+	+	Matching faces on emotion or gender	Implicit processing (match gender) Whole brain: $p<0.05$ FWE C	=	*Connectivity VLPFC and* L Premotor system R middle temporal cortex R precuneus L cerebellum Visual cortex R caudate	 ↑ ↓ ↓ ↓ ↓ ↓
Fales et al.[40]	27 (17F) Age: 33.4 17HDRS: 20	+/-	+	+	Match or ignore fearful faces or neutral houses	Ignore fear> ignore neutral ROI: $p<0.025$, $k\geq9$; post hoc $p<0.006$ Whole brain: $p<0.001$, $k\geq14$	=	L BA 8	=
Mitterschiffthaler et al.[41]	17 (14F) Age: 39.3 17HDRS:20.8 BDI: 38	+/-	+	+	eStroop	Neg> neutral ROI: $p<0.001$+SVC Whole brain: $p<0.05$ FWE C	↓	R precuneus L middle temporal gyrus R cerebellum	↑ ↑(n.s.) ↑(n.s.)

George et al.[22]	11 (2F) Age: 36.6 21HDRS: 15	+/-	+/- **BD :5**	-	eStroop	Sad > control Whole brain: p<0.001	↓ (n.s.)	cerebellum R visual cortex	↑(n.s.)[b] ↑(n.s.)[b]
Canli et al.[42]	15 (12F) Age: 35.1 BDI:23.9	-	+	-	Lexicon decision task	Sad/fear/ happy > neutral words Whole brain: p<0.001 UC, k≥10	=	L sup temporal gyrus L med temporal gyrus R cerebellum	↓ ↓ ↓
Eugene et al.[45]	12 (6F) Age: 33.8 BDI-2:29	+/-	-	+	Negative affective priming task	Inhibition > no inhibition ROI: p<0.06, k≥13; MC Whole brain: p<0.001, k≥13; MC	=	L putamen	↑(n.s.)
Bertocci et al.[46]	23 (23F) Age: 29.7 25HDRS:26.3	-	+	+	Emotional n-back task	Happy/ fearful/ >no distractors ROI: p<0.05, k by MC	=	L putamen	↑ (pos) [c,d]
B. Voluntary									
Wang et al.[49]	19 (12F) Age:39.3 17HDRS:19.9	-	+/-	+/-	Emotional oddball task	Target after sad > target after neutral ROI: p<0.05 Whole brain: p<0.001 UC, k≥5	↓ (n.s.)	L somatosensory cortex	Stronger deactivation
Dichter et al.[50]	14 (7F) Age: 34.8 BDI: 6.9	+/-	+	+	Emotional oddball task	Targets in sad blocks Cluster-based: p<0.05	=	R precuneus R PCG R caudate L motor cortex Fusiform gyrus	↑ ↑ ↑ ↑ ↑

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Lisiecka et al. [52]	50 (33F) Age:43 BDI II:32,5	-	+	+	Cognitive task preceded by emotional task	Neg+pos attention shifting >baseline Whole brain: p<0.05 FWE C	↓		*(pos and neg pooled)*
								SMA/middle cingulum	↓
								R precuneus	↓
								R precuneus/PCC	↓[e]
								Visual cortex	↓[f]
								L visual cortex	↓ (neg)[f]
								cerebellum	↑ (neg)[f]
Townsned et al.[54]	15(6F) Age:45.6 21HDRS:20.1	+/-	+	+/-	Emotional face matching task	Fear+sad> control condition ROI: p<0.05 UC Whole brain: Clusters (Z>2.3): p<0.05 FDR C	=	R inf temporal gyrus	↓
								R middle temporal gyrus	↓
								R putamen	↓
								R cerebellum	↓
								Visual cortex	
Frodl et al.[38]	12 (7F) Age:43.3 21HDRS:17.5	-	+	+/-	Matching faces on emotion or gender	Explicit processing (match emotion) ROI: p<0.05 SVC Whole brain: p<0.001 UC, k≥10	=	cerebellum	↓
Frodl et al.[39]	25 (9F) Age:39.4 HDRS:20.6	+	+	+	Matching faces on emotion or gender	Explicit processing (match emotion) Whole brain: p<0.05 FWE C	=	*Connectivity VLPFC and*	
								L motor system	↑
								R middle and sup temporal cortex	↓
								L inf temporal cortex	↓
								R precuneus	↓
								Visual cortex	↓
								Cerebellum	↓

Abbreviations: BA, Brodmann area; Bi, bilateral; C, corrected; F, female; FC, functional connectivity; FDR, false discovery rate; FWE, family wise error; inf, inferior; k, number of contiguous voxels; L, left; neg, negative; MC, determined by Monte Carlo simulations; n.s., non-significant; PCG, posterior cingulate gyrus; PFC, prefrontal cortex; R, right; sup, superior; ROI, region of interest; SVC, small volume corrected; UC, uncorrected; VLPFC, ventrolateral PFC; 17HDRS, 17-item Hamilton Depression Rating Scale; 21HDRS, 21 item HDRS; BDI, Beck Depression Inventory; +, good (medication: none/washout ≥ 2 months: no ECT ≥ 2 months; comorbidity: no primary comorbid Axis I diagnosis; statistics: main effects and interactions corrected for multiple comparisons); +/-, moderate (medication: medication use in > 50% of sample/washout < 2 months; comorbidity: comorbid Axis I diagnosis in < 50% of sample; statistics: not good: not poor); -, poor (medication: medication use in ≥ 50% of sample/not mentioned; comorbidity: comorbid Axis I diagnosis in ≥ 50% of sample/not mentioned; statistics: uncorrected analysis).

[a] i.e. equal activation during the implicit and explicit condition in MDD; in HC there is a decrease in activation during the implicit condition

[b] imaging method: PET

[c] activation in MDD subjects; deactivation in HC

[d] MDD subjects using antidepressants or benzodiazepines showed decreased activity in response to the neutral or happy condition, respectively, then MDD subjects not using this medication

[e] HC without family history of MDD >MDD without family history of MDD

[f] HC with family history of MDD >MDD with family history of MDD

Table S4. Cognitive control: additional findings (results concern negative emotions unless otherwise stated

Study	No. of MDD subjects Age (mean) HDRS score (mean)	Methodological aspects (Table S1)			Task	Key condition or contrast and statistical threshold	Task performance	Relevant brain regions	Recruitment in MDD vs HC
		Medication	Comorbidity	Statistics					
A. Automatic									
Abler et al.[62]	12 (12F) Age: 41.2 HDRS:18.5	-	+	+	Cued emotional pictures	Expectation of neg pictures ROI: p<0.05 SVC Whole brain: p<0.001, C by k	=	Motor cortex	↑
Bermpohl et al.[63]	15 (10F) Age: 43.3 HDRS:24.7	-	+/- **BD: 2**	-	Cued emotional pictures	Expectation of pos+neg pictures ROI: p<0.001 UC Whole brain: p<0.001 UC	=	*(pos and neg pooled)* L precuneus L PCG Motor cortex Cerebellum Visual cortex L sup temporal gyrus -BA 22 -BA 38 Inf+middle temporal gyrus	 ↓ ↓ ↑ ↓ ↑ ↑ ↓ ↑
Rosenblau et al.[66]	12 (5F) Age: 43.5 17HDRS: 21.2	+	+	+	Cued emotional pictures	Expectation of neg pictures ROI: p<0.005, k≥10 (amygdala: p<0.05, k≥5) Whole brain: p<0.05 FDR C	NA	R precuneus Middle temporal cortex Paracentral lobule L caudate R putamen	↑ ↑ ↑ ↑ ↑
Grimm et al.[65]	19 (11F) Age: 40.0 21HDRS: 33.1	+/-	-	-	Judgment and perception of emotional pictures in an unexpected and expected mode	Expectation of pos+neg pictures Whole brain: p<0.001 UC, k≥5	Less pos ratings of pos pictures	Motor cortex	*(pos and neg pooled)* ↑
Strigo et al.[67]	15 (12F) Age:25.5 BDI-2:27.8	-	+	+	Cued noxious hot or non-noxious warm stimuli	Expectation of painful hot > warm stimuli	Less pos ratings of pos pictures	precuneus PCG Ventral brainstem	↓ ↓ ↓

						Whole brain: $p<0.05$, vol≥ 512 ❡; MC ROI: $p<0.05$, vol≥ 128 ❡; MC		Visual cortex L Motor cortex R sup+med temporal gyrus R caudate	↑ ↑ ↑ ↓
Smoski et al.[68]	14 (7F) Age:30.8 HDRS: 23.5	+/-	+	+	Wheel of fortune task	Anticipation of outcome Whole brain: $Z=2.6$ C,[137] $k\geq5$	=	Precuneus PCG Ventral brainstem Motor cortex Visual cortex R temporal cortex (inferior posterior+middle gyrus, pole) R caudate L somatosensory cortex	*(unexpected valence)* ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓
Knutson et al.[69]	14 (9F) Age:30.7 BDI:25.4	+	+	+	Monetary incentive delay task	Expectation of gain/loss ROI: $p<0.167$ Bonferroni (3 comparisons) Whole brain: $p<0.05$ C, $k\geq4$	=	Motor cortex Somatosenory cortex L lateral BA 8	↑(positive) ↑(positive) ↑(positive)
Pizzagalli et al.[70]	30 Age:43.2 17HDRS: 18	+/-	+/-	+	Monetary incentive delay task	Expectation of gain/loss Whole brain: $p<0.005$, $k\geq12$; MC Findings outside basal ganglia preliminary	↓ RT modulation (n.s. for loss) ↓ pos affect	R occipitofrontal fasciculus L occipitofrontal fasciculus L posterior putamen R middle occipital gyrus Middle frontal gyrus (BA 8) R superior temporal gyrus R lingual gyrus R cerebellum R cerebellum R medial frontal gyrus (BA 8) L postcentral gyrus R PCG L middle temporal gyrus L lingual gyrus	↓ (pos) ↑(pos) ↓ (pos) ↓ (pos) ↑(pos) ↑(pos) ↑(pos) ↑(pos) ↓(neg) ↑(neg) ↑(neg) ↑(neg) ↑(neg) ↑(neg)

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Table S4. Continued

B. Voluntary									
Steele et al.[72]	15 (11F) Age:45.9 HDRS:27.3	-	+	+	Receiving feedback during a gambling task	Temporal difference error signal ROI: 10 mm SVC Whole brain: p<0.05 FWE C	=	*Connectivity between* rACG ↔ L ant cerebellum ant cerebellum ↔ L thalamus	↑ ↓
Remijnse et al.[74]	20(8F) Age:35 17HDRS:19.1 MADRS:29.7	+/-	+/-	+/-	Reversal learning task	Affective switching Whole brain: p<0.05 FDR C (main effects) p<0.001 UC (interactions) ROI: p<0.005 UC (interactions)	=	L frontal pole Sup temporal gyrus Frontal pole (BA 10)/ant PFC	↓ ↑ ↓
Johnstone et al.[76]	21 (13F) Age: 33 HDRS: 21	+/-	+	+	Reappraisal of negative pictures	Reappraise negative> attend negative Whole brain: p<0.01, k by MC	=	Temporal cortex L BA 8	= ↓
Heller et al. [78]	27 (15F) Age: 31.5 HDRS: 21.2	+/-	+	+	Reappraisal of positive pictures	Enhance positive> suppress positive Enhance positive> attend positive Whole brain: p<0.05, k≥50; MC connectivity maps: ROI: p<0.05 SVC, k≥15	NA	R thalamus Lingual gyrus Inferior lingual gyrus L postcentral gyrus	↓sustained activity (pos) ↓sustained activity (pos)
Sheline et al.[77]	24 (12F) Age: 34 HDRS: 21	+/-	+	+	Reappraisal of negative pictures	Reappraise negative> attend negative ROI: p<0.001, k≥14; post hoc p<0.01 Whole brain: p<0.05 C, k≥14	=	Lateral BA 8 Supplementary motor cortex L PCG R precuneus cerebellum	= = = = Less deactivation

Abbreviations: ant, anterior; rACG, rostral anterior cingulate cortex; BA, Brodmann area; Bi, bilateral; C, corrected; F, female; FC, functional connectivity; FDR, false discovery rate; FWE, family wise error; inf, inferior; k, number of contiguous voxels; L, left; med, medial; MC, determined by Monte Carlo simulations; NA, not applicable; neg, negative; n.s., non-significant; PCG, posterior cingulate gyrus; pos, positive; R, right; ROI, region of interest; RT, reaction time; sup, superior; SVC, small volume corrected; UC, uncorrected; Vol, volume; 17HDRS, 17-item Hamilton Depression Rating Scale; 21HDRS, 21 item HDRS; BDI, Beck Depression Inventory; µl, microliter; +, good (medication: none/washout ≥ 2 months: no ECT ≥ 2 months; comorbidity: no primary comorbid Axis I diagnosis; statistics: main effects and interactions corrected for multiple comparisons); +/-, moderate (medication: medication use in > 50% of sample/washout < 2 months; comorbidity: comorbid Axis I diagnosis in < 50% of sample; statistics: not good: not poor), -, poor (medication: medication use in ≥ 50% of sample/not mentioned; comorbidity: comorbid Axis I diagnosis in ≥ 50% of sample/not mentioned; statistics: uncorrected analysis).

PART III

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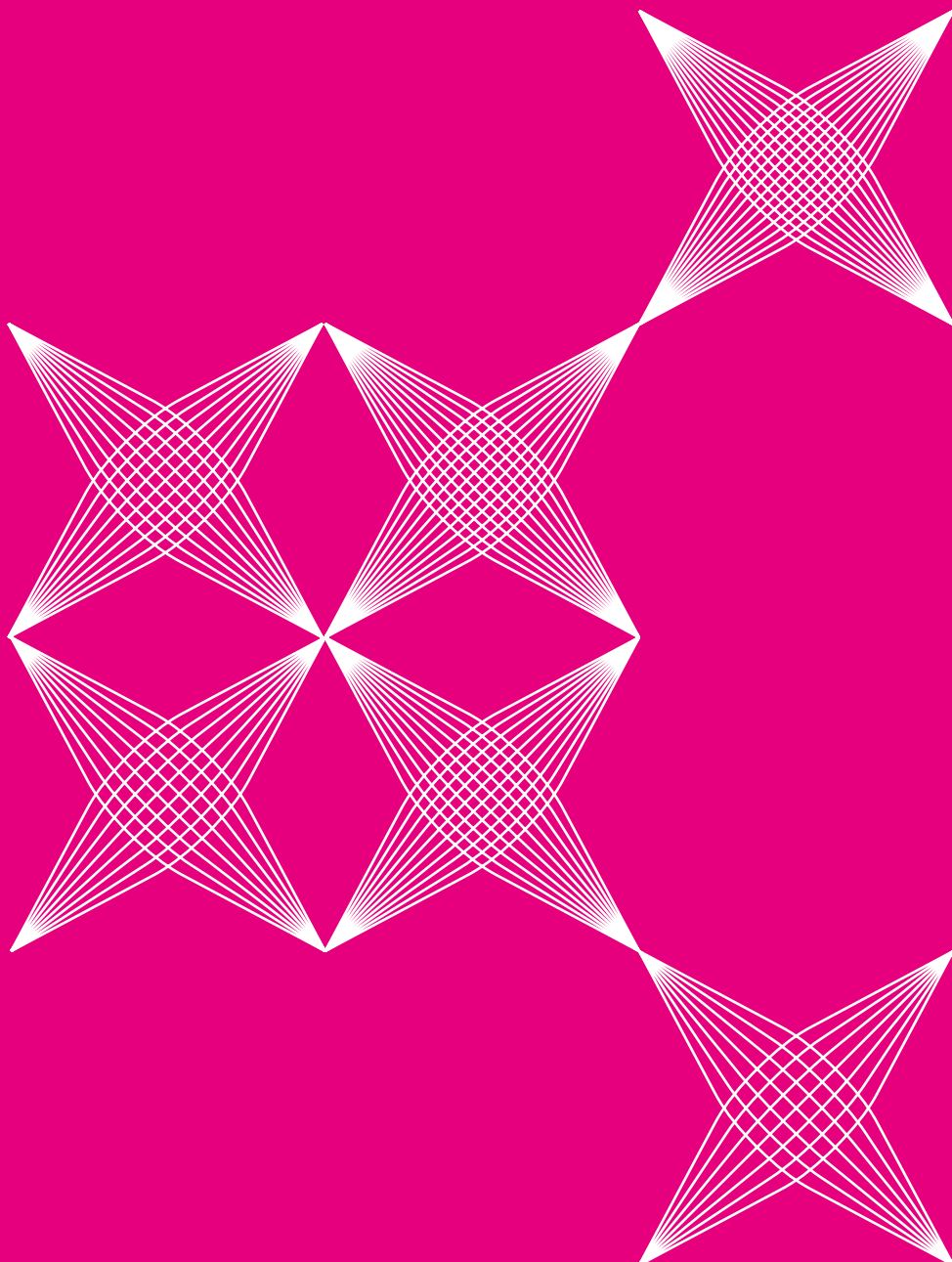
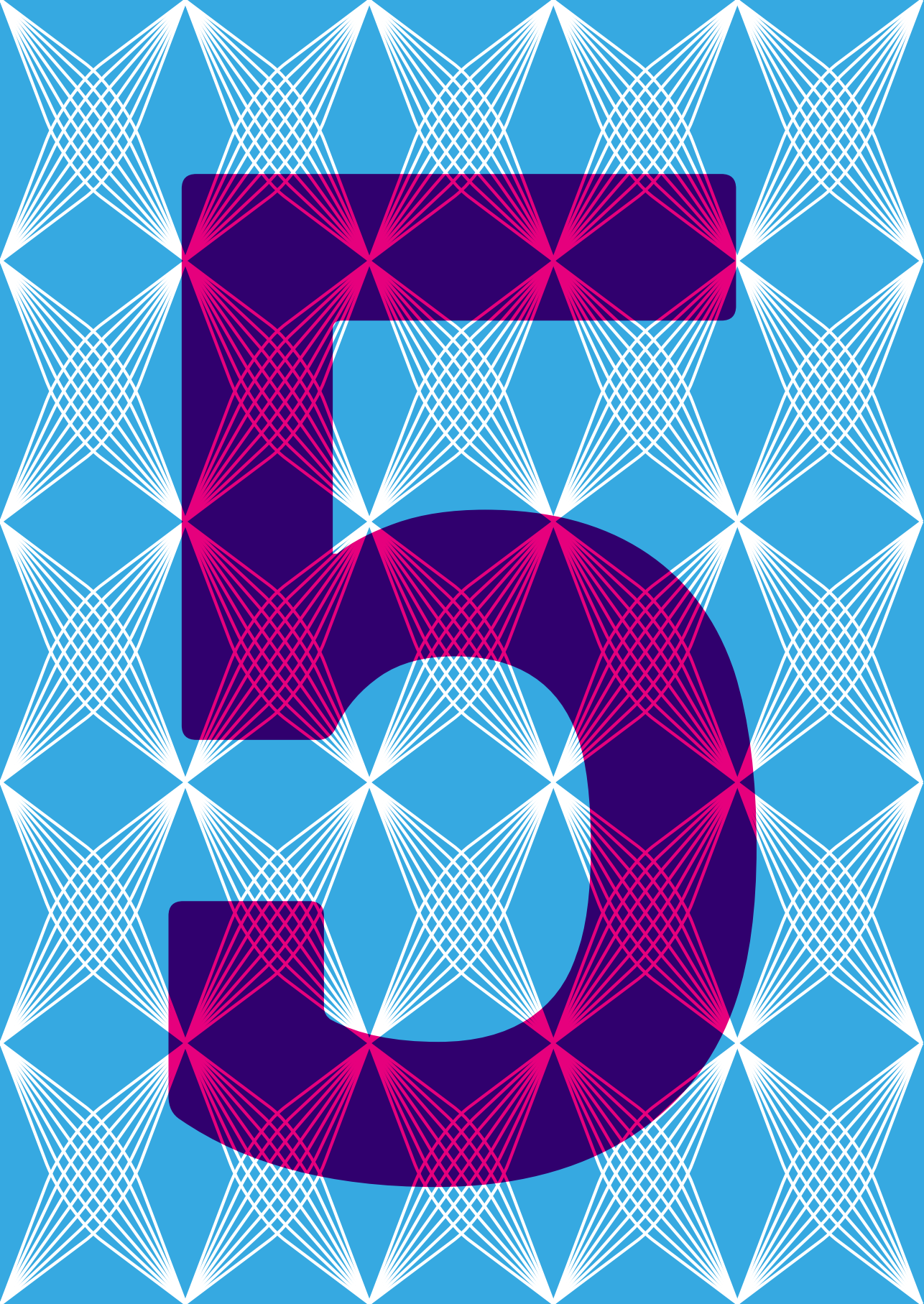
TREATMENT AND OUTCOMES IN SCHIZOPHRENIA





LONGITUDINAL EVIDENCE FOR A RELATION BETWEEN DEPRESSIVE SYMPTOMS AND QUALITY OF LIFE IN SCHIZOPHRENIA USING STRUCTURAL EQUATION MODELING

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Under review

ABSTRACT

Patients diagnosed with schizophrenia often report a low quality of life (QoL). The aim of this study was to investigate whether clinical variables prospectively act on QoL later in life, following a cross-sectional model by Alessandrini and colleagues (n=271).[1] This model showed strong associations between psychotic symptoms and depressive symptoms on QoL, but lacked follow-up assessment. This model was adapted in the current study and the robustness was investigated by using a longitudinal design in which the association between baseline variables (including neurocognition, depression, psychotic symptoms as well as social functioning) and QoL during 3-years of follow-up was investigated. We included patients with a non-affective psychotic disorder (n=744) from a prospective naturalistic cohort-study. In the cross-sectional model, with good measure of fit, both depression as well as social functioning was associated with QoL (direct path coefficient -0.28 and 0.41, respectively). Additionally, the severity of psychotic symptoms was highly associated with social functioning (direct path coefficient -0.70). Importantly, the longitudinal model showed good measures of fit, which strengthens the validity of the initial model and highlights that depression prospectively affect QoL while psychotic symptoms prospectively influence QoL via social functioning. The negative, longitudinal impact of a depression on QoL highlights the need to focus on treatment of this co-morbidity.

1. INTRODUCTION

The World Health Organization (WHO) defines quality of life (QoL) as "*individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*".[2] Despite debate regarding the precise definition of QoL,[3,4] guidelines label it as presumably one of the most important outcome measures in the long-term treatment of patients diagnosed with schizophrenia.[5]

Schizophrenia patients report a substantially lower QoL compared to healthy controls or their non-affected siblings.[6–8] By identifying factors that influence QoL in schizophrenia, specific treatment interventions could be used to improve low QoL. Several studies investigated the association between clinical variables and QoL in patients with schizophrenia[9–14] including a meta-analysis.[14] For example, the severity of psychotic symptoms is known to be negatively associated with QoL[13–15] as well as the level of social functioning.[16] Moreover, several studies consistently showed that QoL in schizophrenia patients is negatively associated with depressive symptoms,[11,12,14] which was also confirmed in a longitudinal study.[9] This is important given the high prevalence of comorbid depressive symptoms in patients with schizophrenia (a median rate of 25%)[17,18] and several options exist to treat comorbid depressive symptoms or depressive episodes in patients diagnosed with schizophrenia (e.g., optimizing antipsychotic dosages, switching to specific antipsychotics, motivating for physical exercise, addition of anti-depressant medication or cognitive behavioural therapy).[19]

It is not surprising that, in general, patients with depressive symptoms or episodes report worse QoL. Although overemphasizing current problems and underestimating the chances of recovery is often part of the depressive illness, feelings of sadness have a direct effect on wellbeing and satisfaction, cognitions about oneself, others and the future, which reinforce each other. Given the complexity of the construct QoL, it is presumable that other clinical variables may influence QoL as well. For example, depressive symptoms may influence social functioning and through this pathway influence QoL or they may have a direct effect on QoL. It is surprising that most recent studies did not use statistical techniques that address the association between different variables and QoL.[9,11,12] Structural equation modeling (SEM) offers the possibility to perform a regression analyses in which different variables are included. Moreover, by using SEM, it is possible to perform longitudinal analyses and to include latent constructs. Lastly, SEM makes it feasible to assign an order by which the included variables affect each other and to what extent.[20] For example, Alessandrini and colleagues[1] used SEM and showed that psychotic symptoms (including positive, negative and general psychopathology symptoms) and neurocognition were directly associated with social functioning, however, no direct association existed between psychotic symptoms and QoL nor between neurocognition and QoL.

In this SEM-study by Alessandrini and colleagues[1] the associations between psychotic symptoms, depression, neurocognition and functioning as determinants of QoL, were investigated in a cross-sectional study including 271 patients with schizophrenia. Their model underlined that depression was the most important determinant that was negatively associated with QoL, while functioning was directly positively associated with QoL. Based on these results, Alessandrini and colleagues suggested to focus on depressive

symptomatology in the treatment of patients with schizophrenia as well as to improve skills involved in functioning (by interventions such as cognitive behavioural therapy), since both depressive symptoms and functioning were important determinants of QoL. However, the findings of Alessandrini and colleagues[1] are probably not generalizable to all schizophrenia patients because they included a relatively small group of patients with a long illness duration. Besides, they studied these patients only cross-sectionally and thereby were not able to address long-term outcomes. Confirmation with a longitudinal assessment is desirable because this strengthens the validity of the original model of Alessandrini and colleagues.[1] Additionally, replication of the initial model in a longitudinal assessment will prove the stability between the different variables over time and thereby enables to formulate hypotheses concerning causal relations when investigating effects of interventions.

Taken together, previous studies show that there are several variables influencing QoL in schizophrenia patients but it remains unclear how these variables relate to each other and QoL. The identification of determinants of QoL is of clinical relevance, since they may guide treatment interventions. Therefore, the aim of the current study is to assess (i) whether the proposed cross-sectional model concerning determinants of QoL by Alessandrini and colleagues is supported by findings from a more diverse and larger group of patients and (ii) whether this model also determines QoL in a longitudinal perspective, in which the association between baseline variables and QoL at three-years of follow-up will be investigated.

2. METHODS

2.1 Subjects

The data for this study was derived from the multicenter study 'Genetic Risk and Outcome in Psychosis' (GROUP) as described earlier.[21] The GROUP study was a longitudinal cohort study that recruited patients (n=1119) diagnosed with a non-affective psychotic disorder based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.[22] As the vast majority (90%) of patients was diagnosed with a schizophrenia-spectrum disorder, we will refer to 'schizophrenia' throughout the manuscript.[21] The GROUP study consisted of three measurements (i.e., baseline (T0), three- (T1) and six-year (T2) follow-up). In the present study, we used data from T1 and T2, since the *Calgary Depression Rating Scale for Schizophrenia* (CDSS) was applied at these time points. For the cross-sectional analyses, we included patients with QoL data at T1 (n=744). For the longitudinal analyses, we included patients for whom QoL data on both T1 and T2 were available (n=544).

2.2 Measures

2.2.1 Quality of life

For assessing QoL, we used the *World Health Organization QoL Scale Brief Version* (WHOQOL-BREF).[23] This self-reporting questionnaire includes 26 items, compromising four domains: i.e., physical health (7 items), psychological health (6 items), social relationships (3 items) and environmental health (8 items). All items are rated on a 5-point Likert-scale, resulting in a mean domain score, in which higher scores reflect better QoL in the concerning domain. Of note, domain sum scores were used in the analyses. The QoL has shown robust validity in an adult psychiatric population in the Netherlands.[24]

2.2.2 Functioning

Social functioning was assessed with the *Global Assessment of Functioning* (GAF) scale.[22] We used the GAF as it is a widely used instrument and it gives a broad reflection of the degree of functioning in a social context, but also recreational. Throughout the manuscript we will refer to the GAF as 'social functioning'. The GAF ranges from 0 to 100 and higher scores reflect better social functioning.

2.2.3 Clinical symptoms

To assess the severity of the depressive symptoms, the CDSS[25] was administered by trained investigators. The CDSS is a structured interview, designed to assess the severity of depressive symptoms in patients with schizophrenia.[26] The CDSS consists of nine items, rated on a scale ranging from 0 (*absent*) to 3 (*severe*). Higher scores reflect more severe depressive symptoms and a score of 6 or higher is often used as cut-off point for a clinically relevant depressive episode.[27] In the present sample, the variance in depression scores was limited and consequently we dichotomized this variable based on a score of ≤5 or >5.

To measure the severity of positive, negative and general psychopathology symptoms the *Positive and Negative Syndrome Scale* (PANSS)[28] was administered. The PANSS consists of 30 items, in which each item is scored on a scale ranging from 1 (absent) to 7 (extreme), measuring three domains: positive symptoms (e.g., delusions, disorganization and hallucinations), negative symptoms (e.g., social and emotional withdrawal) and general psychopathology (e.g., anxiety, poor attention and somatic concern), with higher scores reflecting more severe symptoms. Of note, PANSS total domain scores were used in the analyses.

In line with an earlier study performed in the same sample, we used a composite measure of IQ to assess neurocognition.[8] This composite score consisted of Arithmetic (working memory), Digit Symbol-Coding (processing speed), Block Design (reasoning and problem solving) and Information subtests (verbal comprehension) of the *Wechsler Adult Intelligence Scale* (WAIS) III.[29,30] Additionally, in line with earlier research identifying the important influence of 'age' and 'gender' on outcomes measures,[31,32] we also included both variables in our model.

2.4 Statistical Analysis

For all the analyses release 5.0 of the GROUP database was used. Differences in demographic characteristics and illness severity between patients with both T1 and T2 data available and patients with T1 data only were investigated using $\chi 2$-tests or t-tests. For all the SEM analyses, we used M-plus.[33] SEM is a robust statistical technique that enables to perform a multiple regression analysis. However, compared to other regression analysis techniques, important improvements of SEM are the fact that latent constructs are included (by which the influence of variance is reduced), a direction can be given in which order and to what extent variables are influencing each other.[20]

First, following the earlier proposed model by Alessandrini and colleagues,[1] we investigated the influence of different clinical variables on QoL at T1. Second, we tested whether the proposed model also fitted the longitudinal data: by assessing whether QoL during follow-up (T2) was predicted by clinical variables (i.e., social functioning, clinical symptoms and

neurocognition) three years earlier (T1). Based on previous findings,[31,32] we also investigated in both models whether age and gender influenced QoL.

The fit indices χ2, Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI) and Standardized Root Mean Square Residual (SRMR) were used to evaluate the fit of the models. The chi-square index is a badness-of-fit-index and should be non-significant (p >.05). RMSEA values smaller than 0.08 indicate that the fit of the model is sufficient and values smaller than .05 indicate a good fit. SRMR values smaller than 0.10 indicate a good fit of the model. Lastly, CFI values higher than 0.90 indicate a good fit.[20] QoL and PANSS domain scores were modelled as two latent variables based on the proven validity of both questionnaires (i.e., the PANSS total, referred to as 'psychotic symptoms', based on the positive, negative and general psychopathology subscales and the QoL-questionnaire based on the four different domains). In our SEM model, associations between variables are expressed as standardized regression coefficients.[34] Moreover, *p* - values smaller than 0.01 were regarded as statistically significant.

Our model was theoretically constructed based on the results of Alessandrini and colleagues[1] (Figure 1). In addition, we added some correlations to enhance the fit of the model, all based on modification indices provided by M-plus. The following correlations were added in our *cross-sectional* model: PANSS positive scale with the PANSS negative scale, PANSS total score with depression (i.e., the dichotomized depression score) and PANSS total score with neurocognition. With regard to our *longitudinal* model, we also added one novel correlation (i.e., between the QoL domains 'psychological health' and 'social relationships') while the correlation between PANSS total score with depression appeared to be redundant and was not used in the longitudinal model.

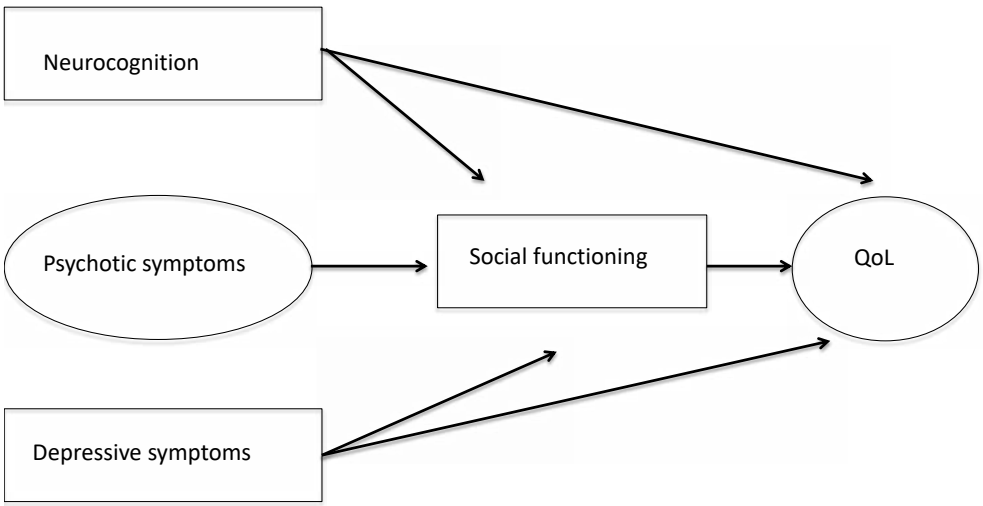

Figure 1. Hypothetical model. Hypothetical model theoretically based on Alessandrini et al.[1]–illustrating the proposed effects of schizophrenia (i.e., positive, negative and general psychopathology as measured with the PANSS) symptoms, neurocognition, depressive symptoms and functioning on QoL. Ovals represent latent variables and rectangles represent observed variables. QoL = Quality of Life.

3. RESULTS

3.1 Sample characteristics

Table 1 summarizes the sample characteristics and clinical variables at T1 and T2. The patients who completed follow-up assessment T2 showed a significantly higher level of social functioning, a lower severity of psychotic symptoms and a more favourable QoL (however only with respect to environmental domain) at T1 compared to the patients who did not complete follow-up (Table 2). Patients with or without complete follow-up data did not differ significantly with respect to the severity of depressive symptoms, the use of antipsychotic medication at T1 and neurocognitive functioning (Table 2).

3.2 Correlations

Pearson's correlations between QoL, neurocognition, social functioning and psychotic symptoms were calculated cross-sectionally (Supplementary Table S1) and longitudinally (i.e., QoL at T2 and clinical variables at T1; Table S2). In both cross-sectional and longitudinal analyses, the direction of the correlations was as expected, i.e., psychotic symptoms were negatively associated with neurocognition, social functioning and QoL. In both analyses neurocognition was not significantly associated with the psychological and social QoL domains, nor with positive symptoms in the longitudinal analyses.

Table 1. Baseline demographic characteristics of the total sample at T1 (n=744)

	n*	Mean (SD)
Age, years	744	30.64 (7.23)
Gender, n (% male)	744	76.5
Age at psychotics onset, years	744	23.13 (6.60)
Use of antipsychotic medication, n (% yes)	627	542 (73)
T1		
QoL		
QoL physical	743	3.63 (0.67)
QoL psychological QoL	744	3.51 (0.65)
social	742	3.34 (0.85)
QoL environmental	743	3.72 (0.61)
GAF	632	60.49 (15.71)
PANSS, positive	728	10.93 (4.47)
PANSS, negative	713	11.72 (5.09)
PANSS, general	718	23.90 (6.99
CDSS	713	2.04 (2.88)
CDSS, % depressed (≥ 6)	713	13.3
Neurocognition	568	98.64 (16.54)
T2		
QoL		
QoL physical	544	3.65 (0.71)
QoL psychological QoL	544	3.50 (0.66)
social	544	3.35 (0.87)
QoL environmental	544	3.76 (0.63)

* Of note, as the used questionnaires differed between participating centers we provide the number of patients of whom questionnaires were available. QoL= Quality of life; GAF = Global Assessment of Functioning; PANSS= Positive and Negative Symptom Scale; CDSS= Calgary Depression Rating Scale for Schizophrenia.

Table 2. Differences in demographic and clinical characteristics at T1 of patients who completed T1 and T2 versus those who only completed T1

	T1+T2 (n=544)		T1 Only (n=200)		p**
	n*	Mean (SD)	n*	Mean (SD)	
Age, years	544	30.74 (7.36)	200	30.35 (6.88)	.51
Gender, n (% male)	544	410 (75)	200	159 (80)	.24
Age of onset first psychosis, years	544	23.18 (6.74)	200	22.99 (6.22)	.73
Use of antipsychotic medication, n (% yes)	460	396 (86)	167	146 (87)	.67
QoL					
QoL physical	543	3.64 (0.68)	200	3.60 (0.66)	.42
QoL psychological QoL	544	3.52 (0.66)	200	3.48 (0.61)	.46
social	542	3.37 (0.84)	200	3.31 (0.89)	.44
QoL environmental	544	3.77 (0.61)	199	3.59 (0.61)	**.001**
GAF	451	62.36 (14.80)	181	55.85 (16.94)	**<.001**
PANSS, positive	536	10.62 (4.20)	192	11.78 (5.04)	**.005**
PANSS, negative	525	11.33 (4.61)	188	12.82 (6.12)	**.003**
PANSS, general	530	23.55 (6.84)	188	24.89 (7.30)	.02
CDSS	524	2.00 (2.82)	189	2.14 (3.03)	.13
CDSS, % depressed (≥ 6)	524	12	189	17	.09
Neurocognition	422	99.68 (16.25)	146	95.61 (17.1)	0.01

* Of note, as the used questionnaires differed between participating centers we provide the number of patients of whom questionnaires were available. ** p-values < 0.01 in bold. QoL= Quality of life; GAF = Global Assessment of Functioning; PANSS= Positive and Negative Symptom Scale; CDSS= Calgary Depression Rating Scale for Schizophrenia.

3.3 SEM – model, cross-sectional

The structural equation model, based on the measures at T1 showed acceptable fit measures (Figure 2): RMSEA = 0.07, CFI=0.92 and SRMR=0.06. Depression and QoL were significantly negatively associated (direct path coefficient -0.28), as were social functioning and QoL (direct path coefficient 0.41). Psychotic symptoms and social functioning were strongly negatively associated (direct path coefficient -0.70), but there were no direct links between depression and social functioning. Non-significant associations were observed between age or gender and QoL. For neurocognition, there was no direct link with social functioning in the model. As we considered neurocognition an important measure, we decided to include neurocognition in our model, but we found a non-significant association between neurocognition and QoL.

3.4 SEM – model, longitudinal

To investigate the pathways contributing to QoL at follow-up, we constructed a second SEM-model in which we substituted QoL at T1 for QoL at T2 and remained all clinical variables as assessed at T1 (Figure 3). Again, this model showed acceptable fit measures (RMSEA = 0.08, CFI=0.90 and SRMR=0.08) and showed identical pathways as for the cross-sectional model. Although slightly less strong, depression and social functioning were both associated with QoL during follow-up (direct path coefficient -0.22 respectively 0.34). Likewise, psychotic symptoms and social functioning were strongly associated (direct path coefficient -0.69). Again, there were no direct links between depression and social functioning, nor between neurocognition and social functioning. Comparable with the cross-sectional model, we found a non-significant association between neurocognition and QoL.

Finally, non-significant associations were found between age and QoL. In contrast to the cross-sectional model, gender was significantly associated with QoL during follow-up (gender direct path coefficient: 0.15, p=0.001).

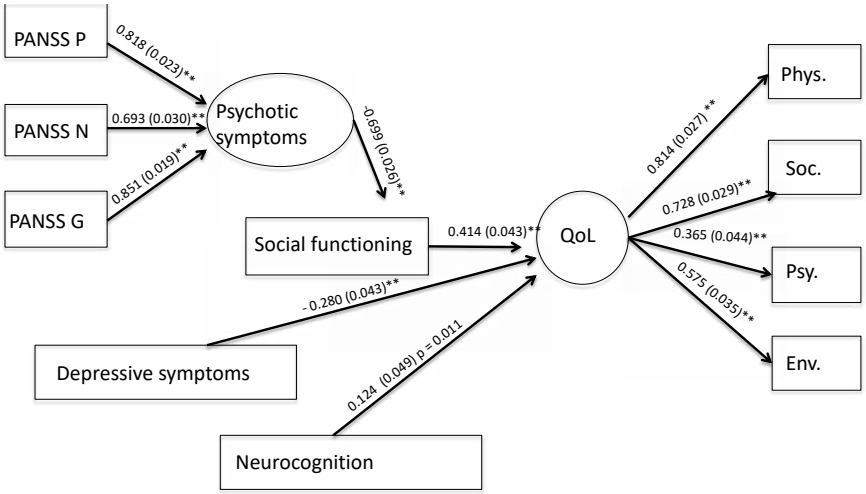

Figure 2. Cross-sectional model at T1 (n=744). Structural Equation Model (SEM) with depressive and psychotic symptoms, functioning and quality of life at T1 (n=744). Above the arrows the standardized parameter estimates, between the brackets the standard error. Ovals represent latent variables and rectangles depict observed variables. Schizophrenia symptoms and QoL were both modeled as latent variables. CDSS = Calgary Depression Scale for Schizophrenia; GAF = Global Assessment of Functioning; PANSS= Positive and Negative Symptom Scale; PANSS P = Positive factor; PANSS N=Negative factor; PANSS G= General psychopathology factor; QoL= Quality of life; Env = Environmental domain; Psy = Psychological domain; Soc=Social domain; Phys= Physiological domain. Of note, although not included in the figure the model also included the variables age and gender. ** indicates p < 0.001.

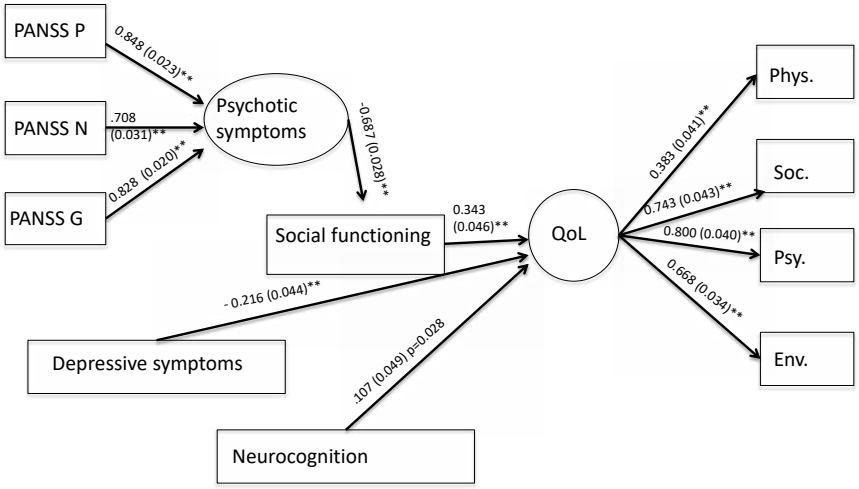

Figure 3. Longitudinal SEM-model (n=544). Structural Equation Model (SEM) with depressive and psychotic symptoms, neurocognition, functioning at T1 and quality of life at T2 (n=544). Above the arrows the standardized parameter estimates, between the brackets the standard error. Ovals represent latent variables and rectangles depict observed variables. Schizophrenia symptoms and QoL were both modeled as latent variables. CDSS = Calgary Depression Scale for Schizophrenia; GAF = Global Assessment of Functioning; PANSS= Positive and Negative Symptom Scale; PANSS P = Positive factor; PANSS N=Negative factor; PANSS G= General psychopathology factor; QoL= Quality of life; Env = Environmental domain; Psy = Psychological domain; Soc=Social domain; Phys= Physiological domain. Of note, although not included in the figure the model also included the variables age and gender. ** indicates p < 0.001.

4. DISCUSSION

In the current study, we extended an earlier cross-sectional SEM-model by Alessandrini and colleagues[1] in a prospective cohort study. The current study demonstrated that first, depression negatively affect QoL directly, second, social functioning is directly associated with QoL and third, psychotic symptoms prospectively influence QoL via an indirect pathway, which is via social functioning. By using SEM, which enables to investigate several variables concomitantly, this study reveals an adequate fit of both a cross-sectional and prospective model, applied to a large sample of schizophrenia patients (n=744).

An important feature of this study was that we could reproduce the relations in the model of Alessandrini and colleagues both in a longitudinal and cross-sectional design. Replication of initial results, in general, is difficult,[35] but feasible for the initial model determined by Alessandrini and colleagues.[1] Moreover, our longitudinal assessment strengthens the validity of the initial model and emphasizes the association between variables included in this model.

Depression contributes to a lower QoL cross-sectionally and also contributes to a lower QoL three years later. As mentioned by Alessandrini and colleagues,[1] the significance of depressive symptoms were earlier demonstrated by, among others, the study of Fervaha and colleagues.[36] The latter study compared the association between symptom domains and illness severity (which was rated by clinicians but also by patients). They showed that the strongest correlation between the patients-rated illness severity was with depressive symptoms, while the strongest correlation of the clinicians-rated illness severity was found for positive symptoms. In sum, clinicians might concentrate on psychotic symptoms, while patients experience the most nuisances from depressive symptoms.

The negative impact of a depressive episode on QoL highlights the need to enhance treatment availabilities against this co-morbidity. Interventions against depressive symptoms and depressive episodes in patients with schizophrenia were recently reviewed by our group.[19] Unfortunately, treatment studies investigating depressive symptoms as primary outcome are sparse, the duration of these studies was often short and the majority focused on depressive symptoms (instead of depressive episodes), which hampers generalization of results to distinct depressive episodes. Nevertheless, depression and depressive symptoms are treatable and the present study indicates the relevance of recommendations regarding the existing treatment options. Moreover, verified associations between depression and suicide, substance abuse and reduced treatment adherence[9,37–39] should urge clinicians to treat a depressive episode.

Depression did not influence the level of social functioning. These results are slightly different from those of Alessandrini and colleagues,[1] who report a weak association (direct path coefficient -0.11, p=.026). However, the use of different questionnaires to measure social functioning, the overall lower mean score of depression severity in our sample and the use of a dichotomized variable of depression score in our study might explain this difference. Alessandrini and colleagues[1] referred to the findings of Galderisi and colleagues[40] to explain the observed weak association between depression and social

functioning. Galderisi and colleagues[40] included 921 patients diagnosed with schizophrenia and used SEM to investigate the association between several variables (including illness related variables, context-related factors and personal resources) with real-life functioning (measured by a scale that included 'social, vocational, and everyday living outcomes').[40] They found no association between depression and real-life functioning, which was explained by the hypothesis that depression might negatively affect a 'person's self-evaluation of functioning', but does not lead to a worse real functioning.[40]

Psychotic symptoms were strongly negatively associated with social functioning (direct path coefficient of -0.71) and social functioning was directly influencing QoL (direct path coefficient of 0.41). These results are comparable with those of Alessandrini and colleagues[1] who showed a direct path coefficient of -0.7 between psychotic symptoms and functioning and of 0.26 between functioning and QoL. The first finding underscores the widely accepted notion that treating psychotic symptoms is needed to improve social functioning.[5] However, the latter finding underlines that improvement of social functioning is needed to eventually improve QoL. Indeed, social functioning covers a wide concept including the possibilities to have work, daytime activities and contact with others, which are all important factors in the long-term treatment of patients. Interestingly, several studies in the field focused on treatments enhancing social functioning, including interventions to improve social cognition, meta-cognition or social skills training.[41–43]

Finally, Alessandrini and colleagues[1] showed a weak association between neurocognition and functioning. However, in our model there was no association between neurocognition and social functioning. Although we included neurocognition in our model, we found non-significant associations between neurocognition and QoL. The fact that neurocognition has less influence on QoL, has been previously revealed by a meta-analyses showing non-significant or inverse associations between most neurocognitive measures and QoL.[44] Of note, the assessment of neurocognition in our study included only certain domains of neurocognitive functioning[45] which also might explain the difference between our study and that of Alessandrini and colleagues.[1] Furthermore, estimated IQ in the present patient sample was relatively high (mean: 98.64), even though the patient group scored approximately 1SD below the control group,[21] this relatively high IQ suggests that we included a relatively high functioning group of patients which may also explain the lack of associations between QoL and neurocognition. Further SEM-models should elaborate on these results by also including other cognitive domains (e.g., visual learning).[45]

Many studies have investigated the associations between clinical variables and different definitions of QoL. There is an ongoing debate regarding the precise definition of QoL and which domains are part of the construct, and this is reflected by the wide use of different instruments to measure QoL.[3]

Apart from our large dataset and our cross-sectional and longitudinal design, some limitations need to be taken into account. First, although we included multiple clinical variables, we are aware that there might be more determinants of QoL or social functioning (e.g., the use of medication, medication side effects including extrapyramidal side effects, insight, personality traits etc.), which especially might influence longitudinal measures of

QoL. The GROUP study used a naturalistic design. Consequently, patients were included with substantial variation in medication regimes (i.e., with respect to dosage, type and duration of treatment), other treatments (e.g., occupational therapy or cognitive behavioural therapy) and differences in treatment setting, which could not be adequately modelled. Second, patients who were lost to follow-up represent a subgroup with more severe psychopathology and, consequently, our longitudinal results are only applicable to a group of patients with relatively good social functioning. It therefore remains insufficiently clear whether the observed associations are generalizable to those with (initially) lower social functioning. Third, as mentioned earlier, we are aware that we did not include social cognition and only a few cognitive domains. Therefore, including other cognitive domains might have led to different findings.

5. CONCLUSION

In this unique longitudinal study investigating depressive symptoms in patients with schizophrenia, we were able to retest an earlier constructed SEM model in a cross-sectional but also in a longitudinal design, hereby enhancing the validity of this model. SEM analyses enabled us to include several (latent) variables and to allocate an order in which clinical variables are associated with each other and QoL, and to what extent. In this study, depressive symptoms were associated with patients-rated QoL, highlighting the need to target treatment of depressive symptoms. Moreover, social functioning had a direct influence on QoL, while psychotic symptoms were indirectly, via social functioning, associated with QoL.

ACKNOWLEDGEMENT

We are grateful for the generosity of time and effort by the patients, their families and healthy subjects. Furthermore we would like to thank all research personnel involved in the GROUP project, in particular: Joyce van Baaren, Erwin Veermans, Ger Driessen, Truda Driesen, Karin Pos, Erna van 't Hag, Jessica de Nijs, Atiqul Islam, Wendy Beuken and Debora Op 't Eijnde.

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SUPPLEMENTARY MATERIAL

1. SUPPLEMENTARY TABLES

Table S1. Cross-sectional correlations between variables at T1 (n=744)

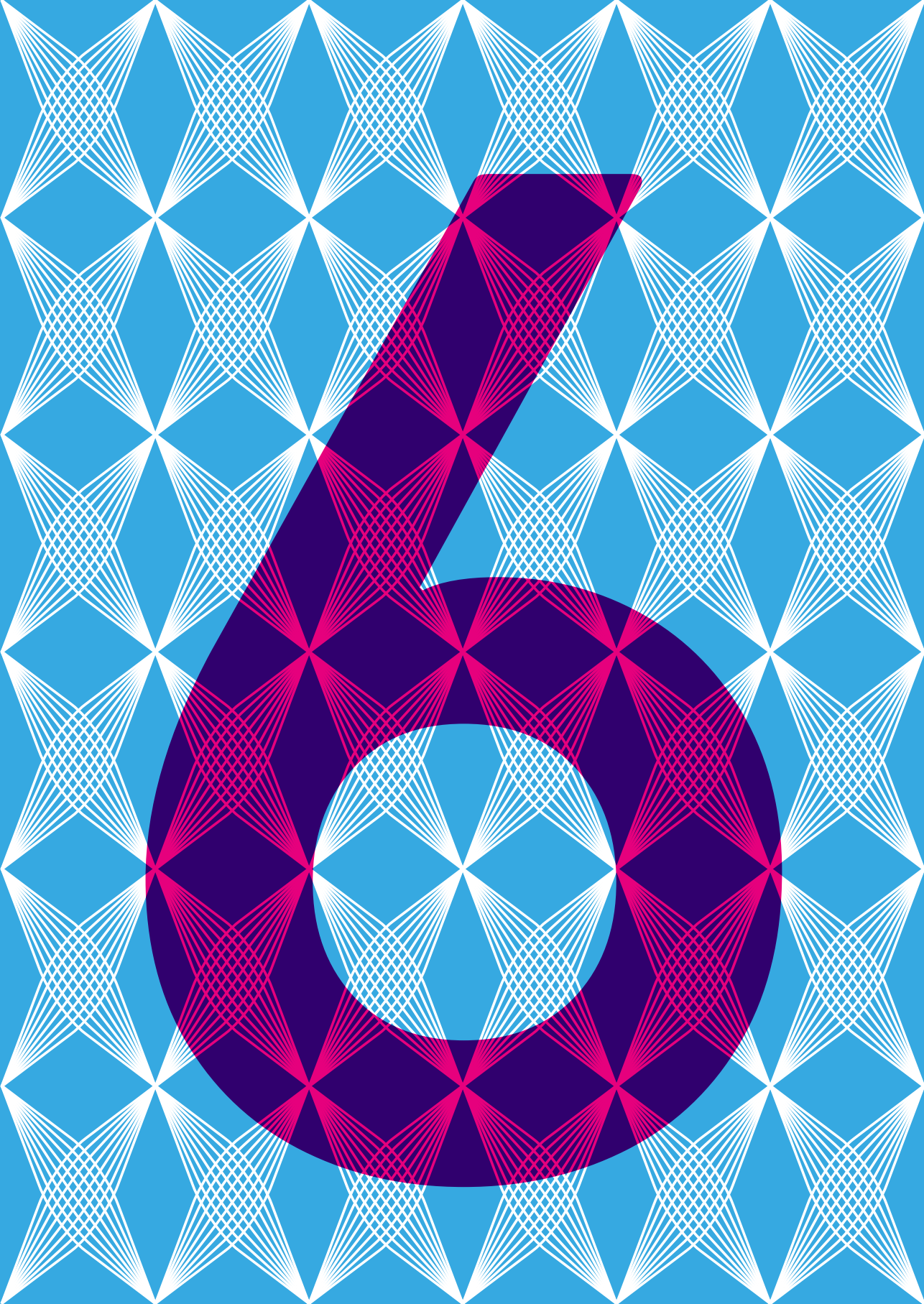
	QoL phys.	QoL psy.	QoL soc.	QoL env.	PANSS, positive	PANSS, negative	PANSS, general	CDSS (≥ 6)	GAF	Neuro-cognition
QoL phys.										
QoL psy.	0.66									
QoL soc.	0.44	0.57								
QoL env.	0.60	0.58	0.49							
PANSS, positive	-0.33	-0.24	-0.21	-0.31						
PANSS, negative	-0.28	-0.30	-0.29	-0.31	0.33					
PANSS, general	-0.44	-0.41	-0.28	-0.36	0.71	0.58				
CDSS, (≥ 6)	0.38	0.47	0.28	0.34	0.28	0.31	0.42			
GAF	0.41	0.35	0.28	0.39	-0.61	-0.48	-0.58	0.32		
Neuro-cognition	0.14	0.08 (*p*=0.06)	0 (*p*=0.97)	0.16	-0.13	-0.25	-0.18	0.29	0.21	

Cross-sectional Pearson's correlations between QoL domains, functioning, neurocognition and schizophrenia symptoms: all results were 2-tailed significant ($p \leq 0.01$) unless otherwise stated. Given the dichotomized depression variable, associations between other variables were expressed by Cramérs'V (V-values ranging between 0 and 1, higher values represent stronger associations). CDSS= Calgary Depression Rating Scale for Schizophrenia; GAF = Global Assessment of Functioning; PANSS= Positive and Negative Symptom Scale; QoL= Quality of Life; env = environmental domain; psy = psychological domain; soc=social domain; phys= physiological domain.

Table S2.. Longitudinal correlations between variables (n=544)

	QoL phys.	QoL psy.	QoL soc.	QoL env.	PANSS, positive	PANSS, negative	PANSS, general	CDSS (≥ 6)	GAF	Neuro-cognition
QoL phys.										
QoL psy.	0.67									
QoL soc.	0.42	0.50								
QoL env.	0.64	0.59	0.49							
PANSS, positive	-0.28	-0.22	-0.17	-0.29						
PANSS, negative	-0.19	-0.18	-0.25	-0.24	0.30					
PANSS, general	-0.37	-0.35	-0.26	-0.37	0.70	0.59				
CDSS (≥ 6)	0.35	0.39	0.22	0.36	0.30	0.34	0.46			
GAF	0.36	0.25	0.27	0.34	-0.58	-0.48	-0.56	0.37		
Neuro-cognition	0.16	0.08 (p=0.09)	0.06 (p=0.21)	0.21	-0.11 (p=0.05)	-0.20	-0.14	0.31	0.19	

Longitudinal Pearson's correlations between QoL domains, functioning, neurocognition and schizophrenia symptoms: all results were 2-tailed significant ($p \leq 0.01$) unless otherwise stated. Given the dichotomized depression variable, associations between other variables were expressed by Cramérs'V (V-values ranging between 0 and 1, higher values represent stronger associations). CDSS= Calgary Depression Rating Scale for Schizophrenia; GAF = Global Assessment of Functioning; PANSS= Positive and Negative Symptom Scale; QoL= Quality of Life; env = environmental domain; psy = psychological domain; soc=social domain; phys= physiological domain.



MEASURING PROCESS INDICATORS AND ADVERSE EVENTS TO ASSESS THE QUALITY OF CARE FOR INPATIENTS WITH PSYCHOSIS

Jentien M. Vermeulen, Geeske van Rooijen, M. van Dijk, M. van Tricht, L. de Haan

Under review

ABSTRACT

Introduction: Research into quality of care in psychiatry is scarce. Data collection is falling behind that for other fields of medicine and therefore the opportunity to improve care is missed.

In this medical record study we aim to determine: (i) whether or not patients' physical health indicators are assessed and pharmacological and behavioural treatment interventions applied; (ii) the incidence and nature of adverse events in psychotic inpatients.

Methods: Medical records of inpatients with psychosis admitted to psychiatric wards at the Academic Medical Center (AMC) in Amsterdam (The Netherlands) were screened with a previously developed and tested two-step patient safety tool.

Results: Data of 299 admissions were included. Physical health indicators were not assessed in one third of cases. Fifty-five percent of the patients were smokers but only 1% received an intervention. The family was actively involved in 43% of the cases. During 11403 admission days, 235 adverse events had been recorded. The most frequent adverse event was adverse drug reactions (40%), which were mostly related to antipsychotic medication.

Conclusion: In conclusion, quality of care auditing is useful to prioritize areas that need improvement. Future research should focus on interventions to improve the quality of psychiatric care.

1. INTRODUCTION

The importance of quality and safety of health care is firmly established since 2000 by the reports 'Crossing the quality Chasm: A new health system for the 21st century' and 'To Err is Human'.[1, 2] Both reports highlight six key elements of high quality care: safe, effective, timely, efficient, equitable and patient-centered. Still, the impact of that message in psychiatry is very limited. The poor data infrastructure to measure quality of care in psychiatry might be one of the explanations for this backlog.[3, 4] Consequently, improvement opportunities are often missed.[4, 5] A first important step to identify areas for improvement of care is an accurate measurement of quality of care.[2, 6] Particularly the dramatic mortality rates among patients with psychosis – mainly caused by cardiovascular disease – warrant greater attention.[7] Patients with a psychotic disorder live up to 25 years shorter than the general population.[7, 8]

Quality of care is a complex construct. The most frequently used framework to categorize the various measures is the Donabedian Framework, which describes quality indicators in the categories 'structure', 'process' and 'outcome' (Figure 1). The structure indicators reflect mostly organizational factors used to compare health care facilities on a system level (e.g. nursing-to-bed ratio). The process indicators, on the other hand, refer to what was done *for* or *to* the patient to improve his/her health and can be measured by the rate of physical assessments and evidence-based treatments such as antipsychotic medication or psychotherapy. Lastly, the outcome measures reflect the actual patient outcomes, for example the level of improvement after treatment or unwanted outcomes such as premature death.

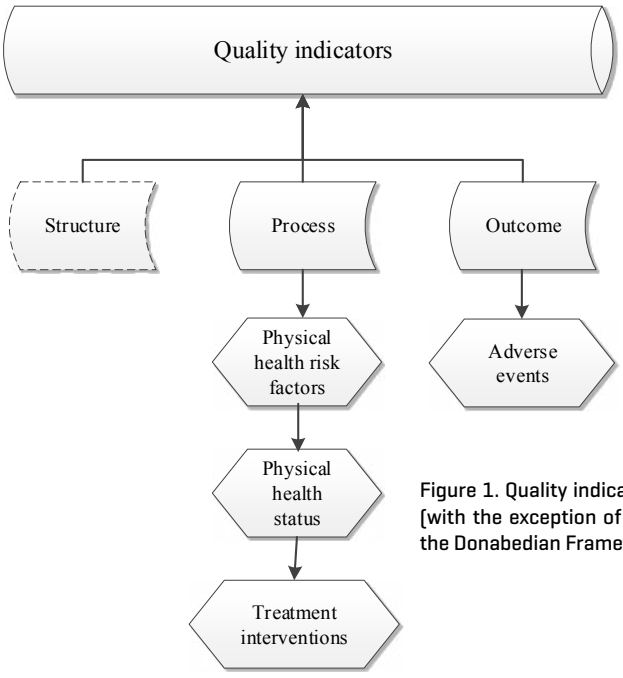


Figure 1. Quality indicators as assessed in current study (with the exception of structure indicators) based upon the Donabedian Framework

Process indicators have been studied in a large sample of schizophrenia patients from the United Kingdom.[9] The researchers concluded that assessment of risk factors, such as weight and blood pressure, as well as treatment rates of these risk factors were far below standard.[9]

Although process indicators provide a good picture of what was done for or to a patient, a broader scope is needed to oversee the actual outcome, for instance by combining process and outcome measures of inpatient care.[10] An internationally recognized outcome indicator is the occurrence of adverse events (AEs) - AE are defined as the negative unintended consequences of clinical care that led to injury, impairment, or other harm.[11, 12] A previous safety study reported that severe mentally ill patients admitted to medical-surgical wards experienced a mean number of almost six AEs per hospitalization.[13] A first study into safety of hospitalized psychiatric patients reported that approximately one in five patients experienced a patient safety event (AEs or medical errors).[14] To our knowledge, a study evaluating process and outcome indicators of psychiatric inpatient care for patients with psychosis is lacking.

We undertook a study to gain insight in the quality of care provided to psychotic patients admitted to psychiatric wards in the Netherlands by combining different indicators to assess processes and outcomes in order to identify areas that need improvement. Specifically, we aimed to answer the following questions: (i) to what extent are physical health risk and status assessed and are pharmacological and behavioural treatment interventions applied (e.g., process indicators); (ii) what adverse events occur and what are their incidences; and (iii) what clinical characteristics are associated with adverse events (i.e., outcome indicators).

2. METHODS

2.1 Setting and study sample

In this retrospective study, we included data of patients with a psychotic disorder discharged from three psychiatric wards of the Academic Medical Center (AMC) in Amsterdam between January 2014 and October 2015; i.e., a high care unit, a medium care unit and an early psychosis unit. Patients were offered a multidisciplinary treatment program during admission (based on national guidelines)[15] that matches the illness phase, e.g. first episode or chronic. During treatment and depending on the progress, patients gained more autonomy and were stimulated to transfer from the high care unit to the medium care unit or early psychosis unit as quickly as possible. The treatment program consisted of a diagnostic phase and pharmacologically focused treatment by medical doctors and behavioural focused treatment by nurses, psychologists, movement therapists, occupational therapists and social workers. The main goal of this program was to promote recovery in such a way that transfer to an ambulatory (home setting) was possible again. Alcohol drinking, cannabis use and the use of other drugs are prohibited during admission to our hospital. Smoking was allowed, however, inside three smoking areas in the building or in the garden of the wards.

Inclusion was restricted to patients diagnosed within the psychotic spectrum or bipolar I disorder with psychotic features, according to the Diagnostic and Statistical Manual of

Mental Disorders, Fourth Edition, 2000. This study has been submitted to the Medical Ethics Committee of the AMC and was granted exemption of the Dutch Medical Research Involving Human Subjects Act (WMO, 1999). Anonymized data were used for analysis and reporting.

2.2 Definitions and procedure

Process indicators: Process indicators were selected based on a national audit program for schizophrenia in the United Kingdom.[9] These indicators are originally extracted from the NICE guidelines on schizophrenia (NICE, 2009) and therefore we selected only those which are also applicable according to the local multidisciplinary Schizophrenia Guidelines.[15] A test or intervention was assumed not to have taken place if it was not documented.[9] The local guidelines dictate that each patient should be offered a basic somatic screening at intake. The percentage of patients not screened might thus reflect refusal or failure to offer screening.

Adverse events: AEs were defined as the negative unintended consequences of clinical care that led to injury, impairment, or other harm.[11, 12] Adverse drug reactions/event (ADRs) were defined as 'a negative, unintended consequence of a medication that resulted in functional impairment or other significant harm'.[14] An ADR was assumed to be present if it matched one or more of three criteria: (A) an 'always' list of reactions or symptoms, such as (benign) elevated liver enzymes; (B) medication stopped, held or additional medication was started due to an adverse reaction; and (C) impaired basic functioning (e.g., standing, walking, seeing, hearing, thinking, breathing).[16] The definitions of all adverse events have been included as an appendix (Appendix 1) and described elsewhere.[14]

We identified AEs from the patient files with the 'Hospital Medical Record Data Collection Manual of Patient Safety in Inpatient Psychiatry' tool, based on the methodology of the Harvard Medical Practice Study.[14] This tool, tested and in-depth described in a previous study,[14] includes nine predefined types of AEs, ranging from assaults to ADRs (for an overview, see primary outcomes or Appendix 1).[17] The patient files were reviewed in a two-stage method by three clinical reviewers: two supervised master students screened all files and the first author performed the final AE identification. All reviewers had been trained in audio-recorded training sessions presided by the creators of the tool.[16] To this aim, the three reviewers individually reviewed the same 20 training files, and discussed the individual results in consensus meetings. Subsequently, ten extra training files were screened, after which the interrater reliability among the two screeners was determined. This was considered adequate (unweighted Cohen's kappa was 0.69).[18] The second stage, the actual identification of AEs from the patient files was conducted by a physician (JMV); if necessary a psychiatrist (LdH) was consulted.

2.3 Outcome measures

The following primary outcome measures were determined:

1. Rates of process indicators, including: i) Physical health risk factors: antidiabetic medication, antihypertensive medication, lipid lowering medication, cannabis misuse or abuse, alcohol misuse or abuse, tobacco use, polypharmacy, obesity reported as comorbidity; ii) Physical health measures: glucose and lipids screening, blood pressure measurement, weight measurement; iii) Treatment interventions during admission:

evidence-based tobacco cessation intervention, consultation of a dietician, cognitive behavioural therapy initiated, social worker involved, occupational therapy, family involvement e.g., family attendance in psycho-education meetings, initiation of new antipsychotic medication. Family history of risk factors for cardiovascular disease was not consistently recorded and could therefore not be included.

2. Percentage of admissions with one or more AE, total number of AEs and number of AEs per 1000 patient days.
3. Nature of AEs and characteristics associated with the occurrence of AE. Nine different types were distinguished (Appendix 1): fall, self-harm or other injury to self, sexual contact with other admitted patients, elopement, contraband on unit, patient assault (victim or perpetrator), medication error, adverse drug reaction and other non-drug patient safety events.

2.4 Statistical analysis

Characteristics of the study sample are presented as numbers and percentages for categorical data. Normally distributed continuous variables are presented as mean (standard deviation) or median (interquartile ranges) in case of non-normally distributed continuous variables. Process indicators are presented as rates (number of patients that had a risk factor, assessment or intervention divided by the total sample size). Frequencies and types of adverse events are listed as countable frequencies and percentages. The incidence density was calculated as the number of adverse events occurring per 100 admissions and as the number of adverse events per 1000 patient days. Characteristics of patients with and without AEs were compared using the chi-square test or Mann-Whitney test. A p-value of 0.05 (two-sided) was considered statistically significant. All analyses were performed in SPSS statistics (IBM Corp, Armonk, NY, USA), version 24.

3. RESULTS

3.1 Study sample

We included data of 299 admissions of 237 unique patients with a psychotic disorder. Fifty-eight percent of patients had been diagnosed with schizophrenia (Table 1). The total length of stay was 11403 days; the median length of stay was 31 days (IQR 14-53).

3.2 Process indicators

Rates of process indicators are shown in Table 2. The most frequent physical health risk factors were nicotine use (55%) and cannabis abuse or misuse (28%). Physical health status had been assessed in 75% of the patients whose laboratory results had been documented and in 69% of the patients whose weight measurements had been documented. One percent of patients who smoked had received an evidence-based smoking-cessation intervention during admission. Occupational therapy was the most frequent treatment intervention (70%). The family was actively involved in 43% of the cases.

3.3 Adverse events and associated characteristics

We found a total number of 235 AEs in 118 admissions, corresponding to 21 AEs per 1000 patient days (Table 3). The highest number of AEs recorded per admission was eight. One

or more AEs had been documented for 39% of all admissions. The following admission characteristics were associated with AEs: length of stay (p<.001), compulsory admission (p=.037) and seclusion during admission (p=.003) (Table 1).

Most of the AEs were adverse drug reactions (40%), followed by elopement (17%) and assault (13%) (Table 2). The antipsychotic medication was switched in 47%, the dose was reduced in 18%, additional medication was started in 25% and treatment remained unchanged in 10% of the adverse drug reactions. One adverse drug reaction, classified as a post-olanzapine injection syndrome, resulted in severe harm (i.e., resuscitation with subsequently good outcome). Self-harm (n=4) was the least frequent AE. No falls, suicides or suicide attempts had been documented.

Table 1. Study sample characteristics and associations with adverse events during admission (n=299)

Variables	With adverse event n=118 (39%)	No adverse event n=181 (61%)	p-value
Gender, male/female, n (%)	79 (66.9) / 39 (33.1)	121(66.9) / 60 (33.1)	.99
Age, median (IQR)	33 (23-39)	30 (23-42)	.85
Diagnosis, n (%)			.64
-Schizophrenia	67 (56.8)	105 (58.0)	
-Psychosis NOS	23 (19.5)	36 (19.9)	
-Schizophreniform	6 (5.1)	12 (6.6)	
-Schizoaffective	15 (12.7)	18 (9.9)	
-Bipolar with psychotic features	7 (5.9)	7 (3.9)	
-Other psychotic disorders*	0	3 (1.7)	
Length of stay in days, median (IQR)	44 (27-66)	21 (10-43)	**<.001**
Compulsory admission, n (%)	68 (57.6)	81 (44.8)	**.04**
Seclusion during admission, n (%)	22 (18.6)	13 (7.2)	**.003**

*Other psychotic disorder can be specified as brief psychotic disorder and psychotic disorder due to medical condition. NOS=Not otherwise specified, GAF= global assessment of functioning; IQR=interquartile range. Significant findings are shown in **bold**.

Table 2. Rates of process indicators in admissions (n=299)

Physical health risk factors	**Frequencies (%)**
Tobacco use	55%
Cannabis misuse or abuse	28%
Alcohol misuse or abuse	8%
Antidiabetic medication	6%
Polypharmacy*	6%
Obesity as comorbidity	6%
Antihypertensive medication	5%
Lipid lowering medication	2%
Physical health measurements	
-Glucose and lipids screening	75%
-Blood pressure measurement	71%
Weight -At least 1 measurement (Range in kg)	69% (37-137)
Treatment interventions during all admissions	
Occupational therapy	70%
Initiation of new antipsychotic medication	63%
Family involvement	43%
Social worker involved	25%
Dietary consultation	10%
CBT initiated	4%
Tobacco cessation in smokers	1%

Kg=kilograms; CBT= cognitive behavioral therapy. *Polypharmacy was defined by five or more medications.

Table 3. Types and frequencies of adverse events (n=235)

Type of adverse event		***n* (%)**	***n* per 100 admissions**	***n* per 1000 patient days**
1.	**Adverse drug reactions**	93(40)	31	8
	of which:			
	-Induced by SGA	*50*		
	-Induced by FGA	*41*		
	-Induced by other medication[1]	*2*		
2.	**Patient elopement**	40(17)	13	4
3.	**Assault**	31(13)	10	3
4.	**Medication error**	27(11)	9	2
5.	**Contraband on unit**	26(11)	9	2
6.	**Other patient safety events**[2]	9(4)	3	<1
7.	**Sexual contact**	5(2)	2	<1
8.	**Self-harm or injury to self**	4(2)	1	<1
9.	**Patient Fall**	0	0	0
Total		235(100)	79	21

SGA= second generation antipsychotic; FGA= first generation antipsychotic; [1]Other medication= mood stabilizer and somatic medication;[2] Patient readmission within three days or not allowed smoking at wards.

4. DISCUSSION

In this study, the quality of inpatient care for patients with psychosis was evaluated by combining process and outcome measures, expressed as adverse events. Strikingly, physical health assessment was missing in one third of the patients and therewith potential treatment interventions could have been missed. Although most patients smoked, only 1% of smokers received an evidence-based smoking cessation intervention. With respect to treatment interventions, in only 43% of cases the family was actively involved in the treatment. Adverse drug reactions were the most frequent type of adverse events in inpatients with psychosis and these had been mainly induced by antipsychotic medication.

4.1 Process indicators

Regarding the performance on process indicators, a national audit of schizophrenia patients in the UK showed, for example, that physical health indicators were measured in 51% of the patients having their BMI being assessed during the previous 12 months,[9] compared to 69% our patients. The UK sample consisted of both in- and outpatients, which might perhaps explain the discrepancy with our findings. The most plausible explanations for the finding of the current study are that patients refuse (parts of) the examination or that measurements are performed but not documented. Unfortunately, data is missing regarding the number of patients who refused and, consequently, we cannot distinguish between refused and not documented physical examinations. Nevertheless, we believe that hospitalization is a window of opportunity to perform somatic screening – especially in severe mentally ill patients, given their poor physical health, and their limited access to medical care.[19]

Tobacco use is an undisputed risk factor for early death. A previous study showed that adults with schizophrenia were almost ten (SMR 9.9, 95%CI 9.6-10.2) times as likely to die from chronic obstructive pulmonary disease (COPD) than adults from the general population.[7] This number should be a strong argument against the old-fashioned view that treating tobacco addiction might not be one of the priorities during treatment of an acute psychosis. We argue that treating addiction to smoking is as important as recovery from psychosis and that evidence-based cessation interventions should be implemented into current care paths. There is sound evidence on achievement of smoking cessation in individuals with schizophrenia.[20] Implementation of treatment programs in combination with smoke-free hospitals may eventually help to reverse the dramatic reduction in life span of patients with psychotic disorders.[21] Besides, research showed that prohibiting smoking in psychiatric hospitals was associated with reduced rates of aggression, which might further motivate hospitals to change smoking guidelines.[22]

Finally, there is substantial evidence that active family involvement improves the care for patients with psychosis, for example with respect to adherence to antipsychotic medication.[23] In the present study, family was actively involved in 43% of cases. Previous research found that implementation of active family involvement often falls behind due to the paradigm shift in professionals from *contact with* to *working with* family.[24] Although the early psychosis unit in the current study organizes regular family meetings and offers psychoeducation and training to the family members of patients, the acute wards have not yet implemented this and this could be a plausible explanation for the relatively low numbers.

4.2 Adverse events

In this study, the occurrence of AEs (31 per 100 patient discharges) was slightly higher than in a recent study (28 per 100 patient discharges) in 40 acute psychiatric units from medical centers in the national Veteran Health Administration (VHA) system.[14] In the present study, the occurrence of AEs was associated with longer length of stay, seclusion during admission and compulsory admissions were related with. Longer length of stay and seclusion can also be a result of an AE, for example in the case of assault. Prevention of AEs, especially in compulsory admitted patients, could therefore result in a shorter length of stay, and in turn, further reduce the occurrence of AEs.

Adverse drug reactions occurred more than twice as often as any other AE. In many cases these were caused by antipsychotics use, but reactions varied, such from weight gain, movement disorder to akathisia.[25] A previous study on AEs during psychiatric hospitalizations also found that adverse drug reaction was the most frequent AE.[14] A reason for the high frequency of adverse drug reactions might be the precarious balance between efficacy and tolerability.[25] In our opinion, adverse drug reactions caused by antipsychotics must be systematically evaluated in every patient-physician contact. Severity of an adverse reaction can be assessed by instruments such as the Barnes Rating Scale for Akathisia,[26] and if necessary, dosages should be adjusted.

The limited number of AE to somatic medications is somewhat surprising. We can only speculate why this should be so: somatic medication might have been little used or clinicians paid little attention to side-effects of somatic medication. The high frequency of elopements (17% of all AEs) is mostly explained by patients returning substantially later than agreed or not returning from temporary leave. As these events might endanger the safety of the patient and its environment, these were also scored as an AE. Temporary leave is included in the treatment program as a means of regaining autonomy but it is subject to risk of harm. Lastly, interventions aimed to reduce aggressive behavior that may lead to assault form an important quality improvement area. There are several interesting developments in the field, such as *Safewards*, which in a randomized controlled trial was found effective in reducing harmful situations.[27]

4.3 Research findings and implications

Despite the efforts of international committees to introduce valid and reliable process and outcome measures,[28, 29] improvement of the quality of care for psychotic patients so far is hindered by the lack of data.[30] A Cochrane review from 2012 showed that an audit of performance indicators and feedback of this data to care providers can improve quality of care.[31] The feedback to providers may be even more effective when: baseline performance of providers is low, the source of feedback is a supervisor or a colleague, feedback is provided more than once both in verbal and written formats and when it includes explicit targets and an action plan.[31] Quality outcomes may well serve to improve care paths – with for example 'Plan Do Study Act-cycles' (PDSA).[32] A PDSA-cycle can guide quick improvement of a quality gap, also when working with small sample sizes.[32] Our study shows that retrospective data collection from electronic medical records can be used to audit process and outcome measures without an additional burden to patients or clinicians; it provides easily interpretable results and does not intervene with the care process. On the other hand,

this approach is labor-intensive as long as machine-learning strategies to identify events, such as a tool that identifies extrapyramidal side effects, are not yet used.[33](32)

4.4 Limitations

The results of the current study should be interpreted in the light of the following limitations. First, the retrospective design could have induced measurement error. Recall bias may have influenced the results since clinicians could have omitted to report AEs, risk assessment or treatment interventions. Consequently, frequencies might have been underestimated. Still, tools which use predefined outcome measures to identify AEs retrospectively as used in the current study yield at least ten times more AEs than a conservative method like voluntary reporting.[34] Second, although the interrater-reliability was adequate, differences in assigning AEs or process indicators may have influenced the results. Third, we chose to measure process and outcome indicators (e.g., AEs) over the limited period of a patient's admission. As recommended by the Organization for Economic and Community Development's Health Care Quality Indicators Project (OECD-HCQI), inclusion of additional long-term outcome indicators such as mortality and re-admission after inpatient care is preferred.[35] Fourth, we assumed that a test or intervention had not taken place if it was not documented.[9] However, patients with psychosis might suffer from a lack of illness insight and therefore might have refused assessments. As mentioned earlier, we could not distinguish between refusal and missed assessments. Lastly, generalizability is limited because this was a single center study. Particular characteristics, such as being allowed to smoke in designated areas, hinder the comparison with smoke-free hospitals in other countries.

In *conclusion*, this study is novel in that it presents data on the quality of processes and outcomes derived from medical records of psychotic patients, which can provide a solid base to start improving care. Having applied this approach, we conclude that patients diagnosed with schizophrenia or other psychotic disorders are prone to adverse events and especially to adverse drug reactions. High-quality care is needed because patients with psychosis frequently have somatic comorbidities and a huge excess of mortality. The overarching goal of measuring quality is improvement of care – and collecting quality data is an important means to achieve this. Future studies should focus on interventions to improve the care and outcomes of patients with psychosis.

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Appendix 1. Definitions of Adverse Events as described by Marcus et al.[14]

Type of event	Definition
Adverse Events	The negative unintended consequences of clinical care that lead to injury, impairment or other harm.
Patient fall	Falls regardless of the extent of the fall (to floor, onto bed), or whether the patient experienced harm/required treatment. Exclusions: events documented as intentional or faked; and falls secondary to a primary medical event, such as during cardiac arrest or seizure.
Patient self-harm or injury	Harm or injury experienced by the patient due to his or her own actions, regardless of intent. The most extreme case of patient self-harm is suicide. Patient injury can also occur even if the patient did not intend to harm him or herself (e.g., patient punches wall out of anger and sustained a laceration). Exclusions: suicidal ideation or threats unaccompanied by actions to harm self; and superficial or minor injuries indicated by the absence of bruising, swelling, bleeding or treatment.
Patient sexual contact	Incidents of a sexual nature between a patient and another patient, a visitor or a staff member. Sexual contact is defined as physical contact and includes, but is not limited to: intentional touching either directly or through the clothing, of the genitalia, anus, groin, breast, inner thigh or buttocks. Exclusions: non-physical contact (e.g., blowing a kiss or sexual talk); physical contact without implication of sexuality (e.g., pat on the back); kissing or hugging in greeting or farewell between a patient and a visitor; and events where a staff member was a passive and unwanted recipient of sexual contact from a patient.
Elopement	Patients leaving the unit, hospital or grounds without permission including failures to return from a pass, home visit or other approved departure from the unit, but does not include attempted but unsuccessful elopements.
Adverse drug event (ADE)	The negative, unintended consequences of a medication that results in functional impairment or other significant harm. In order to distinguish ADEs from the side effects often associated with psychotropic or other medications, ADEs had to meet one of the following criteria: 1) be on a specified list of medication reactions that have been determined by prior research to always be categorized as an ADE; 2) resulted in the medication being stopped, held, discontinued or replaced by another medication due to the adverse reaction; or 3) the reaction or symptom(s) impaired the patient's functioning. Since it can be difficult to distinguish between adverse reactions to medication and side effects of medication, we relied upon methodology previously established for appropriately identifying ADEs.
Contraband	Potentially dangerous items on the inpatient unit, including sharp objects (razors, knives, box cutters, scissors, or pins); matches and lighters; plastic bags and balloons; alcohol, illegal drugs and prescription medications; and rope-like items (belts, shoelaces, pantyhose, neckties, headphone wires, electrical cords, etc.).
Patient assault	Forcible physical contact with staff, other patients or visitors on the unit. This category includes patients who are the victim or the perpetrator of an assault. Exclusions: altercations that were only verbal in nature or characterized as only light or minimal physical contact; and assault to staff without documented injury experienced by the staff member.
Other non-drug adverse events	Events that resulted in stopping treatment and/or functional impairment (i.e., impairing a basic function such as thinking, standing, walking, seeing, hearing, breathing, etc.)


7

TREATING DEPRESSIVE EPISODES OR SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

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Accepted for publication CNS Spectrum

ABSTRACT

Depressive episodes or symptoms occur frequently in patients with schizophrenia and may have far-reaching consequences. Despite the high prevalence rate and clinical relevance of this comorbidity, knowledge about treatment options is still limited. The aim of this review is to provide an overview of the literature concerning treatment options for depressive episodes or symptoms in schizophrenia. Based on the current evidence, we present a stepwise treatment approach. The first step is to evaluate the current antipsychotic treatment of psychotic symptoms and consider lowering the dosage, since increased blockade of the dopamine D2 receptors may be associated with a worse subjective sense of wellbeing and dysphoria. A second step is to consider switching antipsychotics, since there are indications that some antipsychotics (including sulpiride, clozapine, olanzapine, aripiprazole, quetiapine, lurasidone, or amisulpride) are slightly more effective to reduce depressive symptoms compared to other antipsychotics or placebo. In the case of a persistent depressive episode, additional therapeutic interventions are indicated. However, the evidence is indecisive regarding the treatment of choice: either starting cognitive behavioural therapy or adding an antidepressant. A limited number of studies examined the use of antidepressants in depressed patients with schizophrenia showing modest effectiveness. Overall, additional research is needed to determine the most effective treatment approach for patients with schizophrenia and depressive episodes.

CLINICAL IMPLICATIONS

1. Depressive symptoms occur frequently in patients with schizophrenia (with an estimated modal prevalence rate of 25%).
2. Validated questionnaires (e.g., the Calgary Depression Rating Scale for Schizophrenia) are considered useful for diagnosing depressive episodes in this patient group.
3. Current evidence suggests that sulpiride, clozapine, olanzapine, aripiprazole, quetiapine, lurasidone and amisulpride have a modest beneficial effect on the reduction of depressive symptoms compared to other antipsychotics.
4. Physical activity is highly recommendable when patients suffer from depressive symptoms, given its beneficial effects on symptom severity and the lack of adverse effects.
5. Although based on a few studies, additional treatment with antidepressants or cognitive behavioural therapy showed modest effectiveness in depressed patients with schizophrenia.

1. INTRODUCTION

Depressive symptoms are often seen in patients with schizophrenia, with an estimated modal prevalence rate of 25%.[1,2] Because of this frequently co-occurring symptomatology, there is an ongoing debate whether mood symptoms should not be considered as part of the symptom profile of schizophrenia.[2]

The recognition and diagnosis of depressive episodes or symptoms in patients with schizophrenia can sometimes be challenging due to its conceptual overlap with negative symptoms. Nevertheless, diagnosing depressive episodes is highly relevant since it is associated with a higher risk of suicide,[3–5] a poorer quality of life[6] and decreased treatment adherence.[6] Clinicians may focus on the treatment of psychotic symptoms, while patients report that depressive symptoms bother them most and have the greatest impact on their satisfaction with life.[7] The above led to the inclusion of depressive symptoms as one of the dimension scores in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5, section III).[8] Next to the dimension of depression, the DSM-5 incorporates 7 other dimensions (i.e., hallucination, delusion, mania, disorganized speech, abnormal psychomotor behavior, negative symptom, impaired cognition). By offering the Clinician-Rated Dimensions of Psychosis Symptom Severity Scale, more emphasis is given on the differences in occurrence and severity of several symptom dimensions. This may facilitate administration of specific interventions.[9]

Despite the high prevalence rates of depressive symptomatology in schizophrenia, treatment studies that use reduction of depressive symptoms as the primary outcome of interest are scarce. However, some new studies that investigated the addition of antidepressants[10] to care as usual and the effectiveness of exercise[11] on depressive symptoms have not yet been included in recent guidelines and articles on this topic.[12–14]Therefore, the present review aims to give an overview of treatment possibilities for depressive episodes and symptoms in schizophrenia. Based on the current evidence, we will provide a stepwise approach that can be applied when treating a patient with schizophrenia and depressive episodes or symptoms.

2. METHODS

Articles included in this review were selected after performing a literature search in Pubmed (Medline). To find the most relevant studies on this topic we combined the following search terms: 'schizophreni*', 'psychos*' and ' 'depress*. The search was last performed on June 14th, 2017. For this review, we restricted our search to meta-analyses, systematic reviews or randomized controlled clinical trials, which were performed in the last 10 years. Articles were included if they investigated effectiveness on depressive episodes or symptoms as primary or secondary outcome in patients diagnosed with schizophrenia.

Diagnosing depressive episodes in schizophrenia

In the current literature, the terms 'comorbid depression', 'depressive symptoms' and 'depression' are often used interchangeably. For the uniformity of this review we will use the term 'depressive episode(s)' if patients were included who met the criteria for a major depressive episode (in accordance with the DSM-5 criteria) and/or a validated questionnaire

was used for diagnosing a depressive episode in patients with schizophrenia. Of note, these episodes are often recurrent. In all other cases, including subsyndromal depression, we will use 'depressive symptoms'.

The conceptual overlap of depressive symptoms with other symptoms (e.g., negative symptoms and/or extra-pyramidal side-effects) might provide another explanation for the broad range of prevalence rates and the clinical challenge to diagnose a depressive episode in patients with schizophrenia. To give some clinical guidance, a depressive episode is characterized by a depressed mood, while a flat or blunted affect and emptiness rather points to negative symptoms. Furthermore, feelings of hopelessness, guilt and suicidal thoughts are seen more frequently in the case of depressive symptomatology.[2,14] Because of these differences, it is recommended to use validated questionnaires to diagnose a depressive episode in patients with schizophrenia. For example, the Calgary Depression Rating Scale for Schizophrenia (CDSS)[15] is specifically designed to distinguish between depressive symptoms and other symptom domains (i.e., negative and or extrapyramidal side effects).[16,17] Nevertheless a thorough clinical evaluation, which integrates several important factors (i.e., time of onset, course of symptomatology and relation between the use of medication and depressive symptomatology) remains crucial when diagnosing a depressive episode in patients with schizophrenia. Hausmann et al.[18]has provided a clinically useful overview on this topic.

Moreover, clinicians should be aware of several somatic disorders, which can contribute to the emergence of a depressive episodes or symptoms. This can occur, among others, in endocrine disorders, malignancies and cardiovascular diseases.[19] This is highly important, since the prevalence of cardiovascular and oncological diseases is higher in patients with schizophrenia compared to healthy controls.[20] Additionally, depressive symptoms can also occur after the use (or discontinuation) of certain medications (e.g., (lipophilic) antihypertensive agents and corticosteroids) and the use of substances (i.e., drugs, alcohol and caffeine).[21]

Possible causes and explanations for depressive episodes in schizophrenia

In the last few decades, different studies have tried to elucidate the high prevalence rates of depressive symptomatology in patients with schizophrenia. On the one hand, there are several biological studies, which tried to investigate the difference in underlying pathophysiology of patients diagnosed with schizophrenia with and without depressive symptomatology. The neurobiological studies that investigated both disorders (i.e., schizophrenia and unipolar depression) showed a large overlap between both disorders with respect to potential factors contributing to the pathophysiology of both disorders. These include comparable risk factors during youth (such as childhood trauma and neglect),[22] changes in immune-inflammatory system, [23] and structural changes in brain morphology from neuroimaging studies.[24] These observations may point to a common pathophysiology, which might explain why depressive episodes or symptoms are often seen in patients with schizophrenia, and/or that patients with schizophrenia are vulnerable for developing depressive symptoms.[23] On the other hand, several studies[13,22,25] emphasized the effects of different psychological factors, which are believed to play an important role in the onset of depression (e.g., depression as a psychological reaction to being diagnosed with schizophrenia and the social consequences of this disease or as a reaction to a psychotic relapse(s)).

The evidence to date regarding possible causes and explanations for depressive episodes in patients with schizophrenia is sometimes conflicting and appears highly dependent on selection of samples and sample-sizes. It is beyond the scope of this review to discuss the pathophysiology of depressive episodes in-depth. For a more comprehensive discussion on this topic, we refer to a review by Upthegrove et al.[13] In sum, there is no evidence for a single, straightforward explanation of the high prevalence of depressive episodes in schizophrenia. In line with the plausible causal pathways of unipolar depression, current evidence points towards a multifactorial etiology including psychosocial, neurobiological and environmental risk factors.

The treatment of depressive episodes and symptoms in schizophrenia

Below we will first review studies focused on pharmacological treatment (antipsychotics; antidepressants in addition to antipsychotics and other pharmacological treatments) and non-pharmacological interventions. When evidence is available we will first discuss the effects on depressive episodes and then the effects on depressive symptoms. We will also consider the most important limitations of the current reports. Current findings are summarized in a practical stepwise approach (Figure 1). Lastly, we briefly discuss treatment aspects of suicide, as the risk on suicide is elevated by the presence of depressive episodes or symptoms.

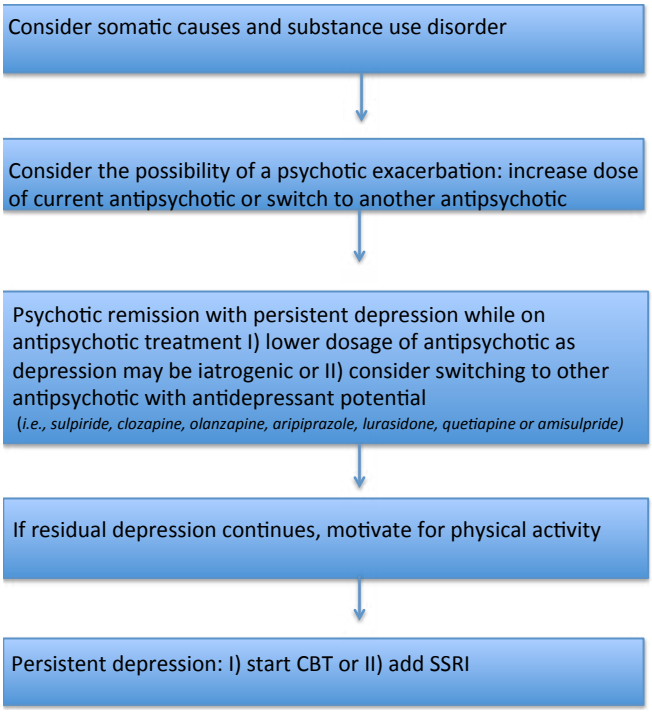

Figure 1. Framework for treating a depression in patients with schizophrenia. Based on the framework as designed by Bosnac & Castle.[14]

First phase of treatment

In the acute phase of psychosis it is advisable to treat depressive symptoms primarily with antipsychotics only, because depressive symptoms can improve or disappear with the remission of a psychosis.[26,27] For example, when patients suffer from severe positive symptoms (such as delusions and hallucinations), these may potentially lead to social isolation and in turn cause depressive symptoms. Resolution of psychotic symptoms by D_2 antagonists might therefore lead to improvement of depressive symptoms. However, previous research also showed that an increased blockade (i.e., higher dosages or higher affinity of antipsychotic agent) of the dopamine D_2 receptors by antipsychotics is associated with a worse subjective wellbeing and/or dysphoria.[28–30] Likewise, the induction of EPS by antipsychotics has previously been associated with 'neuroleptic dysphoria'.[31,32] It seems plausible that especially an unwarranted high dosage of antipsychotics is associated with these side effects and dysphoria, which might especially manifest itself after the acute phase treatment of psychosis. Consequently, the first step of treating depressive symptoms is to adequately treat positive symptoms with antipsychotics but also to optimize the dosage of this medication and when possible to lower the dosage of current D_2 antagonists. Herein, we acknowledge the complex balance of efficacy and tolerability of antipsychotic treatment in the case of depressive symptoms.

Pharmacological treatment

Antipsychotics

Over the last few decades, several studies investigated the antidepressant effect of antipsychotics. However, the number of studies investigating the effectiveness of antipsychotics for treating depressive episodes in schizophrenia specifically are limited as shown in a Cochrane review by Furtado et al.[33] Possible effects in this Cochrane review were expressed as 'weighted mean differences' (WMD), which calculates the difference between decreases of a score on a depression rating scale by different interventions, weighted by the pooled variance of these differences.

From the few included studies in this review, one study compared sulpiride versus chlorpromazine in a double-blind design (in which it was unclear whether participants were randomly assigned to the treatment conditions). Sulpiride was associated with a significant decrease in depression scores compared to patients receiving chlorpromazine (n = 19 and n=17, respectively, WMD = -0.70, 95% CI [-1.2, -0.2], p = 0.0058). In another included double-blind study, quetiapine gave no significant improvement in depression scores compared with patients receiving haloperidol (n=94 and n=86, respectively, WMD = - 0.57, 95% CI [-1.4, 0.3]). The authors of this Cochrane review concluded that there was insufficient evidence to determine whether or not newer atypical antipsychotics were more effective compared to older antipsychotics in the treatment of depressive episodes in patients with schizophrenia.

Furthermore, in contrast to the above Cochrane review, some meta-analyses pooled additional studies comparing the effectiveness of antipsychotics *on depressive symptoms* (instead of depressive episodes). Leucht et al.[34] investigated whether some antipsychotic drugs were more effective compared to placebo assessing several outcome measures including depressive symptoms. This meta-analysis showed that a number of antipsychotics were significantly more effective in reducing depressive symptoms relative to placebo.

Amisulpride (2 trials, n = 261, pooled ES = - 0.50; 95% CI [-0.75, -0.24], p = 0.0001), olanzapine (3 trials, n = 479, pooled ES = - 0.28, 95% CI [-0.47, -0.10], p = 0.0024), ziprasidone (3 trials, n = 404, pooled ES = - 0.33, 95% CI [-0.52, -0.13], p = 0.0011) and zotepine (1 trial, n = 79, pooled ES = - 0.48, 95% CI [-0.92, -0.03], p = 0.0349) were significantly more effective than placebo. Haloperidol had a beneficial effect on depressive symptoms (2 trials, n = 299, pooled ES = -0.33, 95% CI [-0.56, -0.11], p =0.0039) compared to placebo. No significant differences in effect between the agents clozapine, quetiapine, risperidone or sertindole were found.

The effectiveness of haloperidol in the treatment of depressive symptoms, with its high potency for dopamine D_2 receptor antagonism, is in apparent contradiction with research which describes the worse subjective wellbeing and/or dysphoria due the blockade of the D_2 -receptor.[28–30] There are various explanations to assert this contradiction: for example, haloperidol might effectively treat psychotic symptoms, which in turn causes a decrease in depressive symptomology (as outlined earlier). Based on these findings there is no conclusive evidence to support switching when depressive symptoms initially appear and when a patient is already treated with haloperidol but instead lowering the dose could be considered, while balancing efficacy and tolerability of the drug as adequately as possible.

In a second meta-analysis of Leucht et al.,[35] nine second generation atypical antipsychotics were compared with first generation antipsychotics, with depressive symptoms as the measured outcome. From this study, amisulpride (9 trials, n = 900, pooled ES = -0.37, 95% CI [-0.51, -0.24], p <0.0001), aripiprazole (1 trial, n = 1278, pooled ES = -0.12, 95% CI [-0.24, -0.01], p = 0.040), clozapine (6 trials, n = 426, pooled ES = -0.51, 95% CI [-.0.87, -0.14], p = 0.006), olanzapine (12 trials, n = 2893, pooled ES = -0.27, 95% CI [-0.35, -0.19], p <0.0001), and quetiapine (4 trials, n = 442, pooled ES = -0.23, 95% CI [-0.41, -0.04], p = 0.016) were more effective in treating depressive symptoms than first generation antipsychotics. In contrast to the earlier mentioned meta-analysis of Leucht et al.,[34] zotepine and ziprasidone were not more effective in this analysis in comparison to other antipsychotic treatments. Of note, risperidone and sertindole were both found to be ineffective compared to first generation antipsychotics in reducing the severity of depressive symptoms. Limitations of this second meta-analysis were the small effect sizes (apart from clozapine), the short follow-up of the included studies (i.e., 81% of the studies had a duration of 12 weeks) and in most studies (95) antipsychotics were compared to haloperidol, mostly in relatively high doses (as pointed out in published comments).[36,37] Given the findings of previous research that showed that an increased blockade (i.e., higher dosages) of the dopamine D_2 receptors by antipsychotics is associated with a worse subjective wellbeing and/or dysphoria,[28–30] the favourable effect sizes (ES) of second generation antipsychotics compared to first generation antipsychotics, these results might reflect an overestimation due to high doses of the comparator drug.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) - trial[38] also examined whether second generation antipsychotics were more effective compared to first-generation antipsychotics in the treatment of depressive symptoms in schizophrenia patients (n = 1460).[39] In the first phase of this double-blind study, patients were randomly assigned to perphenazine, olanzapine, quetiapine, risperidone, or ziprasidone and followed for 18 months. In these 18 months, depressive symptoms decreased in all treatment groups and there were no significant differences between these groups. If

only the patients were taken into account (n=448) that had clinically relevant depressive symptoms (i.e., patients with a score of 6 or higher on the CDSS) at baseline, mixed model analyses showed that the patients who were treated with quetiapine had significantly lower depression scores at outcome compared to the group receiving risperidone. However, this was observed at 4 out of the 7 measurements during follow-up and only small differences were found between both groups.

Regarding the more recently approved antipsychotic lurasidone, this agent showed to be effective in the treatment of depressive symptoms.[40] Nasrallah et al.[40] pooled the results of double-blind randomized controlled trials, which investigated the effect of lurasidone on depressive symptoms. Although, the duration of these trials was short (6 weeks), patients treated with lurasidone showed a significant, though small decrease in depressive symptoms compared to placebo (4 trials, n = 898 and n=432, respectively, pooled ES = -0.24, p <0.001).

A most recent meta-analyses and meta-regression[41] was published regarding the effectiveness of antipsychotic augmentation, which is highly debated considering its costs and ambiguous evidence. Considering the effectiveness for depressive symptoms, augmentation did not lead to a significant improvement in severity of depressive symptoms, although the pooled effect size was moderately large and significant at a trend level (10 trials, n=351, pooled ES = -0.69, 95% CI [-1.42, 0.05], p=0.066).

In summary, since blockade of dopamine D_2 receptors is possibly associated with a worsening subjective wellbeing and/or dysphoria, the first step is to lower the dosage of current antipsychotic treatment while maintaining remission from psychosis and/or to treat when depressive symptoms occur. There is not enough evidence to encourage switching amongst antipsychotics when depressive symptoms initially appear while a patient is treated with high potency D_2 receptor antagonists. In that situation it is advisable to reconsider the dosage of the drug to balance effectively and tolerability. All first and second-generation antipsychotics antagonize D_2 receptors to a greater degree as dosing increases. Most guidelines suggest lowering to the most effective antipsychotic dose,[12,42,43] which may improve depressive symptoms. However, if depressive symptoms persist there are indications that a number of antipsychotics (including sulpiride, clozapine, olanzapine, aripiprazole, quetiapine, lurasidone and amisulpride) have a slightly favorable effect than other antipsychotics or placebo when treating depressive symptoms in patients with schizophrenia a switch may be warranted. Although haloperidol might also be effective, the increased effectiveness of second-generation antipsychotics in comparison to first generation antipsychotics may be explained by the fact that several second generation antipsychotics have a lower affinity for the dopamine D_2 receptor and an antagonistic action on the 5-HT_2 receptor, which may both contribute to an antidepressant effect. Some second-generation antipsychotics may potentially partially agonize D_2, D_3, $5HT_{1a}$ or antagonize $5HT_{2c}$, $5HT_3$ or $5HT_7$: all of which have theoretical antidepressant properties.[44–46] In this light, it is also important to mention brexpiprazole which may have an antidepressant effect in patients with schizophrenia due to its receptor profile (including partially agonizing at D_2 and $5HT_{1a}$ receptors and antagonizing at $5HT_{2a}$ and noradrenaline $\alpha_{1b}$and α_{2c} receptors).[47] Correll et al. performed a meta-analyses on the effectiveness of brexpiprazole in one phase II study and two phase III studies, showing a significant reduction on a depression/anxiety

factor in one phase III study compared to placebo.[48] However, some uncertainties remain regarding depressive episodes, because most studies evaluated the effect on depressive symptoms instead of treatment of depressive episodes. Moreover, studies investigating second-generation antipsychotics were using relatively high doses of first generation drugs, which limits comparability.[49] Most second-generation antipsychotics possess antidepressant properties at their lower doses.

Antidepressants in addition to antipsychotic medication

Efficacy and tolerability

In 2002, a Cochrane review by Whitehead et al.[50] was published regarding adding antidepressants to antipsychotics in the case of *depressive episodes* in patients with schizophrenia. Based on the small sample sizes and poor quality of the six randomized controlled trials (RCTs), the authors concluded that the addition of antidepressants to an antipsychotic in comparison to the addition of a placebo did not significantly reduce depression (6 trials, n = 261, WMD = -2.1, 95% CI: [-5.04, 0.84]). No conclusions were made regarding the effectiveness of individual agents.

The earlier mentioned Cochrane review by Furtado et al.,[33] which investigated the antidepressant effect of atypical antipsychotics, also included one short study that compared clozapine with other, unspecified antipsychotics in combination with an antidepressant or placebo in a double-blind design. Severity of depression significantly decreased in patients treated with clozapine (n=18) in comparison with the group of patients who received an antipsychotic agent in combination with mianserin (n= 11, WMD = -5.53, 95% CI: [-8.23, -2.8], p < 0.0001), as well as in comparison with the patients receiving an antipsychotic agent in combination with moclobemide (n=14, WMD = -4.35, 95% CI [-6.7, -2.03], p = 0.00024), as well as in comparison with the patients receiving an antipsychotic agent in combination with amitriptyline (n=12, WMD = -3.61, 95% CI [-6.58, -0.64], p = 0.017), and also compared to the patients who received an antipsychotic agent in combination with a placebo (n=15, WMD = -6.35, 95% CI [-8.6, -4.1], p <0.00001).

After these Cochrane reviews, some additional reviews and meta-analyses were published that further evaluated the addition of antidepressants in patients with schizophrenia on several outcomes, including *depressive symptoms* (instead of depressive episodes).[10,51–55] The most recent of these, which also included the majority of the studies, is a meta-analysis by Helfer et al.,[10] which included 82 RCTs (n = 3608). By making use of wider inclusion criteria (i.e., including non-blinded clinical trials and trials that used control conditions in which no treatment was given), the authors included more studies at the expense of a lower level of study-quality.

Of 82 included studies, 42 trials used depressive symptoms as outcome. Based on these studies, antidepressants provided a significant (although limited) decrease in depressive symptoms compared with control conditions (i.e., placebo or no active treatment, 42 trials, n = 1849, pooled ES = -0.25, 95% CI: [-0.38, -0.12], p = 0.0001). However, in stratified analyses, the studies using selective serotonin re-uptake inhibitors (SSRIs) showed a non-significant decrease in depressive symptoms (19 trials, n = 859, pooled ES = -0.19, 95% CI [-0.40, 0.02]). The following individual antidepressants were significantly more effective in reducing

depressive symptoms: trazodone (1 trial, n = 60, pooled ES = -0.98, 95% CI [-1.51, -0.44], p = 0.0004), duloxetine (1 trial, n = 40, pooled ES = -0.80, 95% CI [-1.45, -0.16], p = 0.01), sertraline (4 trials, n = 205, pooled ES = -0.51, 95% CI [-0.91, -0.12], p = 0.01) and amitriptyline (4 trials, n = 138, pooled ES = -0.34, 95% CI [-0.68,0.00], p = 0.05).

In an additional analysis, the authors found no indication of an increased efficacy of antidepressants in patients with *'pronounced depressive symptoms'* compared to patients with lesser severity (p=0.38). However, in contrast to the overall non-significant effects of SSRIs against depressive symptoms, SSRIs were beneficial in schizophrenia patients with depressive episodes (7 trials, n=422, pooled ES = –0.48, 95% CI [–0.84, –0.11], p=0.01). These additional analyses suggest that antidepressants in general, and more specific SSRIs, are beneficial when patients meet the criteria for a depressive episode. Future high quality studies are required to validate these results.

Additionally, *tolerability* is a relevant outcome when adding antidepressants for the treatment of depressive episodes. This is of high importance since patients diagnosed with schizophrenia are - in general - already being treated with antipsychotics prone to side effects. Patients treated with additional antidepressants had significantly more complaints of abdominal pain, constipation, dizziness and dry mouth, which are common adverse effects of antidepressants. However, psychotic exacerbations were not more frequently observed in the group treated with antidepressants.

Interactions due to combined antipsychotic-antidepressant treatment

Most pharmacokinetic interactions between antipsychotics and antidepressants are the result of a competitive binding with different cytochrome P450 (CYP) enzymes.[56] These interactions results in changing plasma levels of drugs (increase or decrease depending on the inhibition or induction of specific CYP enzymes). Some new antidepressants, act as inhibitors of different CYP enzymes, where most antipsychotic drugs do not have these inhibiting effect but are indeed metabolized (i.e. substrates) by these enzymes.[56] Due to the inhibitory effect of the antidepressants, the elimination of antipsychotic drugs might be diminished, resulting in higher plasma levels of antipsychotic drugs. A constantly updated overview of the strength of the inhibitory effects of different antidepressants can been found in the 'Drug Interaction tables' (available at http://medicine.iupui.edu/clinpharm/ddis/main-table).[57]

Since there are SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs) (e.g., sertraline, (es)citalopram and duloxetine) with mild-moderate inhibitory effects of CYP enzymes, it may be recommended to use one of these drugs, especially if monitoring of serum levels of antipsychotics is not available. Moreover, it is advisable to use Therapeutic Drug Monitoring (TDM) of the antipsychotic. These blood levels can be done before and during the process of adding an antidepressant, and might clarify the intra-individual interactional effects. However TDM results might be difficult to interpret, especially since large intra-individual differences have been described.[56] Whenever there is too little evidence for the application of TDM (e.g. for aripiprazole and quetiapine) and/or where TDM is not available,[58] as a third option correction factors could be applied. Correction factors give an indication if and how a dosage of a substrate (i.e. those drugs that are metabolized by CYP enzymes)

should be reduced in the case of adding an antidepressant to antipsychotic medication (for an extensive overview of correction factors when combining specific combinations of antidepressant and antipsychotics, we refer to a review by Spina & Leon).[56]

Additionally, pharmacodynamic interactions (at the level of binding to receptors) are also important. These effects are, in contrast to the pharmacokinetic interactions, not a result of changes in plasma levels and may result in improved or reduced effectiveness but at the same time in more or less adverse drugs reactions. However, the possible occurring effects when combining antidepressants and antipsychotics are poorly investigated, although these interactions are more likely to occur with mirtazapine and bupropion.[56] Prolonged QTc interval, with torsades de pointes as a rare but possible lethal outcome, is described when SSRIs and second-generation antipsychotics are combined. Additive risk factors include a 'family history of sudden death; personal history of syncope, arrhythmias or heart conditions; hypokalaemia, hypomagnesaemia and co-prescription of other medications that increase QTc'.[56] If aforementioned situations are applicable, electrocardiogram(s) (ECG) are recommended.[56]

Other pharmacological treatments

Two Cochrane reviews[59,60] investigated the effect of the addition of lithium or valproate respectively on depressive symptoms in patients with schizophrenia neither treatment showed a significant improvement on depressive symptoms. With respect to lithium, to the best of our knowledge, there are no studies to date that investigated the effect of lithium-addition in the combination with both antipsychotics and antidepressants. This indeed could be a plausible strategy, considering the effects of lithium addition in the case of non-response to antidepressants in patients with unipolar depression.[19]

In summary, there is evidence that the use of antidepressants to treat depressive symptoms and depressive episodes may be of help to some degree in patients with schizophrenia. However, interactions between antidepressants and antipsychotics should be taken into account. There is not enough evidence to indicate which antidepressant is preferred as an additive to antipsychotic medication, however the best available evidence supports the use of SSRIs. Within the group of SSRIs, no advice can be given regarding the effectiveness of individual agents, nonetheless agents with mild-moderate inhibitory effects on CYP enzymes might be preferable to reduce pharmacokinetic interactions.

Non-pharmacological interventions

Recently, a systematic review and meta-analysis by Dauwan et al.[11] examined the effect of exercise in patients with schizophrenia on several outcome measures, including depressive symptoms. They compared exercise to both a passive and an active control condition (the 'active' control group existed, for example, of patients with schizophrenia who played table soccer or followed occupational therapy, where the 'passive' condition consisted of patients with schizophrenia who were on a waiting list). There were seven trials included (n = 296) that examined the effect on depressive symptoms and these showed that exercise reduced depressive symptoms in patients with schizophrenia compared to control conditions (pooled ES = -0.71, p <0.001). Qualitative assessment showed that patients had to perform physical activity for at least 30 minutes, three times weekly, at a considerable intensity, for

at least three months. The positive effects of exercise are extremely important, especially in patients with schizophrenia who are mostly treated with antipsychotics for a longer period of time. In particular since antipsychotics are known for harmful side effects including weight gain, diabetes mellitus and dyslipidaemia.[61]

Regarding cognitive behavioural therapy (CBT), most studies focus on the effectiveness of CBT on psychotic symptoms and no studies investigated the effectiveness of this intervention on depressive symptoms as primary outcome.[13] Nevertheless, the National Institute for Clinical Excellence (NICE, 2014)[12] described a small to moderate positive effect (ES = -0.30) on the reduction of depressive symptoms in comparison with standard treatments[62] or other psychosocial treatments.[63] Given the beneficial effects of CBT in patients with unipolar depression, CBT is an interesting intervention to further investigate in patients with schizophrenia and a depressive episode.[19]

Other therapeutic interventions, which are frequently used in the treatment of unipolar depressive disorder,[19] such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), have also been investigated in schizophrenia. A Cochrane review[64] investigated the effectiveness of ECT in (n=30) patients with schizophrenia showing that there is no evidence that ECT is effective in the treatment of depressive symptoms, which is at least remarkable considering the success rates of ECT in the treatment of resistant unipolar depression. Another Cochrane review of Dougall et al.[65] examined the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in patients with schizophrenia on various outcomes, including depressive symptoms. These studies, which evaluated the effectiveness of rTMS on depressive symptoms (5 trials, total sample size ranging between 22-43), suggested some beneficial effects. These findings are in need of further replication since the included studies were of limited quality and of small size. Thus, there is currently no evidence available to support the use of ECT and insufficient evidence to fully support rTMS for the treatment of depressive symptoms in patients with schizophrenia.

Suicide

Suicide is an important cause of death in patients diagnosed with schizophrenia, responsible for approximately 5% of the mortality in patients.[66,67] An in-depth review regarding the treatment and management of suicidality in patients with schizophrenia is beyond the scope of this review (e.g., see Harvey and Espaillat).[66] However, previous (and current) depressive episodes form an important risk factor for suicide and suicide attempts in patients with schizophrenia.[3–5,66] An earlier meta-analysis on this topic showed that previous depressive episodes are associated with (completed) suicide in patients with schizophrenia (OR=3.03, 95% CI [2.06-4.46]). Here, we think it is important to mention that treatment with clozapine diminishes suicidality in patients with schizophrenia, as proved by the International Suicide Prevention Trial (InterSePT).[68] This was further established in a meta-analysis[69] based on five studies, which compared clozapine to other agents. This meta-analysis showed a 2.9-fold reduction of completed suicide in patients treated with clozapine compared to other agents (pooled risk ratio= 2.9 favouring clozapine, 95% CI [1.5, 5.7], p=0.002).[69]

DISCUSSION

In the present review we aimed to provide an overview of the current evidence regarding treatment of depressive episodes and symptoms in patients diagnosed with schizophrenia. Depressive symptoms are often seen in patients with schizophrenia, however prevalence rates vary widely.[1,2] There is a strong urgency to diagnose and treat depressive episodes, since it is associated with serious consequences. Regarding the treatment of depressive episodes and symptoms we provided a practical stepwise approach when facing a patients with schizophrenia and depressive episode (figure 1). In general, more research concerning the effectiveness of therapeutic interventions for depressive episodes in patients with schizophrenia is needed.[13] The overall interpretation of the results of the treatment studies is complicated by the use of different questionnaires, which were not always validated for diagnosing depressive episodes or assessing severity of depressive symptoms in patients with schizophrenia. Additionally, the follow-up of these studies is often short and there is considerable variation in the populations studied. The recommendations of this review need to be considered in the light of the following limitations. At first, it should be noted that this review cannot be considered a systematic review, although we aimed to provide a comprehensive overview of the most important studies on this topic. Secondly, differences between countries regarding the registration and availability of specific antipsychotic agents may reduce the choices described. However, we aimed to give an overview despite these differences. Consequently, we summarized the international available evidence, which should be combined with the availability and registration of antipsychotics per country.

CONCLUSION

Based on the current evidence, it is advisable to treat depressive episodes and symptoms in the acute phase of psychosis primarily with antipsychotics only, because depressive symptoms can also improve or disappear with the remission of a psychosis. If depressive symptoms persist (or develop later) it must be determined whether the depressive symptoms are the result of a too powerful and persistent dopamine D_2 receptor blockade. If so, decreasing the dosage of antipsychotics or switching to an antipsychotic with a weaker affinity for dopamine D_2 receptors (or a partial agonist) or those with other potential antidepressant properties may be appropriate. Current evidence suggests that sulpiride, clozapine, olanzapine, aripiprazole, quetiapine, lurasidone and amisulpride have a modest beneficial effect on depressive symptoms in patients with schizophrenia compared with other antipsychotics. Physical activity is recommended when depressive symptoms are present, given its beneficial effects and the favourable balance between effect and side effects. If the depressive symptoms persist, and especially if there is a depressive episode diagnosed, a next step is recommended. Based on current evidence, it is difficult to advice whether to choose between start CBT or add an antidepressant (i.e., SSRIs). When antidepressants are chosen, the possibility of pharmacological interactions reducing the antipsychotic effects and/or increasing side effects must be considered.

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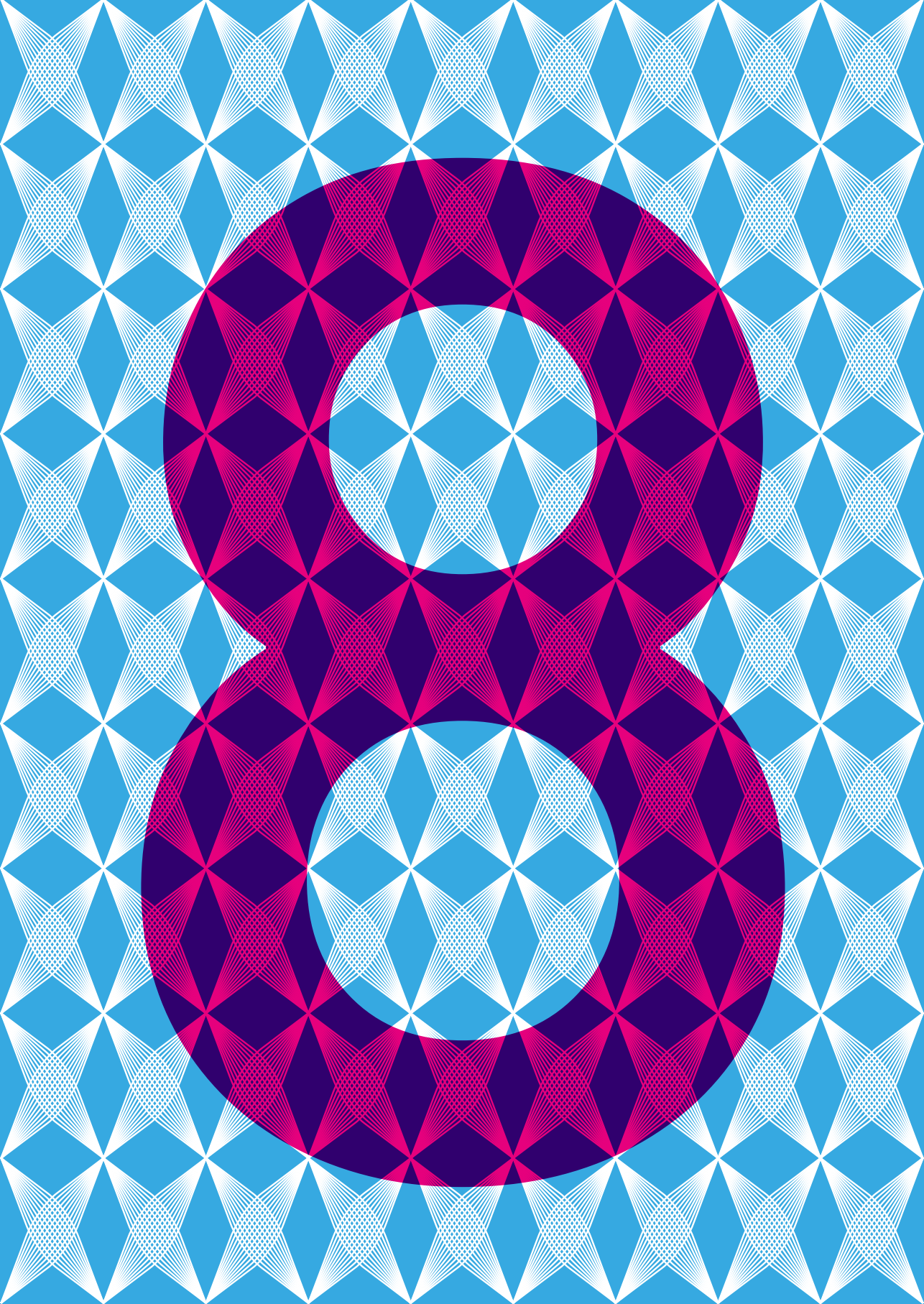

ANTIPSYCHOTIC MEDICATION AND LONG-TERM MORTALITY RISK IN PATIENTS WITH SCHIZOPHRENIA; A SYSTEMATIC REVIEW AND META-ANALYSIS

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Psychological Medicine 2017; 47: 2217-2228

ABSTRACT

Patients with schizophrenia have a higher mortality risk than patients suffering from any other psychiatric disorder. Previous research is inconclusive regarding the association of antipsychotic treatment with long-term mortality risk. To this aim, we systematically reviewed the literature and performed a meta-analysis on the relationship between long-term mortality and exposure to antipsychotic medication in patients with schizophrenia. The objectives were to i) determine long-term mortality rates in patients with schizophrenia using any antipsychotic medication; ii) compare these to mortality rates of patients using no antipsychotics; iii) explore the relationship between cumulative exposure and mortality; and iv) assess causes of death. We systematically searched the EMBASE, MEDLINE and PsycINFO databases for studies that reported on mortality and antipsychotic medication and that included adults with schizophrenia using a follow-up design of more than 1 year. A total of 20 studies fulfilled our inclusion criteria. These studies reported 23,353 deaths during 821,347 patient years in 133,929 unique patients. Mortality rates varied widely per study. Meta-analysis on a subgroup of four studies showed a consistent trend of an increased long-term mortality risk in schizophrenia patients who did not use antipsychotic medication during follow-up. We found a pooled risk ratio of 0.59 (LL: 0.46 UL:0.76 p value < 0.001) favouring any exposure to antipsychotics. Statistical heterogeneity was found to be high ($Q=39.31$, $I^2=92.37\%$, p value < 0.001). Reasons for the increased risk of death for patients with schizophrenia without antipsychotic medication require further research. Prospective validation studies, uniform measures of antipsychotic exposure and classified causes of death are commendable.

1. INTRODUCTION

Adults with schizophrenia have the highest mortality risk compared to other patients suffering from psychiatric disorders.[1] Compared to the general population, their life expectancy is about 20-25 years shorter.[2] Somatic disease contributes most to this high mortality risk.[3] Recent publication of a large cohort of patients with schizophrenia mentioned that cardiovascular disease was the most common cause of death (403.2/100,000 person years); the all-cause mortality for the total sample was 1539.5 per 100,000 person years.[3] Patients with schizophrenia tend to make little use of health care resources while they are known to have a bad physical health, reflecting a multifactorial etiology.[4,5] The role of antipsychotic medication and its potential influence on premature mortality is highly debated. Antipsychotic mediation reduces the severity of psychotic symptoms and the incidence of psychotic relapse in most patients.[6] On the other hand, antipsychotics may increase cardiovascular mortality risk by induction of weight gain, diabetes mellitus and dyslipidemia.[7,8] It is not clear, however, whether exposure to antipsychotics is associated with a shortened life expectancy for patients with schizophrenia.

Short-term trials and safety extension studies reported lower mortality in patients exposed to antipsychotics compared to patients receiving placebo.[9,10] The most common cause of death in these trials was suicide. Though, when deaths related to suicide were excluded, natural cause mortality rates still exceeded those of the general population.[10] A synthesis of the literature specifically on the long-term effects of antipsychotics on mortality risk was published in 2009.[11] The authors concluded that there was some evidence that long-term exposure to antipsychotics increases mortality. However, they acknowledged that this conclusion was based on observational studies reporting doubtful results regarding mortality trends. While some reviewed studies reported higher cardiovascular mortality in patients using antipsychotic medication, other studies found lower all-cause mortality.[12,13] After publication of this review, the largest follow-up study so far was published.[14] In this cohort study the authors made use of a Finnish nationwide database and their results contradicted the conclusion of Weinmann et al.[11] by showing that long-term exposure significantly lowered the risk of death compared to no antipsychotic medication.[14] However, some of these Finnish results were eventually appraised by other authors as 'problematic' to interpret.[15] Several methodological limitations were underlined and discrepancies of results stated by Tiihonen et al. compared with those from other Finnish registry studies were found.[15]

In summary, the high mortality rate in patients with schizophrenia is argued to be partly related to increased risk of somatic disease associated with antipsychotic medication. However, current evidence is equivocal with respect to the association between long-term use of antipsychotics and mortality. A systematic review of long-term studies is therefore needed to shine light on this topic. Therefore we aimed to i) determine long-term mortality rates in patients with schizophrenia using any antipsychotics; ii) compare these with mortality rates of patients who did not use antipsychotic medication during follow-up; iii) explore the relationship between cumulative exposure of antipsychotic medication and mortality; and iv) assess the most common causes of death.

2. METHODS

This review was conducted following the guidelines of the PRISMA statement.[16] A protocol was published in the PROSPERO database under registration number CRD42016043452. We searched EMBASE, MEDLINE and PsycINFO from inception through February 29, 2016. The search strategy was developed by a clinical librarian together with the first author (JV) (presented as supplement 1). This strategy included terms for schizophrenia, antipsychotic medication (with additional description of 15 frequently prescribed antipsychotics in general names, trade names and numbers), mortality (e.g. death, years of life lost) and most frequent causes of death (e.g. suicide, myocardial infarction). Reference lists of eligible articles were hand searched to identify eligible studies not previously identified through the database search (forward- and backward tracking of literature).

2.1 Study selection

Two reviewers (JV and EN) independently screened titles and abstracts of retrieved citations on following inclusion criteria: The study 1) included patients older than 18 years diagnosed with schizophrenia and related disorders; 2) used antipsychotic medication as an outcome measure or this was likely to be reported in full text; 3) used mortality as outcome measure or this was likely to be reported in full text; 4) was an original research paper that used a follow-up design; and (5) was written in English. Conflicts in study inclusion were resolved in consensus meetings. If a clear decision concerning inclusion criteria could not be made during abstract screening, the full text was consulted. Subsequently, articles that met the following exclusion criteria were excluded during full-text reading: The study 1) did not use one of the following designs: a cohort study, case-control or controlled clinical trial with or without randomization or blinding; 2) had a follow-up of 52 weeks or less; 3) did not describe number or any other measure of death rate from all causes; 4) did not describe use of antipsychotic medication; 5) did not compare patients with schizophrenia receiving antipsychotic treatment to an adequate control group (patients without antipsychotics or other antipsychotic medication); and 6) was published before 1990. We argued that from the year 1990 both atypical antipsychotics and clozapine had entered the international markets and were available to the majority of schizophrenia patients.[17] The first 100 articles selected were reviewed in full text by two reviewers independently and conflicts were settled through discussion. In view of the fact that overlap was high, other articles were reviewed by the first author (JV).

2.2 Data extraction

Data were extracted by two researchers independently (JV and GvR) and accuracy was discussed in regular meetings. The following data were extracted: first author's name, year of publication, country, years of data collection, years of follow-up or patient years (follow-up multiplied by sample size), sample source, specific diagnoses, population (e.g., inpatient, outpatient or subgroup), method of diagnosis of schizophrenia, primary outcome(s), sample size, number of deaths and total number of control or comparison group, number of lost to follow-up, cause(s) of death if available, source of mortality-data, source of information on antipsychotic medication (such as dose, length of exposure and concomitant use) and (if reported) confounders.

We aimed to include studies that reported on antipsychotic medication, dose and length of exposure. Corresponding authors were contacted to ensure accuracy and completeness of data when studies lacked sufficient information about the number of patients who did not use antipsychotic medication. All-cause mortality numbers were extracted and if possible categorized cause-specific into natural (e.g., cardiovascular) and unnatural causes (e.g., suicide). Quality of the studies was assessed with the Cochrane risk of bias tool for randomized trials or the Newcastle Ottawa scale for observational studies by the first author.[18, 19] In case of overlapping samples, the largest was included in the main analysis.

2.3 Statistical analysis

To answer the first question, we calculated unadjusted all-cause mortality rates per 1000 patient years for unique patients receiving any type of antipsychotic medication during follow-up. The following formula was used to estimate patient years if not provided by authors:

$$\textit{Patient years} = \left[\frac{\textit{number of people at risk at the beginning} + \textit{number of people at risk at the end of the time interval}}{2}\right] \times [\textit{number of years in the time interval}]$$

If studies consisted of subgroups using various antipsychotics or with different duration of illness, we calculated a composite rate for each study. Furthermore, we aimed to conduct a sub-analysis on studies that described data for patients that used any type of antipsychotics during versus no antipsychotic medication during follow-up. Crude risk ratios from mortality rates per person years were calculated, pooled and are presented in a forest plot using a DerSimonian-Laird random-effects model.[20] Variance was assessed using eyeballing, Q- and I^2 -statistics.[21] Publication bias was tested by means of a funnel plot and Egger's test if applicable. All analyses were conducted in software named Comprehensive Meta-Analysis, version 2.0.

3. RESULTS

3.1 Study selection

The initial search yielded 5,125 articles, of which 382 remained after screening of titles and abstracts (Figure 1). Most of the 362 studies that we excluded after full text review, had a short duration of follow-up (52 weeks or less) or no assessment of mortality. Seventeen overlapping samples were removed, resulting in 20 original samples subjected to quantitative synthesis and four to meta-analysis.

3.2 Study characteristics

Clinical data per study are presented by type of study design (Table 1). The included randomized open label trials, cohorts and case-control studies originate from over ten different, mostly western countries. Clinical and methodological characteristics of the studies were heterogeneous. Although all samples matched the inclusion criterion of schizophrenia and related disorders, some also included few patients with bipolar diagnoses or unspecified diagnoses. Various clinical subgroups and a wide range of antipsychotics were studied (Table 1). Follow-up time ranged from 1.25 to 14 years. Two studies were prematurely terminated after completion of one year follow-up of the last

patient because the predetermined difference in effectiveness was achieved or the drug in question, sertindole, was taken from the market.[22,23] A descriptive arm of a randomized trial was published in a separate paper and we combined data from both papers in question into a single composite rate.[22,24] Quality of the studies was variable but in most cases scored as moderate (see supplement 2-4).

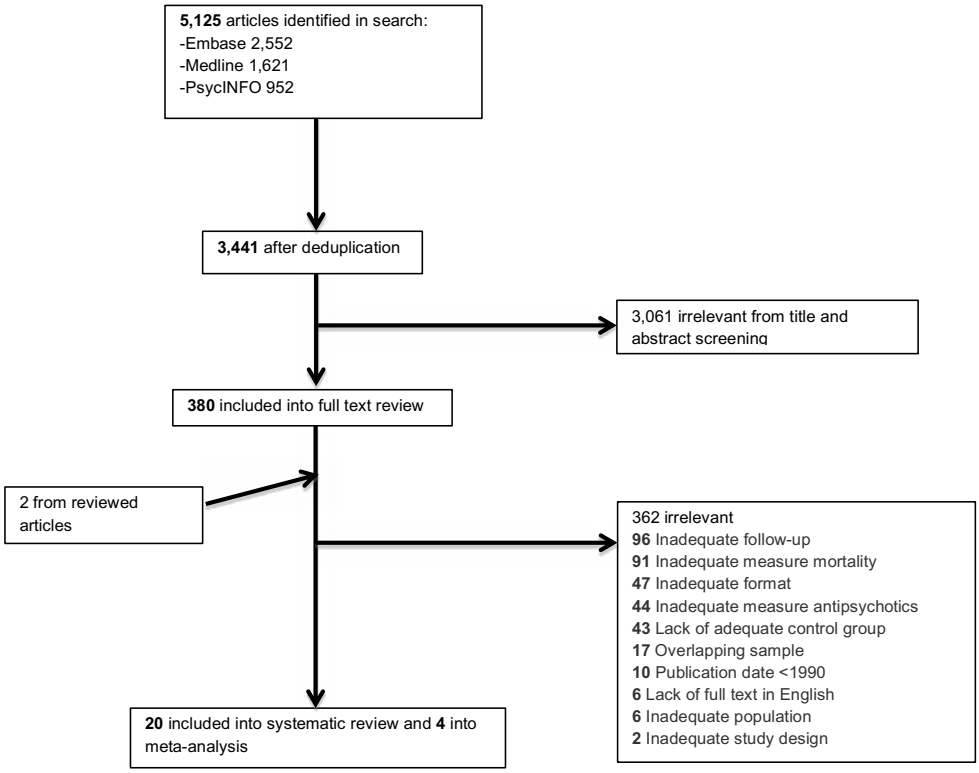

Figure 1. Flowchart of study selection

Table 1. Study characteristics of all studies included in the forest plot

First Author, year Nationalities	Sample Diagnoses (n) Subgroup details	Total sample size (n) Source	Length of follow-up in years (inclusion period)	Comparisons	Characteristics Mean age[a], Gender (m/f) (n), Mean duration of illness in years
Randomized trials, open label					
Alphs *et al.*, 2015[25] **United States of America, Puerto Rico**	Schizophrenia (450) Outpatients, history of incarceration, homeless	450 Recruitment from non-traditional locations	1.25 (2010-2013)	Paliperidone palmitate versus oral antipsychotics	38.1, 383/61, specified in strata
de Arce Cordon *et al.*, 2012[24], Gaebel *et al.*, 2010[21] **Multinational**	Schizophrenia (585) Schizoaffective (126) In- and outpatients previously treated ineffectively or had side effects	711 Recruitment routine care settings	2 (2004-2007)	Risperidone long-acting injection versus quetiapine verus aripiprazole	41.6, 411/300, n.s.
Meltzer *et al.*, 2003[26] **Multinational**	Schizophrenia (609) Schizoaffective (371) High risk suicide	980 n.s.	2 (1998-2001)	Clozapine verus olanzapine	37.1, 302/378, n.s.
Ritchie *et al.*, 2010[27] **Australia**	Schizophrenia (66) Under care of old age psychiatrists, currently on conventional antipsychotics	66 Recruitment from psychiatric treatment settings	3.5 (1997-2000)	Olanzapine versus isperidone	69.8, 19/47, n.s.
Thomas *et al.*, 2010[28] **Multinational**	Schizophrenia (9,809) Intolerant for 1 other antipsychotic	9,809 Recruitment by psychiatrists	1.4 (2002-2008)	Sertindole versus Risperidone	37.1, 5,426/4,383, specified in strata
Cohorts, prospective					
Girgis *et al.*, 2011[29,b] **China**	Schizophrenia (122) Schizophreniform(38) In- and outpatients First episode patients	160 Medical records	9 (1995-2007)	Clozapine versus Chlorpromazine	28.7, 84/76, n.s.
Kasper *et al.*, 2010[23] **Europe**	Schizophrenia (2,219) 102 patients without primary diagnoses of schizophrenia	2,321 Recruitment by investigator	1.5 (1997-1998)	Sertindole verus other	40.6, 1,325/996, n.s.
Montout *et al.*, 2002[30] **France**	Schizophrenia (3,325) In- and outpatients	3,325 Question naires	4 (1993-1997)	First and second generation	39.3, 2,127/1,198, specified in strata
Ran *et al.*, 2015[31] **China**	Schizophrenia (510) Patients from rural county townships	510 epidemiologic al data	14 (1994-2008)	Never treated verus ever treated	44.6, 237/273, 13.7|11.9

Cohorts, retrospective

Cullen *et al.*, 2013[32] **United States of America**	Schizophrenia (2,132) Outpatients	2,132 Database	10 (1994-2005)	First and second generation versus First generation ever	42.0, 1,130/1,002, n.s.
Deslandes *et al.*, 2015[33] **United Kingdom**	Schizophrenia (n.s.) Schizoaffective (n.s.) Parts of patients were non-responders to clozapine	176 Medical records	5 (2006-2013)	Risperidone long-acting injection versus Aripiprazole	n.s. for total cohort
Hayes *et al.*, 2015[34] **United Kingdom**	Schizophrenia (9,437) In- and outpatients	9,437 Database	5[c] (2007-2011)	Clozapine newly prescribed versus first and second generation versus no antipsychotics	43.2[e] , 7,985/6,769, n.s.
Kelly *et al.*, 2010[35] **USA**	Schizophrenia (964) Schizoaffective (561) Psychosis NOS (161)	1,686 Database	6-10 (1994-2000)	Clozapine versus risperidone	39.8, 1,059/627, n.s.
Pridan *et al.*, 2014[36] **Israel**	Schizophrenia (527) Inpatients Elderly 2x previously treated unsuccessfully	527 Medical records	5 (2007-2012)	Amisulpride versus other antipsychotics	67.4, 184/343, 35.7 years
Tenback *et al.*, 2012[37] 2012 **Netherlands**	Schizophrenia(7,415)	7,415 Database	3 (2006-2008)[d]	First versus second generation antipsychotic versus combined use	45.5, 4,538/2,877, n.s.
Tiihonen *et al.*, 2009[14] **Finland**	Schizophrenia and related disorders (n.s.) At least one hospital stay	66,881 Database	11 (1973-2006) (mean 7.8 users antipsychotics and 8.9 years never treated patients)	No antipsychotics versus cumulative exposure strata	51.0, 30,803/36,078, n.s.
Torniainen *et al.*, 2015[38] **Sweden**	Schizophrenia[c] (22,722) 1. Chronic patients (21,492) 2. First Episode Patients (1,230)	22,722 Database	1. 5(2006-2010) 2. No mean specified[d]	No exposure versus low exposure versus moderate exposure versus high exposure	45.0, 15,856/8,866, n.s.

Case-controls

Chen *et al.*, 2015[39] **Taiwan**	Schizophrenia (1,624) >30 DDD in the first year after diagnoses	1,624 Database	Mean 3.81 and 3.91 (1998-2008)	Second versus first generation antipsychotics	38.7, 970/654, n.s.
Sernyak *et al.*, 2001[40] **United States of America**	Schizophrenia (4,245) n.s.	4,245 Database	6 (1992-1998)[d]	Clozapine ever versus Clozapine never	43.4, n.s., n.s.
Taylor *et al.*, 2009[41] **United Kingdom**	Schizophrenia (250) Schizoaffective (29) Bipolar (27) Other (16)	779 Database	Mean 4,67 and 2,25 years (2002-2004 and 2006)	Clozapine versus Risperidone long-acting injection	36.4|RLAI n.s.[e], n.s., n.s.

[a]*Mean age is reported for the whole study population if available*

3.3 Mortality rates for patients using antipsychotic medication

A number of 14,643 deaths during 657,400 patient years was reported for unique patients with schizophrenia and related disorders using any antipsychotic medication. Unadjusted mortality rates per 1,000 patient years for patients taking antipsychotic medication are presented per study (Figure 2). Because of the great diversity in study designs and clinical characteristics, we refrained from pooling these results into a meta-analysis.

Study name	Rate	Number of death	Patient years
Alphs 2015	1,91	1	524
Gaebel/de Arce Cordón 2010	3,58	5	1398
Meltzer 2003	10,71	20	1868
Ritchie 2010	26,74	5	187
Thomas 2010	8,84	125	14147
Girgis 2011	2,95	4	1355
Kasper 2010	17,58	19	1081
Montout 2002	16,01	178	11118
Ran 2015	24,86	110	4424
Cullen 2012	17,16	337	19635
Deslandes 2015	2,32	2	863
Hayes 2014	20,07	443	22078
Kelly 2010	10,51	136	12944
Pridan 2014	43,31	103	2378
Tenback 2012	3,71	82	22122
Tiihonen 2009	26,84	11458	426940
Torniainen 2015	14,41	1420	98515
Chen 2015	12,41	76	6123
Sernyak 2001	14,25	95	6667
Taylor 2009	7,91	24	3033

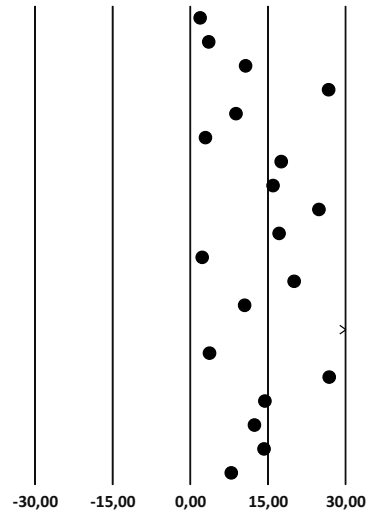

Figure 2. Mortality rates for patients using any antipsychotic medication. Studies are ranked by design according to Table 1. All rates are presented as crude mortality rates per 1,000 patient years

3.4 Comparison of patients with any antipsychotic use versus no use

A total of 22,141 deaths in 715,904 patient years were identified in four cohort studies comparing patients with any antipsychotic use to patients who did not use antipsychotic medication during follow-up. The corresponding author of one of these retrospective cohort studies, which combined medical record data with natural language processing tools, provided additional data.[34] All four studies showed that mortality rates of patients with any use of antipsychotic medication is lower than no antipsychotic treatment during long-term follow-up (Figure 3). The pooled risk ratio was 0.59 (LL: 0.46 UL:0.76 *p* value <0.001). Heterogeneity was found to be high (Q=39.31, I^2=92.37%, *p* value < 0.001). Publication bias was difficult to interpret from the few included studies but was not suggested from a funnel plot (not shown, available on request) or Egger's test (β=3.57 SE=1.77 and (1-tailed) *p*-value 0.090).

3.5 The relationship between cumulative exposure and mortality

Torniainen et al.[38] showed that both no and very high exposure (expressed as defined daily dose per day) is related to high mortality rates. This U-shaped mortality curve was found in chronic schizophrenia patients compared to the general population. Authors of the largest cohort study observed an inverse relationship between mortality and duration of

cumulative exposure (up to 11 years) for patients with at least one filled prescription.[14] The lowest adjusted hazard ratio concerned patients using antipsychotic medication from 0-0.5 years [aHR 0.49 (95% CI 0.46-0.52)] compared to no antipsychotic medication. Since details about antipsychotic dose and length of exposure were missing in many articles or reported in substantively inconvertible measures, we were unable to perform a meta-analysis. Units of measurement that we encountered were for example any use over time, use at baseline, proportion of doses (defined daily dose per day) or mean chlorpromazine equivalents per treatment arm. Therefore, we merely describe the results of latter Scandinavian studies that specifically presented results on cumulative exposure and (adjusted) hazard rates.

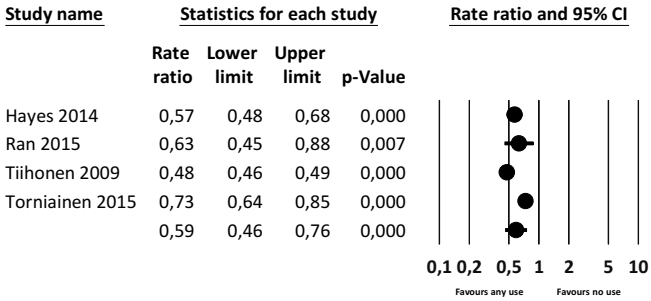

Figure 3. Mortality rate ratios of no antipsychotic use versus any antipsychotic use. Heterogeneity: Q=39,31 I^2= 92,37 p=0,000

3.6 Causes of death

Thirteen of all 20 studies reported data, to a varying extent, on the causes of death. Cardiovascular disease was reported to be the cause of death in 15.7% of 14,818 deaths, and suicide in 6.7%. The remaining causes were described as other natural, unnatural or were undetermined. For patients without use of antipsychotic medication, causes of death were reported in two studies representing 173 out of 8,710 deceased patients. Cardiovascular disease was reported for 59 (0.7%) and suicide for 22(0.3%) patients. Since data was found to be scarce, we dropped presenting results in a table or figure.

4. DISCUSSION

4.1 Summary

To our knowledge, current study is the first quantitative synthesis that used meta-analysis to explore the association between long-term mortality and antipsychotic use in schizophrenia patients.

This review aimed to assess this association by answering four subquestions. Our primary aim was to assess unadjusted mortality rates for schizophrenia patients using any antipsychotic medication. It appeared that these vary widely per study. Furthermore, our aims were to compare mortality rates of patients with any antipsychotic exposure to patients who did not use antipsychotic medication. Additionally, exploration of the association of cumulative exposure to antipsychotic medication with mortality was performed. Lastly, we aimed to assess causes of death in exposed and non-exposed patients.

4.2 Mortality rates and methodological limitations of included studies

Large differences in unadjusted mortality rates were found for patients using any antipsychotic medication, ranging from 1.91 to 43.31 per 1,000 patient years. Interpretation and evaluation of these mortality figures was difficult in view of the substantial methodological limitations, as also reported in the previous review.[11] A recently published retrospective cohort study that did not report any measures for antipsychotic exposure, found a crude all-cause mortality rate of 15.39 per 1,000 patient years.[3] This cohort was at least ten times as large as the largest retrospective cohorts that we included which found deviating unadjusted mortality rates for patients exposed to antipsychotics (14.41 and 26.84 per 1,000 patient years).[14,38] The latter cohort studies were national record linkage studies in which administrative data from different sources was matched. Several forms of bias may have been introduced that tend to make interpretation of the observed rates difficult. This pertains, for example, to database studies that often provided little information on lifestyle factors such as smoking, diet and substance use, which limits adjustment for influential confounders. For other studies, flaws were also noticed in measurement of decisive factors such as duration of illness or somatic comorbidity. Another minor point of bias was a systematic measurement error of antipsychotic exposure. Included randomized trials tended to study very specific clinical subgroups such as high suicide risk patients. Generalizability of these mortality rates is therefore limited. The highest mortality rate (43.31 per 1,000 patient years)[36] could be explained by an older aged sample and may not be representative for adult populations. Some studies used medication prescriptions as a reflection of exposure and thereby disregarded possible non-compliance with therapy. This systematic measure error is important, in particular since earlier clinical trials showed high non-compliance rates in patients with schizophrenia.[42] Furthermore, type of antipsychotic medication that patients were assigned to within studies was often a misrepresentation of the whole follow-up period. Two studies surpassed this problem by calculating defined daily doses and testing associations for current and cumulative use or on average low, medium or high exposure.[14,26] Also, a couple of studies did not address limitations such as immortal time bias when comparing exposed and non-exposed individuals. Immortal time refers to a period during follow-up when patients are not assigned to any treatment group while death could occur.[43] Hereby, underestimation of death rates could be introduced since patients who end up in the exposed group have survived until antipsychotic treatment is started. Lastly, others did not account for survival bias and selected only a group of chronic patients and thereby possibly underestimated mortality rates. Taking everything into consideration, the need for high-quality, long-term, studies researching standardized outcomes of antipsychotic exposure and mortality is undisputable. The cornerstone design to monitor drug toxicity is a prospective cohort study and one may even resort to 'restrictive cohorts' to review the effect of antipsychotic medication on long-term mortality.[44;45] Girgis et al. showed another valid design of converting a randomized trial after two years into a prospective cohort following the patients for seven extra years.[29] Overall, our findings did not allow to present a summary estimate rate of long-term mortality for patients using any antipsychotic medication. Therefore, firm conclusions about the association between antipsychotic use and long-term mortality were not drawn.

4.3 Comparison of patients with any antipsychotic use versus no use

A striking result was found by meta-analysis that showed lower risk of all-cause mortality for patients with any antipsychotic exposure compared to patients who did not use any antipsychotic medication. This association was determined using four large retrospective cohort studies with moderate to high quality. Since we found consistent evidence for a higher all-cause mortality risk in patients who did not use antipsychotic medication during follow-up, we are keen to elaborate on the many factors that could explain this. It has been hypothesised that patients without antipsychotic medication make little use of both mental and somatic health care and therefore do not use antipsychotics.[5] These schizophrenia patients could represent the most severely ill group whose social deprivation and lack of illness insight could impose a relevant threshold to access health care, with undertreatment as a result. Consequently, these patients could have a higher mortality risk as a result of somatic risk factors on the one hand and on the other hand have severe psychiatric symptoms that may lead to psychiatric events such as suicide or violence. Thus, increased attention for patients who do not use antipsychotic medication is commendable. Besides, differentiating between natural and unnatural reasons of death could further clarify this association.

4.4 The relationship between cumulative exposure and mortality

Remarkably, most studies lacked an adequate measurement of cumulative exposure. Short-term trials express cumulative time of exposure to antipsychotics in units of patient exposure years.[9,10] Long-term retrospective observations, for example, in a Swedish cohort study were grouped as no, low, moderate or high exposure in windows of average defined daily dose per day. Contrary to patient exposure years, this unit of measurement allows not only length of exposure but also doses and polypharmacy to play a role. In this study, low and moderately dosed antipsychotic treatment was associated with lower mortality than no or high dose antipsychotic treatment.[38] This is partly underlined by Tiihonen et al., however cumulative exposure was presented slightly different namely in strata of years of cumulative exposure.[14] These authors pointed out that the lowest risk for death is found in patients with short-term exposure (0-0.5 years) as suggested by previously named short-term trials. Overall, we found some evidence that on average low and medium exposure or long-term treatment is associated with a lower risk of death.

4.5 Causes of death

Due to a paucity of results we could not meaningfully report on most common causes of death in patients not using or using any antipsychotic medication. Tiihonen et al. stated that no increased risk for mortality due to ischaemic heart disease was found after 7-11 years of cumulative exposure to antipsychotics.[14] Osborn et al. studied death because of heart disease specifically and observed that patients receiving high doses of antipsychotic treatment are more likely to die from heart disease than patients receiving lower doses, no medication or than the general population.[13] Torniainen et al. stated that the excess of overall and specifically cardiovascular mortality in schizophrenia is not related to antipsychotics when used in low or moderate doses based on a U-shaped morality curve.[38] Reasons of death could clarify clinical implications of an increased risk of death and therefore future research is required.

4.6 Strengths and limitations

By providing an overview of evidence regarding antipsychotic use and long-term mortality in schizophrenia, we could add new insights. Recently published studies that used substantial sample sizes were compared to other unadjusted mortality rates and we demonstrated large differences. To our knowledge, we performed the first meta-analysis looking into the association between mortality and antipsychotic exposure in schizophrenia patients so far. The pooled estimate rate showed an increased risk for death for patients who did not use antipsychotic medication. This patient group requires further research into the reasons and risk factors for mortality. Despite these strengths, limitations of current study need to be acknowledged. First, heterogeneity was a complication factor for all outcomes of interest. Apart from the impossibility to compare and pool all data due to the large variation in clinical and statistical characteristics, insufficient data provided by studies such as cause of death obstructed answering our subquestions. Second, we did report clinical subgroups of patients with schizophrenia (Table 1.) though we were unable to correct for any of these characteristics. Due to methodological inequalities and substantial difference in the use of confounding factors for observational studies, we regarded presenting (incomparable) adjusted rates unwise. Third, we did not compare mortality rates of included patients to those in the general population and could therefore not correct for geographical differences. Lastly, we chose all-cause mortality per patient years as it is a robust outcome that is less likely to be affected by lack of blinding. One might argue that patient reported or other clinical outcomes such as quality-adjusted life-years (QALYS) more adequately cover the perspective of patients.[46]

5. CONCLUSIONS

To our knowledge, this is the first quantitative synthesis of the risk of long-term mortality for patients with schizophrenia who use antipsychotic medication. The long-term unadjusted mortality rates varied widely between studies. Heterogeneity in clinical and statistical characteristics was high. The true relationship between the adverse effects of antipsychotic medication and the consequence of this for long-term mortality risk in patients with schizophrenia remained unrevealed. Aggregate findings of four studies suggested a noteworthy association between patients who did not use antipsychotic medication and an increased long-term mortality risk. Validation of our results and reasons for these patients to be prone for premature mortality need further research. Uniform units of cumulative exposure measurement and reporting causes of death are required to understand clinical implications.

ACKNOWLEDGEMENT

We thank J.G. Daams, clinical librarian of the Academic Medical Center, for help with the literature search. We also thank Richard Hayes who kindly supplied extra data. Jentien Vermeulen received a PhD-Scholarship in 2015 from the Academic Medical Center of Amsterdam.

CONFLICTS OF INTEREST

Lieuwe de Haan received an investigator initiated grant from E. Lilly in 2003. Other authors have declared that there are no conflicts of interest in relation to the subject of this study.

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SUPPLEMENTARY MATERIAL

SUPPLEMENT 1. SEARCH STRATEGY MEDLINE, EMBASE, PSYCHINFO

20160229 Medline

exp schizophrenia/ or schizophrenic psychology/
(schizophreni* or severe mental illness).ab,jw,kf,ti
or/1-2 [schizophrenia]
exp Dopamine Antagonists/ or exp antipsychotic agents/
(anti psychotic* or antipsychotic* or neuroleptic*).ab,kf,ti
(olanzapine or Zyprexa or Clozapine or Clozaril or leponex or Quetiapine or Seroquel or Risperidone or Risperdal or Chlorpiprazine or Perphenazine or perfenazine or Trilafon or Pimozide or Mozep or Pimodac or Aripiprazole or Abilify or Lurasidone Hydrochloride or Latuda or Haloperidol or Haldol or Penfluridol or Semap or Flumap or pipamperone or carpiperone or floropipamide or fluoropipamide or Flupenthixol or Depixol or Fluanxol or Sulpiride or Dogmatil or Dolmatil or Eglonyl or Espiride or Modal or Prometar or Sulpor or Chlorpromazine or Thorazine or Largactil or Amisulpride or Amazeo or Amipride or Amival or Solian or Soltus or Sulpitac or Sulprix or Zuclopenthixol or Cisordinol).ab,kf,ti
or/4-6 [antipsychotics]
exp mortality/ or survival analysis/ or kaplan-meier estimate/ or suicide/ or suicide, assisted/ or exp heart arrest/
mortality.fs
(mortalit* OR death* or (fatal adj3 outcome?) or fatality or "years of life lost" or suicide OR Kaplan* OR survival or surviving or survivor?).ab,kf,ti
(cardiac arrest or cardiac infarct* or heart attack? or heart arrest or cardiovascular stroke or myocard* infarct*).ab,kw,ti
or/8-11 [mortality outcomes]
3 and 7 and 12
(NCT02220504 or NCT00493233 or NCT00222807).mp.
13 or 14
animals/ not humans/
15 not 16
..dedup 17

20160229 Embase

exp *schizophrenia/
(schizophreni* or severe mental illness).ab,jx,kw,ti
or/1-2 [schizophrenia]
exp *dopamine receptor blocking agent/ or *neuroleptic agent/ or neuroleptic agent/ dt or *chlorpromazine/ or *flupentixol/ or *haloperidol/ or *penfluridol/ or *pimozide/ or *pipamperone/ or *atypical antipsychotic agent/ or *amisulpride/ or *aripiprazole/ or *clozapine/ or *olanzapine/ or *paliperidone/ or *quetiapine/ or *risperidone/ or *sulpiride/ or schizophrenia/dt
(anti psychotic* or antipsychotic* or neuroleptic*).ab,kw,ti

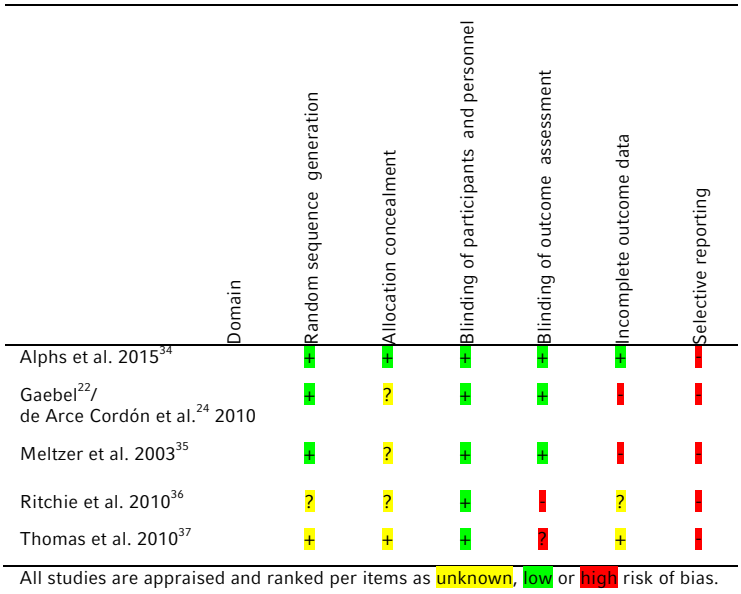
(olanzapine or Zyprexa or Clozapine or Clozaril or Quetiapine or Seroquel or Risperidone or Risperdal or Perphenazine or perfenazine or Trilafon or Pimozide or Mozep or Pimodac or Aripiprazole or Abilify or Lurasidone Hydrochloride or Latuda or Haloperidol or Haldol or Penfluridol or Semap or Flumap or pipamperone or carpiperone or floropipamide or fluoropipamide or Flupenthixol or Depixol or Fluanxol or Sulpiride or Dogmatil or Dolmatil or Eglonyl or Espiride or Modal or Prometar or Sulpor or Chlorpromazine or Thorazine or Largactil or Amisulpride or Solian or Zuclopenthixol or Cisordinol).ab,kw,ti
("132539-06-1" or "5786-21-0" or "111974-72-2" or "106266-06-2" or "58-39-9" or "2062-78-4" or "129722-12-9" or "52-86-8" or "26864-56-2" or "1893-33-0" or "2709-56-0" or "23672-07-3" or "50-53-3" or "71675-85-9" or "1246833-58-8").ab,rn
or/4-7 [antipsychotics]
*mortality/ or *cancer mortality/ or *cardiovascular mortality/ or *premature mortality/ or *standardized mortality ratio/ or *survival/ or exp *cancer survival/ or *long term survival/ or *overall survival/ or *post treatment survival/ or *short term survival/ or *survival factor/ or *survival prediction/ or *survival rate/ or *survival time/ or *suicide/ or exp *heart arrest/ (mortalit* OR death* or (fatal adj3 outcome?) or fatality or "years of life lost" or suicide OR Kaplan* OR survival or surviving or survivor?).ab,kw,ti
(cardiac arrest or cardiac infarct* or heart attack? or heart arrest or cardiovascular stroke or myocard* infarct*).ab,kw,ti
or/9-11 [mortality outcomes]
3 and 8 and 12
(NCT02220504 or NCT00493233 or NCT00222807).ab,cn,kw,ti
13 or 14
(animal/ or animal experiment/ or animal model/ or nonhuman/ or rat/ or mouse/ or (rat or rats or mouse or mice).ti.) not human/
15 not 16
..dedup 17

20160229 PsycINFO

schizophrenia/ or acute schizophrenia/ or catatonic schizophrenia/ or paranoid schizophrenia/ or process schizophrenia/ or "schizophrenia (disorganized type)"/ or schizophreniform disorder/ or undifferentiated schizophrenia/
(schizophreni* or severe mental illness).ab,jx,id,ti
"3213".cc
or/1-3 [schizophrenia]
neuroleptic drugs/ or aripiprazole/ or clozapine/ or olanzapine/ or quetiapine/ or risperidone/ or sulpiride/ or haloperidol/ or dopamine antagonists/ or chlorpromazine/ or thioridazine/ or Perphenazine/ or pimozide/
(anti psychotic* or antipsychotic* or neuroleptic*).ab,id,ti
(olanzapine or Zyprexa or Clozapine or Clozaril or leponex or Quetiapine or Seroquel or Risperidone or Risperdal or Chlorpiprazine or Perphenazine or perfenazine or Trilafon or Pimozide or Mozep or Pimodac or Aripiprazole or Abilify or Lurasidone Hydrochloride or Latuda or Haloperidol or Haldol or Penfluridol or Semap or Flumap or pipamperone or carpiperone or floropipamide or fluoropipamide or Flupenthixol or Depixol or Fluanxol or Sulpiride or Dogmatil or Dolmatil or Eglonyl or Espiride or Modal or Prometar or Sulpor or Chlorpromazine or Thorazine or Largactil or Amisulpride or Amazeo or Amipride or Amival

or Solian or Soltus or Sulpitac or Sulprix or Zuclopenthixol or Cisordinol).ab,id,ti
or/5-7 [antipsychotics]
"death and dying"/ or exp suicide/
(mortalit* OR death* or (fatal adj3 outcome?) or fatality or "years of life lost" or suicide OR Kaplan* OR survival or surviving or survivor?).ab,id,ti
(cardiac arrest or cardiac infarct* or heart attack? or heart arrest or cardiovascular stroke or myocard* infarct*).ab,id,ti
or/9-11 [mortality outcomes]
4 and 8 and 12
(NCT02220504 or NCT00493233 or NCT00222807).mp.
13 or 14
limit 15 to ("0100 journal" or "0110 peer-reviewed journal" or "0400 dissertation abstract")

Supplement 2. Quality assessment of included studies with randomized design



All studies are appraised and ranked per items as unknown, low or high risk of bias.

Supplement 3. Quality assessment of included studies with cohort design

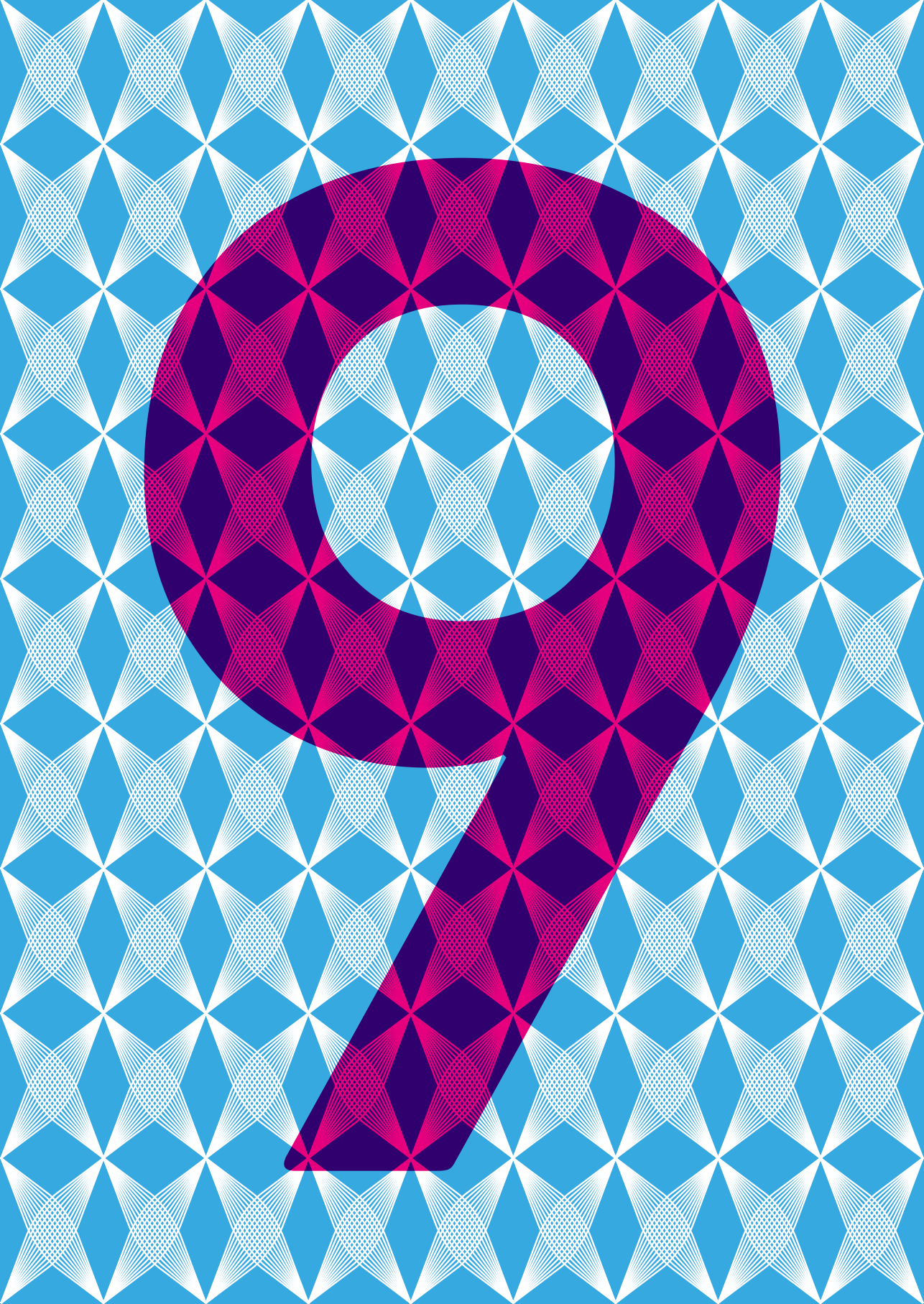
Domain	Selection (out of 4)	Comparability (out of 2)	Outcome (out of 3)	**Total number of stars (out of 9)**
Girgis et al. 2011[32]	***	**	**	**7**
Kasper et al. 2010[23]	***		*	**4**
Montout et al. 2002[38]	****		**	**6**
Ran et al. 2015[39]	**		***	**5**
Cullen et al. 2012[40]	****		***	**7**
Deslandes et al. 2015[41]	**		**	**4**
Hayes et al. 2014[25]	****	*	**	**7**
Kelly et al. 2010[42]	*	*	**	**4**
Pridan et al. 2014[27]	**		**	**4**
Tenback et al. 2012[43]	***		**	**5**
Tiihonen et al. 2009[14]	****	*	***	**8**
Torniainen et al. 2015[26]	***	**	***	**8**

*Each star represents a positive score in that particular domain

Supplement 4. Quality assessment of included studies with case-control design

Domain	Selection (out of 4)	Comparability (out of 2)	Exposure (out of 3)	**Total number of stars (out of 9)**
Chen et al. 2015[44]	****	**	**	**8**
Sernyak et al. 2001[45]	****	**	*	**7**
Taylor et al. 2009[46]	**	*		**3**

*Each star represents a positive score in that particular domain



CLOZAPINE AND LONG-TERM MORTALITY RISK IN PATIENTS WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF STUDIES LASTING 1.1-12.5 YEARS

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Accepted for publication in Schizophrenia Bulletin

ABSTRACT

Introduction: Patients with schizophrenia have an elevated mortality risk compared to the general population, with cardiovascular-related deaths being the leading cause. The role of clozapine use in the long-term mortality risk is unclear. While clozapine treatment may increase the risk for cardiovascular mortality, it may have protective effects regarding suicidal behavior.

Methods: We systematically searched EMBASE, MEDLINE and PsycINFO and reviewed studies that used a long-term follow-up (i.e., >52 weeks) and reported on mortality in adults diagnosed with schizophrenia-spectrum disorders who had received clozapine treatment.

Results: Altogether, 24 studies reported on 1327 deaths from any causes during 217 691 patient years in patients treated with clozapine. The unadjusted mortality rate in 22 unique samples during a follow-up of 1.1-12.5 (median=5.4) years was 6.7 (95% confidence interval (CI)=5.4-7.9) per 1000 patient years. Long-term, crude mortality rate ratios were not significantly lower in patients ever treated with clozapine during follow-up, but significantly lower in patients continuously treated with clozapine compared to patients with other antipsychotics (mortality rate ratio=0.56, 95%CI=0.36-0.85, p-value=0.007). Few studies reported on rates of long-term cause-specific mortality (suicide and ischemic heart disease), which showed no significant difference in patients using clozapine compared to patients using other antipsychotics. Statistical heterogeneity was high in all analyses.

Discussion: Continuous clozapine treatment in schizophrenia patients was associated with a significantly lower long-term all-cause mortality rate compared to other antipsychotic use. These findings, combined with the known efficacy of clozapine, give reason to re-evaluate the hesitancy to prescribe clozapine in regular care settings.

1. INTRODUCTION

Patients with schizophrenia-spectrum disorders have an estimated 2.5 times elevated mortality risk compared to the general population[1,2] and live 15-25 years shorter.[3,4] The main cause of death in these patients has been related to cardiovascular diseases.[5] Considering the efficacy of antipsychotics, while also acknowledging their potential role in elevating the risk of developing cardiovascular diseases, the benefit- risk ratio considering mortality risk has been equivocal.[6] Clozapine is a unique antipsychotic agent with superior efficacy in patients with schizophrenia who are treatment-resistant[7-9] or have suicidal ideations and behaviour.[10]

The question of long-term mortality risk is of special clinical interest for patients treated with clozapine. In 1975, clozapine was immediately withdrawn from the international markets after reports of agranulocytosis leading to death, but was reintroduced around 1990 due to its efficacy with strict blood monitoring requirements.[11] Consequently, the use of clozapine is in many countries restricted to patients with schizophrenia who have not adequately responded to at least 2 other antipsychotics.[12] Apart from agranulocytosis, there are several reasons why clozapine might be associated with higher long-term mortality compared to other antipsychotics. For instance, clozapine is - compared to other antipsychotics - associated with the highest risk of metabolic adverse effects, such as weight gain, dyslipidaemia and hyperglycemia.[13] All of these cardiometabolic adverse effects are part of the metabolic syndrome that has been associated with cardiovascular morbidity and mortality risk, which is the main cause of premature death in patients with schizophrenia.[13] Nevertheless, several large cohort studies have shown a decreased risk of death for clozapine compared to other antipsychotics, but this risk reduction was not always statistically significant.[3,14,15]

On the other hand, clozapine has proven to be effective in the prevention of suicide, as shown by a meta-analysis of long-term studies focusing on suicide (n= 240 564), which demonstrated a 2.9-fold (95%CI=1.5-5.7) overall risk reduction of completed suicide during long-term exposure to clozapine.[16]Despite a meta-analysis[6] and a systematic review[17] each having investigated the association between the use of antipsychotics and long-term mortality there are, to the best of our knowledge, no systematic reviews or meta-analyses that focus on clozapine and its association with long-term mortality risk from all causes. Consequently, it is currently uncertain to what degree clozapine might play a role in the all-cause mortality excess of patients diagnosed with schizophrenia in the long-term.

In summary, whether the benefits of enhanced clinical efficacy outweigh the potential long-term harmful side-effects of clozapine remains an open question. Performing a systematic review and meta-analysis that investigates the long-term mortality rates of clozapine can help provide answers on this clinically relevant topic. Therefore, we aimed to study (i) the long-term mortality rates and (ii) specific causes of death in patients with schizophrenia-spectrum disorders treated with clozapine compared to patients treated with other antipsychotics or no antipsychotics.

2. METHODS

This review was performed according to the guidelines of the PRISMA statement.[18] The protocol was registered in the PROSPERO database under registration number CRD42017069390. The search strategy was developed and conducted with the help of a clinical librarian (see supplement 1). Relevant studies were identified through searching MEDLINE, EMBASE and PsycINFO from database inception through 27th of June 2017. The reference lists of retrieved articles were hand searched (forward and backward tracking of the literature up to March 2018) to identify additional eligible studies.

2.1 Selection of studies

Two reviewers (M.v.d.K. and G.v.R.) independently screened titles and abstracts to identify eligible studies. The following inclusion criteria were used: The study (1) included patients ≥18 years old diagnosed with schizophrenia-spectrum disorders (including schizophrenia, schizoaffective disorder, schizophreniform disorder and psychotic disorder not otherwise specified); (2) patients ever or currently used clozapine (at any dose); (3) had mortality as an outcome; (4) was an original research paper that used a follow-up design longer than 52 weeks). The first 30 conflicts in study inclusion were resolved in consensus meetings and since overlap was high, other conflicts were reviewed by one author (M.v.d.K.). The full article was obtained for further inspection, in case a clear decision concerning inclusion criteria could not be made during abstract screening. Subsequently, studies were excluded by several authors (G.v.R., M.v.d.K., A.S. and C.C.) during full-text reading if: the study (1) had a follow-up duration of ≤52 weeks, and/or (2) only cause-specific mortality was available even after contacting the authors (e.g., several studies reported the number of patients who died due to myocarditis during treatment with clozapine, but did not provide the total number of deaths). In order to obtain homogenous samples, authors from articles that included >10% patients diagnosed with other diagnoses (e.g., neurological diseases, cognitive disorders) were contacted to request number of death within the patient group diagnosed with a schizophrenia-spectrum disorder (in case these numbers were not available articles were excluded).

2.2 Data extraction

Data were extracted by 2 independent researchers (J.V. and M.v.d.K.) and accuracy was discussed in regular meetings. Corresponding authors were contacted to provide additional data when studies lacked sufficient information (which was the case for six studies). We extracted the following data: country of study, years of data collection, follow-up in years or patient years, sample source, characteristics of population (e.g., elderly, high risk of suicide or treatment-resistant), diagnoses and diagnostic assessment, primary and secondary outcome(s), comparison group(s), sample size (clozapine and comparison group(s)), number of death (all-cause and cause-specific), death assessment, statistical method for adjusting for group differences, medication details (dosage, length of exposure and concomitant medications), age at inclusion, sex, and if possible information regarding confounders (e.g., duration of illness, medical history, smoking status). In the case of overlapping samples, the study with the smallest sample size was excluded. Risk of bias of the studies was assessed on outcome level with the Cochrane Risk of bias tool for randomized studies or the Newcastle Ottawa scale (NOS) for observational studies (range=0-9).[19,20] For observational

studies with an ineligible comparison group or convenience samples, we used the NOS (range=0-6)[19] without the items regarding comparison groups. A NOS score of ≤5 was deemed as indicating high risk of bias.

2.3 Statistical analyses

2.3.1 Mortality rates in patients who used clozapine

All statistical analyses were performed using Comprehensive Meta-Analysis, version 3.0. To determine all-cause mortality rates, we calculated crude rates for patients exposed to clozapine per 1000 patient years. The following formula was used to estimate patient years if not provided by the authors: [(Number of people at risk at the beginning of the time interval + number of people at risk at the end of the time interval) / 2] x (number of years in the time interval). The number of patients at risk at the end of the time interval was the total sample size minus the number of deaths and the number of patients lost to follow-up. All studies that reported data on number of deaths for patients treated with clozapine were used to pool a one armed summary mortality rate per 1000 patient years and presented in a forest plot using a DerSimonian-Laird random-effects model.[21] Between-study heterogeneity was assessed using Cochran's Q and the I^2–statistic. According to convention, a chi squared test <0.05 or I^2 ≥50% indicates significant heterogeneity.[22] Publication bias was visually inspected by a funnel plot and statistically assessed using an Egger's test if applicable. A comprehensive series of sensitivity analyses and subgroup analyses were performed to examine possible explanations for the observed heterogeneity. Additionally, meta-regression analysis was applied to examine the potential effect of continuous moderators (mean sample age, % males, % patients diagnosed with schizophrenia, risk of bias based on the NOS score of cohort studies) if reported by at least 10 studies, as suggested by Borenstein et al.[21]

2.3.2 Mortality in patients who ever or continuously used clozapine during follow-up compared to those treated with other or no antipsychotics

Furthermore, we calculated for a subset of all included cohort studies that had a control group, all-cause mortality numbers and patient years not only for clozapine-exposed patients, but also exposure to other antipsychotics and exposure to no antipsychotics. Analyses were further divided into studies that included patients who continuously or ever used clozapine during follow-up. This decision was based on previous literature[23] and the assumption that patients who were ever exposed to clozapine during follow-up but discontinued treatment (e.g., due to a lack of clinical response or intolerability) would likely have a higher mortality risk than those who continued clozapine during the entire follow-up period. Group comparisons were conducted for studies that included: i) clozapine versus other antipsychotics, or ii) clozapine versus no antipsychotics. If possible, results were pooled and presented in a forest plot using a DerSimonian-Laird random-effects model when 3 or more studies were available.[21]

2.3.3 Cause-specific mortality for clozapine users

The studies that also reported on cause-specific mortality were included to perform one-armed meta-analyses of pooled cause-specific mortality rates (i.e., suicide and death due to ischemic heart disease). These 2 causes were selected in line with the largest previously published study so far.[3] Again, whenever possible, analyses were further divided into studies that included patients who continuously or ever used clozapine during complete follow-up.

3. RESULTS

3.1 Study selection

The initial search yielded 11 284 articles, of which 295 remained after title and abstract screening. After full-text reading 273 studies were excluded and 2 articles were added by forward tracking. Most of the excluded articles had no assessment of mortality or an inadequate format (i.e., conference papers). Ten overlapping samples were removed, resulting in 24 studies and 22 unique samples eligible for meta-analysis.[3,10,14,23-43] Details of the selection process are shown in Figure 1.

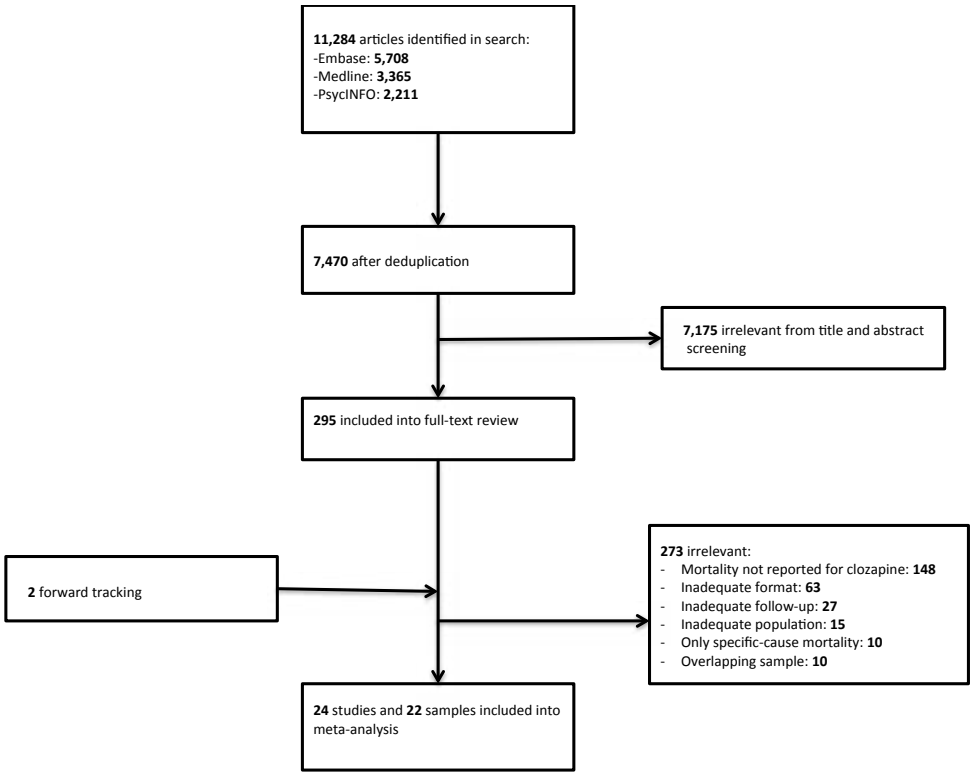

Figure 1. Flowchart of study selection

3.2 Study characteristics

Table 1 summarizes the 24 study characteristics by type of study design.[3,10,14,23-43] One study had an overlapping sample and was excluded from the all-cause mortality analysis, but could be included in the analyses with a comparison group.[27] Two studies had an overlapping sample: one of these studies provided data regarding all-cause mortality[32], while the other study[31] provided cause-specific mortality data and was therefore only used in the analyses regarding cause-specific mortality. Considerable differences existed between studies regarding methodological and clinical characteristics (e.g., study designs and patient subgroups). We included one randomized controlled trial and 23 observational studies.

Most of the studies (n=19) originated from Western countries. The follow-up duration of all included studies ranged from 1.1 to 12.5 (median=5.4) years (see Table 1). The selected studies primarily included patients with a diagnosis of schizophrenia (n=7) or schizophrenia spectrum disorders (n=15) and 3 studies included <10% patients with bipolar disorder or unspecified diagnosis.[33,35,38] One corresponding author provided additional data for patients with schizophrenia and schizoaffective disorder, which made it possible to exclude patients with other diagnoses from the results.[26] The reported data regarding length of exposure to clozapine varied extensively between studies. For example, some studies provided mortality for continuous users during the entire length of follow-up[3,14,23,27,32], whereas the remaining studies reported 'ever' use during follow-up with discontinuation rates. The mean age across all studies was 49.1 (SD 3.2) (range: 28.7-67.4) years, and some studies only presented the age of the participants in strata. All-cause mortality was the primary outcome in 6 studies[3,14,23,26,30,32] and several specific causes of death were the primary outcome in 4 studies.[26-29] The risk of bias of the studies was assessed as 45.8% being low (NOS >5) and 13 studies (54.2%) being high (supplement 2 and 3).

3.3 Mortality rates in patients who used clozapine

A total of 1327 deaths from any causes during 217 691 patient years were reported for patients with schizophrenia spectrum disorders across 24 samples. Mortality rates differed widely, ranging from 0 to 41.0 deaths per 1000 patient years. A forest plot with the pooled summary rate 6.7 (95% CI=5.4-7.9) per 1000 patient years is shown in Figure 2. The Egger's test suggested some evidence of publication bias (β=1.64, SE=0.61, p-value= 0.015). Seven subgroup analyses were performed (Table 2). Large difference in the certainty of continuous exposure to clozapine during the whole period of follow-up was found between studies (e.g., some studies included patients who filled ≥1 prescription of clozapine or used clozapine ever during follow-up). The subgroup of studies that included patients who continuously used clozapine during follow-up showed a pooled all-cause mortality rate of 6.7 (95%CI=4.6-8.9) per 1000 patient years. Besides, the subgroup of patients ever exposed to clozapine showed a pooled mortality rate of 7.1 (95%CI=5.1-9.0) per 1000 patients years (p=0.838). The subgroup meta-analyses of studies with a minimum sample size and patient years or a minimum of 100 patients and a minimum of 5 years follow-up also revealed high heterogeneity levels. After visual inspection of the funnel plot of all studies, we progressively excluded studies with highest and lowest values, but the resulting pooled rate estimates did not yield low heterogeneity levels (I^2<50%).

Categorical sensitivity analyses showed no significant results. The following variables did not significantly moderate mortality rates for patients treated with clozapine: on clozapine ever or continuously during follow-up (p=0.838); continent (p=0.227); treatment-resistant (p=0.103); treatment setting (p=0.621); risk of bias (p=0.749); diagnosis (p=0.087); year of start of the data collection (p=0.193); sample size in patient years (p=0.463) and years of follow-up (p=0.905) (Table 2). Meta-regression with the variables % of males, mean age of the total sample and the NOS score of cohort studies also revealed no significant differences in mortality of clozapine users. A significant result was found for the variable % of patients diagnosed with schizophrenia, indicating a lower mortality rate of clozapine users in studies with a higher percentage of patients diagnosed with schizophrenia only and less patients with schizophrenia related disorders (p=0.032, Table 3).

Table 1. Study characteristics of all 24 studies included in the current study

Authors (Year)	Country	Total Sample Size (n), Source	Length of Follow-up in Years (Years of Data Collection)	DSM/ ICD	Diagnoses (n), Subgroup Details	Comparator Group	Mean Age	Male (%)
Randomized trial, open label								
Meltzer et al.[10]	Multinational	980, n.s.	2 (1998-2001)	DSM	Schizophrenia (609), schizoaffective (371); High risk suicide	Olanzapine	37.1	602 (61.4)
Cohort studies								
Girgis et al.[24]	China	160, medical records	9 (1995-2007)	DSM	Schizophrenia (122), schizophreniform (38); in- and outpatients, first episode, treatment-naive patients	Chlorpromazine	28.7	84 (52.2)
Dickson et al.[25]	Canada	26, n.s.	3 (n.s.)	DSM	Schizophrenia (26); in- and outpatients, treatment-resistant	Continuers, discontinued, and interrupted clozapine users[a]	31.8	24 (92.3)
Hayes et al. [26]	UK	14754[b], medical records	3 (2007-2011)	ICD	Schizophrenia (9437), bipolar disorder (4512)[b], schizoaffective (805) In- and outpatients, newly prescribed clozapine	First- and second generation antipsychotics or no antipsychotics	43.2[b]	7985 (54.1)[b]
Hennessy et al. [27]	USA	12471[c] , database	1.1[c] (1993-1996)	n.s.	Schizophrenia (95632); outpatients, individuals with limited resources	Other antipsychotics or patients without schizophrenia[c]	n.s. (median age group 35-44)	47812 (50.0)
Kelly et al. [28]	USA	1686, database	6-10 (1994-2000)	DSM	Schizophrenia (964), schizoaffective (561), psychosis NOS (161)	Risperidone	39.0[d]	1059 (62.8)
Modai et al. [29]	Israel	5479, medical records	6.7 (1991-1997)	ICD	Schizophrenia (n.s.); inpatients	Other antipsychotics	n.s.	n.s.
Pridan et al. [30]	Israel	527, medical records	5 (2007-2012)	DSM	Schizophrenia (527); elderly inpatients, treatment-resistant	Other antipsychotics (first and second generation)	67.4	245 (46.5)
Ringbäck et al. [31]	Sweden	26046, database	6 (2006-2011)	ICD	Schizophrenia (n.s.), schizoaffective (n.s.); in- and outpatients	First and second generation antipsychotics or no antipsychotics	48.4	14397 (55.3)
Taipale et al. [32]	Sweden	29823, database	5.7 (2006-2013)	ICD	Schizophrenia (n.s.), schizoaffective (n.s.) In- and outpatients	Other antipsychotics (first and second generation) and no antipsychotics	44.9	16999 (57)

Table continued on the next page

Table 1. continued

Tiihonen et al. [3]	Finland	66881, database	8.6[e] (1996-2006)	ICD	Schizophrenia (66881); outpatients, inpatients deaths were excluded[f]	Other antipsychotics and no antipsychotics[f]	51.0[f]	30803[f] (46.0)
Walker et al. [14]	USA	67072[g], database	1.47 (1991-1993)	n.s.	n.s.; in- and outpatients	Current, recent or past clozapine users[h]	n.s. (median age group 35-39)	n.s.
Wimberley et al.[23]	Denmark	2370, database	6.8[i] (1996-2013)	ICD	Schizophrenia and related disorders (2370); in- and outpatients, treatment-resistant	Other antipsychotics or no antipsychotics	n.s.(median age 30.1)	1284 (54.2)
Case-control studies								
Mela and Depiang [33]	Canada	98, medical records	2 (1984-2012)	DSM	Psychotic disorder and related disorders (98) Offenders	Other antipsychotics (first and second generation)	n.s.	94 (95.9)
Schulte et al. [34]	Netherlands	94, medical records	12.3 (1989-2010)	n.s.	Schizophrenia (81), schizoaffective (13); in- and outpatients, patients without diabetes mellitus at start of follow-up	Other antipsychotics	39.0	74 (78.7)
Taylor et al. [35]	UK	779, database	4.67 (2002-2006)	n.s.	Schizophrenia (n.s.), schizoaffective (n.s.), bipolar disorder (n.s.)[j], other (n.s.)[j]	Risperidone long-acting injection	36.4[j]	n.s.
Convenience sample studies								
Gaertner et al. [36]	Germany	23, n.s.	3.8 (1993-n.s.)	ICD	Schizophrenia (23) Outpatients, patients with complete remission of positive symptoms	No comparison	40.0	18 (78.2)
Khan et al. [37]	Australia	503, n.s.	9 (2009-2015)[k]	n.s.	Schizophrenia (503); outpatients, treatment-resistant	No comparison	44.0	397 (78.9)
Lee et al. [38]	Canada	94, database	1.4 (2009-2010)	n.s.	Schizophrenia (75), schizoaffective (17), bipolar disorder (1), delusional disorder (1); patients without anemia prior to clozapine initiation	No comparison	35.9	68 (72.3)
Munro et al. [39]	UK/Ireland	12720, database	8 (1990-1997)	n.s.	Schizophrenia (12760) Treatment-resistant	No comparison	n.s. (modal age 25-35)	8533 (67.1)
Srivastava et al. [40]	India	25, n.s.	3 (1994-1997)	ICD	Schizophrenia (25); treatment-resistant	No comparison	28.8	18 (72.0)

Davis et al. [41]	USA	320, database	n.s.[l] (1993-2007)	DSM	Schizophrenia (n.s.), schizoaffective (n.s.); in- and outpatients, veterans with treatment intolerance or significant risk of suicidal behavior	No comparison	48.0	292 (91.3)
Lindström et al. [42]	Sweden	96, recruited by clinicians	12.5 (1974-1986)	ICD	Schizophrenia (89), schizoaffective (7); in- and outpatients, treatment-resistant or with distressing side effects	No comparison	36.1	64 (66.7)
Rimon et al. [43]	Finland	103, medical records	3.4 (n.s.)	DSM	Schizophrenia (96), schizoaffective (7); in- and outpatients, treatment-resistant	No comparison	36.9	59 (57.3)

Abbreviations: n.s.= not specified; DSM= Diagnostic System of Mental disorders; ICD= International Classification of Diseases.
[a] Comparison group not eligible for our analyses.
[b] Patients with bipolar disorder were excluded from our analyses.
[c] Total sample size of the complete study included patients diagnosed with glaucoma and psoriasis. Only patients with schizophrenia were used in our analyses. As length of follow-up was not provided, we calculated the length of follow-up for patients using clozapine by dividing the patient years by number of patients using clozapine.
[d] Mean age of clozapine group.
[e] Mean follow-up for patients with antipsychotics.
[f] Inpatients were excluded from the analyses.
[g] Total sample size, patients with ages 55-94 years were excluded.
[h] This study was used in the first analyses about mortality rates in clozapine users.
[i] Median follow-up.
[j] Diagnoses and mean age only specified for discontinuers.
[k] Mean follow-up reported in study does not correspond to the years of data collection.
[l] No mean follow-up reported, the mean duration of clozapine exposure was 5.7 years for the patients who were deceased.

3.4 Mortality in patients who ever or who continuously used clozapine during follow-up compared to those treated with other or with no antipsychotics

A total of 7304 deaths in 630 368 patient years were reported in eight cohort studies comparing patients exposed to clozapine to patients exposed to other antipsychotics. Studies including continuous users had a median follow-up of 7.2 years and the studies including patients who ever used clozapine during follow-up had a median length of 5.9 years. Crude mortality rate ratios are shown in Figure 3 and 4. The pooled mortality rate ratio was 0.56 (95%CI=0.36-0.85, p=0.007, k=4), indicating a lower mortality rate for patients continuously exposed to clozapine compared to patients continuously exposed to other antipsychotics. Statistical heterogeneity was high (Q=39.2, p<0.001, I^2=92.3), but the Egger's test showed no evidence of publication bias (β=-0.44, SE=5.28, p-value= 0.940). The pooled rate ratio of studies including patients who ever used clozapine during follow-up compared to other antipsychotics was not significant (0.74 (95%CI=0.38-1.45, p=0.376, k=4) (Figure 4). In the studies that compared patients on continuous or ever use of clozapine treatment during follow-up to patients without the use of antipsychotics, a significant pooled rate ratio of 0.34 was yielded in favour of patients using clozapine (95%CI=0.19-0.62, p=<0.001, k=3) (see supplement 4). Due to the limited data, meta-regression and sensitivity analyses in continuous and ever users during follow-up could not be conducted. To illustrate this, we summarized the adjusted all-cause mortality ratios of clozapine users compared to other antipsychotics from the 4 largest samples included (see supplement 5). Only one of these 4 studies[3,23,27,31] showed a significantly lower adjusted mortality rate in continuous clozapine users compared to perphenazine users (adjusted hazard ratio [aHR]= 0.74, 95%CI=0.60-0.91)[3].

Study name	Comparison	Total	Rate	Lower limit	Upper limit	Z-Value	p-Value
Meltzer et al. 2003	RCT	12 / 913	0.0131	0.006	0.021	3.464	0.001
Girgis et al. 2011	Cohort	2 / 644	0.0031	-0.001	0.007	1.414	0.157
Dickson et al. 1998	Cohort	3 / 74	0.0405	-0.005	0.086	1.732	0.083
Hayes et al. 2015	Cohort	14 / 2481	0.0056	0.003	0.009	3.742	0.000
Kelly et al. 2010	Cohort	92 / 8304	0.0111	0.009	0.013	9.592	0.000
Modai et al. 2000	Cohort	10 / 3725	0.0027	0.001	0.004	3.162	0.002
Pridan et al. 2015	Cohort	8 / 195	0.0410	0.013	0.069	2.828	0.005
Taipale et al. 2017	Cohort	161 / 14460	0.0111	0.009	0.013	12.689	0.000
Tiihonen et al. 2009	Cohort	182 / 32000	0.0057	0.005	0.007	13.491	0.000
Walker et al. 1997	Cohort	396 / 85399	0.0046	0.004	0.005	19.900	0.000
Wimberley et al. 2017	Cohort	32 / 5345	0.0060	0.004	0.008	5.657	0.000
Mela et al. 2016	Case-control	5 / 125	0.0400	0.005	0.075	2.236	0.025
Schulte et al. 2016	Case-control	18 / 1154	0.0156	0.008	0.023	4.243	0.000
Taylor et al. 2009	Case-control	21 / 2471	0.0085	0.005	0.012	4.583	0.000
Gaertner et al. 2001	Convenience sample	1 / 80	0.0125	-0.012	0.037	1.000	0.317
Khan et al. 2017	Convenience sample	29 / 4527	0.0064	0.004	0.009	5.385	0.000
Lee et al. 2015	Convenience sample	2 / 132	0.0152	-0.006	0.036	1.414	0.157
Munro et al. 1999	Convenience sample	144 / 30973	0.0046	0.004	0.005	12.000	0.000
Srivastava et al. 2002	Convenience sample	1 / 66	0.0152	-0.015	0.045	1.000	0.317
Davis et al. 2014	Convenience sample	24 / 2000	0.0120	0.007	0.017	4.899	0.000
Lindström et al. 1989	Convenience sample	4 / 1156	0.0035	0.000	0.007	2.000	0.046
Rimon et al. 1994	Convenience sample	0 / 350	0.0014	-0.003	0.005	0.707	0.480
			0.0067	0.005	0.008	10.563	0.000

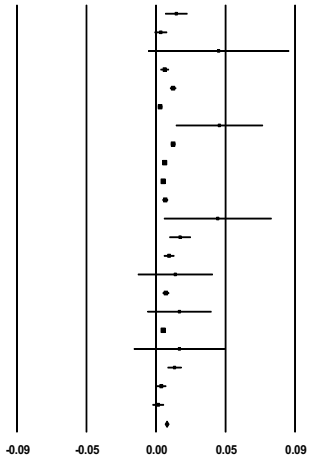

Figure 2. Crude mortality rates for clozapine users. *Heterogeneity:* Q=133.7, *p*-value=<.001, I^2=84.3.
Abbreviations: RCT: Randomized Controlled Trial. *Total*= number of death/ number of patient years

Table 2. Meta-analysis of mortality rate in patients treated with clozapine, including subgroup and sensitivity analyses

	Number of samples	Total number of deaths	Total number of Patient Years	Number of deaths per Patient Year	Lower 95% CI	Upper 95% CI	I^2 (%)
Mortality rate in patients treated with clozapine continuously or ever during follow-up (main analysis)	22	1161	196574	0.0067	0.0054	0.0079	84.3
Subgroup analysis							
On clozapine ever during follow-up	18	390	59370	0.0071	0.0051	0.0090	78.8
On clozapine continuously during follow-up	4	771	137204	0.0067	0.0046	0.0089	94.4
All studies with a comparator group using other antipsychotics	8	523	75339	0.0066	0.0042	0.0090	93.4
On clozapine ever during follow-up and other antipsychotic comparator group	4	124	14705	0.0077	0.0020	0.0133	92.5
No antipsychotic comparator group	3	207	22286	0.0077	0.0039	0.0115	89.0
>100 patients, > 500 patient years	12	1,117	192598	0.0069	0.0056	0.0082	89.7
>100 patients, >5 years follow-up	5	477	63834	0.0073	0.0044	0.0102	94.1
Categorical sensitivity analysis (between group p-value)							
On clozapine ever or continuously during follow-up (p=0.838)							
Ever	18	390	59370	0.0071	0.0051	0.0090	78.8
Continuously	4	771	137204	0.0067	0.0046	0.0089	94.4
Continent (p=0.227)							
Asia	4	21	4630	0.0044	-0.0008	0.0096	60.7
Australia	1	29	4527	0.0064	NA	NA	NA
Europe	10	577	90470	0.0064	0.0047	0.0081	85.4
Multicontinental	1	12	913	0.0131	NA	NA	NA
North-America	6	522	96034	0.0104	0.0051	0.0158	89.0
Treatment-resistant (p=0.103)							
Treatment-resistant patients only	7	217	41530	0.0052	0.0032	0.0072	60.0
Other	15	944	155044	0.0074	0.0057	0.0091	88.1
Treatment setting (p=0.621)							
Inpatient only	2	18	3920	0.0191	-0.0181	0.0563	85.6
Outpatient only	3	212	36607	0.0058	0.0050	0.0066	0.0
In- and outpatients	10	654	113036	0.0066	0.0043	0.0090	88.1
Risk of bias* (p=0.749)							
Low	9	900	149171	0.0078	0.0058	0.0099	91.2
High	13	249	43034	0.0058	0.0039	0.0076	69.2
Diagnosis (p=0.087)							
Schizophrenia only	7	196	39640	0.0049	0.0027	0.0071	64.5
Schizophrenia and related disorders	15	965	156934	0.0073	0.0057	0.0089	87.4
Start of study conduct (p=0.193)							
≤1980	1	4	1156	0.0035	NA	NA	NA
1980-1990	4	167	32602	0.0070	0.0015	0.0126	80.4
1991-2000	11	755	138550	0.0064	000048	0.0080	82.7
2001-2010	6	235	24266	0.0054	0.0054	0.0116	76.0
Sample size patient years (p=0.463)							
0-100							
>100	3	5	220	0.0175	0.0000	0.0350	0
>500	4	15	802	0.0202	-0.0005	0.0410	77.0
>1000	2	14	1557	0.0076	-0.0021	0.0174	80.9
>10,000	9	244	31163	0.0073	0.0049	0.0097	84.4
	4	883	162832	0.0063	0.0046	0.0080	94.5
Years of follow-up (p=0.905)							
0-5 years	11	463	92286	0.0069	0.0041	0.0098	62.3
>5 years	4	227	25530	0.0077	0.0032	0.0123	94.3
>7.5 years	5	449	76448	0.0063	0.0045	0.0081	86.7
>10 years	2	22	2310	0.0091	-0.0028	0.0210	88.8

* Risk of bias of the studies was assessed on outcome level with the Cochrane Risk of bias tool for randomized studies or the Newcastle Ottawa scale (NOS, range=0-9) for observational studies. For observational studies with an ineligible comparison group or convenience samples, we used the NOS (range=0-6) without the items regarding comparison groups, with a score of ≤5 indicating high risk of bias.

Table 3. Mixed-effects Meta-Regression of Moderators of mortality rates of patients treated with clozapine

Moderator variable	Number of comparisons	β	95% CI LL	95% UL	P value
% Males	19	0.0001	-0.0000	0.0003	0.072
% patients with schizophrenia	14	-0.0002	-0.0004	-0.0000	0.032
Mean age total sample	17	0.0002	-0.0001	0.0006	0.192
NOS score of cohort studies	10	0.0010	-0.0002	0.0021	0.099

Abbreviations: NOS, Newcastle Ottawa Scale

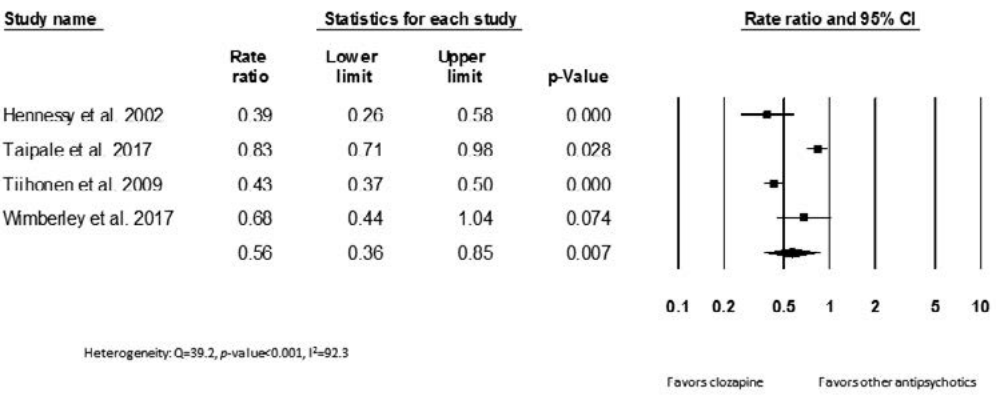

Figure 3. Crude all-cause mortality rate ratios comparing patients who continuously used clozapine during follow up with patients continuously using other antipsychotics. Heterogeneity: Q=39.2, *p*-value<0.001, I^2=92.3

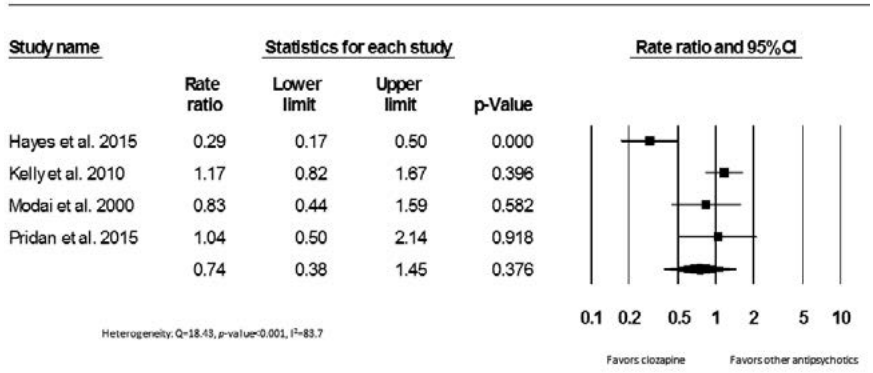

Figure 4. Crude all-cause mortality rate ratios comparing patients who ever used clozapine during follow-up with patients who ever used other antipsychotics. Heterogeneity: Q=18.43, *p*-value<0.001, I^2=83.7

3.5 Cause-specific mortality

Twenty studies reported data on specific causes of death concerning 58.0% (n=5019) of all patients who died. Classification of causes of death was heterogeneous and often incomplete across studies (e.g., cardiovascular-related mortality was defined using different criteria). Subcategorizing data by natural versus unnatural causes was discarded since 2 large cohort studies presented incomplete data by only addressing suicide and/or ischemic heart disease mortality numbers. [3,31] Therefore, we decided to further explore death from suicide and death from ischemic heart disease. Thirteen studies reported data on mortality from suicide. Crude pooled suicide rates are presented in supplement 6, 7 and 8. To summarize, throughout the 13 analysed studies suicide rates ranged widely from 0.00-27.03 suicides per 1000 patient years. A numerical, but non-significantly lower pooled crude suicide rate (p=0.455) was found in patients exposed to clozapine compared to other antipsychotics (supplement 9).[3,29,31]

Death from ischemic heart disease was reported in 9 studies.[3,10,14,25,29,35,36,40,43] We found few studies that reported on rates of long-term cause-specific mortality (suicide and ischemic heart disease) (see supplement 10 and 11). Data about rate ratios for death from ischemic heart disease were reported in only 2 studies and therefore a meta-analyses could not be performed.[3,10] Tiihonen et al. used the largest sample size and found for continuously use of clozapine a non-significant adjusted hazard ratio of 0.78 (95%CI=0.54-1.12) with perphenazine as a reference group.[3]

4. DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis investigating the long-term risk of death from all causes for patients diagnosed with schizophrenia-spectrum disorders that were continuously or ever treated with clozapine during follow-up. The major finding of our study is that although clozapine is known to induce severe side effects, the unadjusted long-term mortality rate during a median of 7 years follow-up in continuous clozapine users was significantly lower compared to those who were continuously treated with other antipsychotics. This finding, combined with the known superior efficacy of clozapine for treatment-resistant schizophrenia,[7-10] is clinically highly relevant and may lead to alleviation of earlier concerns about the mortality risk when switching patients to clozapine.

4.1 Mortality rates for patients continuously or ever treated with clozapine

We found a wide range of mortality rates for schizophrenia patients who were continuously or ever treated with clozapine. By pooling mortality rates, we found an unadjusted mortality rate of 6.7 per 1 000 patient years. This pooled rate is slightly higher than the unadjusted rates that were found in the 2 largest cohort studies that we included.[3,14] Tiihonen et al.[3] and Walker et al.[14] reported unadjusted mortality rate of 5.7 respectively 4.6 per 1000 patient years, respectively. Given the large and international samples that could be included in the current meta-analyses, the provided mortality rate is likely generalizable and a more precise indication of the worldwide 5-year mortality rate in schizophrenia patients treated with clozapine.

4.2 Comparison of mortality in patients continuously or ever treated with clozapine compared to patients treated with other antipsychotics or no antipsychotics

The significantly lower long-term all-cause mortality rate ratio of continuous clozapine users compared to patients treated with other antipsychotics is a new finding. Additionally, the all-cause mortality rate ratio was not statistically significantly different when comparing patients ever treated with clozapine during follow-up compared to patients ever treated with other antipsychotics. Different factors might explain these findings when both results are combined (i.e., significantly lower mortality rates in patients continuously treated with clozapine but non-significant findings in ever treated patients). These findings suggest an exposure-response relationship, meaning that continuous effects of clozapine are most beneficial for prolonging life expectancy and that this effect seems to be diminished or lost when clozapine is discontinued. Another potential explanation could be that patients who were ever treated with clozapine, discontinued treatment due to being unresponsive to clozapine. Consequently, the non-significant findings in the ever-treated subgroup might be a reflection of more severe psychopathology, which may be associated with increased risk for premature mortality. Nevertheless, there are also findings indicating that patients stopping clozapine are at an increased risk of mortality compared to patients never treated with clozapine[23], supporting the notion that clozapine is used in severely ill patients at high risk for mortality and that this protective effect is lost when clozapine is stopped.

A lower mortality risk for schizophrenia patients who are continuously treated with clozapine probably reflects a multifactorial etiology. First of all, clozapine has been found to be highly effective in lowering psychopathological symptoms, which likely increases the level of functioning.[16] Higher levels of functioning could go hand in hand with improvement of several risk factors, such as improved healthy lifestyle and health care seeking behaviours and a higher socio-economic status, which have been clearly associated with a lower risk of mortality.[44-46] Additionally, as mentioned earlier, another possible explanation of a lower mortality risk in clozapine users might be that patients who are prescribed clozapine undergo frequent clinical monitoring (known as performance bias). Performance bias has been mentioned in the light of the improved effectiveness of clozapine (although this was not confirmed in a randomized controlled clinical trial on this topic). [10] Nevertheless, it could be hypothesized that increased monitoring and medical surveillance of cardiometabolic risk factors (e.g., hypertension or hyperglycaemia) or adverse lifestyle behaviours (e.g., smoking) may be one of the mechanisms by which mortality is reduced in patients treated with clozapine, even though they tend to be generally sicker and more severely ill than patients not started on clozapine.

Similarly, the lower mortality observed in clozapine users might also be, at least in part, due to confounding by contraindication, in that a subgroup of patients who already suffer from severe somatic comorbidities (e.g., cardiac comorbidity) and who may therefore be at particularly high risk for mortality may preferentially not be prescribed clozapine. While this potential selection bias excluding a subgroup of patients with severely medical illness may artificially lower the mortality rate in clozapine users, it is unclear how large this group really is. Moreover, it is even more uncertain whether the exclusion of this relatively small group would compensate for the overall greater psychiatric[8] and medical illness severity[44] in treatment-resistant patients who are the subgroup in whom clozapine

is used, whereas the majority of patients on non-clozapine antipsychotics are not as severely ill or treatment refractory.

On the other hand, one could expect a higher risk of mortality in patients who use clozapine compared to other antipsychotics due to confounding by indication (i.e., clozapine is indicated for treatment-resistant patients who are arguably among the most severely ill patients).

This potential confounding could be diminished by survival treatment bias since patients must survive other treatments before clozapine is indicated (i.e., clozapine is not a first-choice treatment and international guidelines advice prescription of clozapine after non-response to 2 other antipsychotics).[47] Additionally, clozapine-treated patients are a subgroup of patients who agree to take this medication requiring special monitoring. Altogether, our findings of a substantially lower long-term all-cause mortality risk in patients continuously treated with clozapine compared to those treated with no or other antipsychotics point toward the fact that the long-term beneficial effects of clozapine outweigh its well documented risks.[13,48] An additional point for consideration is that all of the individual studies using adjusted ratios for patients treated with clozapine also showed a lower, but mostly non-significant difference in mortality risk favouring patients with clozapine treatment.[3,23,27,31] Although, our findings require additional validation with adjustment for important confounders, the current unadjusted findings do not support the hypotheses that the lives saved via clozapine's reduction in suicide may be offset by the deaths due to an increase of cardiovascular risk factors.[49,50]

As recently mentioned by Kane[51], clinicians seem to be too cautious in prescribing clozapine. Nielsen et al.[48] investigated prescription habits of clinicians and showed that discontinuation of clozapine is often not warranted, as adverse effects are treatable in most cases. Therefore, the findings of the overall lower mortality favouring clozapine should encourage clinicians to investigate treatment response to clozapine in every patient in case of unresponsiveness to 2 other antipsychotics (taken at an adequate dose and for a sufficient length of time).

4.3 Mortality rates from specific causes

We were unable to draw firm conclusions regarding the long-term causes of death of patients with schizophrenia due to the incomplete and inconsistent reporting of data. For example, cardiovascular-related mortality was reported according to various definitions (e.g., Tiihonen et al.[3] merely reported deaths due to ischemic heart disease). Therefore, 2 subgroups were explored in more detail: death from suicide and from ischemic-heart disease. Regarding the first outcome, we did not find a significant difference in patients that were treated with clozapine compared to other antipsychotics. A previous meta-analysis into long-term risk of suicide did find a significant difference favouring clozapine.[16] The findings regarding the association between clozapine use and a lower or higher cardiovascular mortality were contradictory in individual studies.[3,28] Future studies, using uniform definitions of cause-specific mortality (e.g., following the ICD-11 index as provided by the World Health Organization) and having a substantial length of follow-up for cardiovascular mortality to occur, are recommended to study this relationship. Studying causes of death is crucial, as by reviewing the causes of death, prevention and interventions to improve the health of patients with schizophrenia can be prioritized.

4.4 Methodological limitations

These findings should be interpreted in the light of the following limitations. First, despite the systematic search, the number of included studies in the main analyses was still relatively small. Second, a high level of heterogeneity was present for most outcomes of interest, despite the numerous additional subgroup and sensitivity analyses that were performed. The sensitivity analyses yielded no significant results for categorical variables. We found no difference between studies including treatment-resistant patients only and other studies. However, although in the other studies, the diagnosis was often solely given as schizophrenia and treatment-resistance was neither defined nor described, it is highly likely that a large proportion of patients in fact was clinically treatment-resistant, as clozapine is rather underutilized in the severely ill and refractory patients than overutilized in the non-refractory patient group.[52,53] Additionally, due to mixed antipsychotic comparison groups in most studies, we were unable to perform a subgroup analysis of clozapine's mortality reducing effect vs. first- or vs. second-generation antipsychotics. Future research should examine this further. In general, high heterogeneity indicates that variation in clinical and statistical characteristics within and between the individual studies was important, which poses a limitation to a reliable interpretation of the results. Nevertheless, all individual studies pointed towards a lower mortality in patients with continuous clozapine use vs. continuous non-clozapine antipsychotic use, indicating that the observed heterogeneity does not challenge the main finding of our meta-analysis. In other words, the heterogeneity was not about whether or not continuous clozapine use is associated with lower all-cause mortality, but rather around the magnitude of this benefit. Therefore, moderators and mediators of the mortality reducing effects of clozapine should be investigated in further studies. Third, we presented and pooled unadjusted mortality rates and performed a meta-regression with 3 potential confounders, yielding no significant results. However, performing a meta-regression with other important confounders was limited by the fact that uniform reporting of relevant sociodemographic and clinical confounders was often lacking. Consequently, our findings need further validation by adjusted rates using more potential confounders.

Fourth, we used rates per patient years to account for sample size and length of follow-up. We encountered several studies from which we had to estimate the length of follow-up based on data collection years, and this could have resulted in an underestimation of mortality rates. Due to the scarcity of high quality studies, this approach represented the most pragmatic way of handling the data.

Fifth, we established broad criteria regarding study design, which lead to the inclusion of low quality studies with methodologically weaker results. However, we performed subgroup analyses based on the risk of bias, but this did not significantly affect the findings. Additionally, to investigate long-term outcomes such as mortality, large sample sizes (including thousands of patients) are required, which is impossible to include in randomized controlled trials (RCTs). As a consequence, the evidence is currently merely based on observational studies.[51]

Sixth, only a few studies provided antipsychotic exposure estimates to investigate the association between cumulative exposure to antipsychotics and mortality rates. For

example, dissimilar measures were used (e.g., defined daily dosages or chlorpromazine equivalents) and information regarding dosages or concomitant medication was frequently missing. Consequently, it was impossible to add cumulative exposure as a covariate in the meta-analysis. Nevertheless, it would be interesting to include this in future studies since earlier research indicated that there is an 'U-shaped' relation between mortality rate and antipsychotic exposure (higher mortality risk for no and high exposure to antipsychotics and lowest mortality risk for modest exposure to antipsychotics).[54] Nevertheless, it is unclear if higher mortality rates in higher antipsychotic dose strata are related to antipsychotic dose per se, or whether there is confounding by indication: more severely ill patients with related variables that are associated with greater mortality risk receive higher antipsychotic doses. Seventh, we subdivided the analyses into continuous users versus ever clozapine users, based on theoretical grounds and in line with previous findings.[23] The assumption that the mortality risk would differ between those 2 groups was not reflected in a subgroup analysis, in which we tested the differences in mortality rates between these 2 groups yielding non-significant results. However, in contrast, when comparing each of these clozapine subgroups to non-clozapine users, as hypothesized the continuous clozapine users, but not the ever clozapine users were at significantly reduced risk for all-cause mortality.

Finally, and most significantly, although we intended to include long-term follow-up studies, the median follow-up period of 5 years across all included studies may not have been long enough to expose the overall mortality risk. This may specifically influence mortality due to natural causes (e.g., cardiovascular) since mortality by suicide tends to occur early during the disorder[55], while mortality by natural causes increases over time.

Besides these (methodological) limitations of the current study, certain forms of bias that apply to the included studies should also be considered. First, survival treatment bias could be in place (e.g., patients had already survived treatment with – often – 2 other types of antipsychotics before clozapine was prescribed which may impose a lower mortality risk).[47] Ideally, this potential bias should be accounted for, especially when comparing patients treated with clozapine to patients with other or no antipsychotics in observational designs. Unfortunately, most studies were not able to account for this type of bias and only corrected for the available clinical and sociodemographic confounders.[23] This omission is often due to the retrospective character of database-studies, which frequently lack data about important confounders. Therefore, future long-term cohort studies that collect decisive clinical confounders are strongly suggested. Second, as earlier mentioned, performance bias could be in place. Since patients who use clozapine are requested to have more clinical contacts, due to frequent blood monitoring, they could have better access to care and may be more adequately treated. Performance bias can be adjusted for, most easily in randomized controlled trials, as shown by Meltzer et al.[10], but also in observational studies when accounting for the number of clinical contacts.[26] However, this confounder was only measured and controlled for in one observational study.[26]

5. CONCLUSION

This meta-analysis showed that continuous clozapine treatment in schizophrenia patients is associated with a significantly lower long-term all-cause mortality rate compared to treatment with other antipsychotics. Future studies with substantial length of follow-up, uniform reporting of causes of death and inclusion of crucial confounders are needed to validate these findings. Nevertheless, these findings are important, given the known effectiveness of clozapine in treating patients with treatment-resistant schizophrenia. Our findings highlight the need of re-evaluation of the role of clozapine in clinical practice. The concern of clinicians that prescribing clozapine will increase the long-term mortality risk of schizophrenia patients by inducing cardiovascular-related adverse effects is not empirically supported in the current systematic review and meta-analysis.

ACKNOWLEDGEMENTS

The authors would like to thank Joost Daams for his help during the search, as well as Richard Garcia for his helpful comments on the first drafts of this manuscript.

CONFLICTS OF INTEREST

Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Neurocrine, Otsuka, Pfizer, ROVI, Sunovion, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Pfizer, Roche, and ROVI. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma. All other authors have nothing to declare.

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SUPPLEMENTARY MATERIAL

Supplement 1. Search strategy Medline, Embase, PsycINFO

	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present. Search date: 27 June 2017	
1	exp "schizophrenia spectrum and other psychotic disorders"/ or schizophrenic psychology/	142138
2	(schizophreni* or schizoaffective or severe mental illness).ab,jw,kf,ti.	119275
3	or/1-2 [schizophrenia]	174722
4	exp Dibenzazepines/	38541
5	(Alemoxan or Azaleptine or Azaleptol or Cloment or Clonex or Clopin or Clopine or Clopsine or Clorazem or Cloril or Clorilex or Clozamed or Clozapex or Clozapin or Clozapina or Clozapine or Clozapinum or Clozapyl or Clozarem or Clozaril or Denzapine or Dicomex or Elcrit or Excloza or FazaClo or Froidir or Ihope or Klozapol or Lanolept or Lapenax or Leponex or Lodux or Lozapin or Lozapine or Lozatric or Luften or Medazepine or Mezapin or Nemea or Nirva or Ozadep or Ozapim or Refract or Refraxol or Refraxol or Schizonex or Sensipin or Sequax or Sicozapina or Sizopin or Sizopril or Sizoril or Syclop or Syzopin or Tanyl or Uspen or Versacloz or Xenopal or Zaclo or Zapen or Zapenia or Zapine or Zaponex or Zaporil or Ziproc or Zopin).ab,kf,ti.	10917
6	"5786-21-0".ab,kf,ti.	4
7	or/4-6 [clozapine]	42827
8	exp mortality/ or survival analysis/ or kaplan-meier estimate/ or suicide/ or suicide, assisted/ or exp heart arrest/	558826
9	mortality.fs.	507538
10	(mortalit* or death* or (fatal adj3 outcome?) or fatality or "years of life lost" or suicide or Kaplan* or survival or surviving or survivor?).ab,kf,ti.	1909320
11	(cardiac arrest or cardiac infarct* or heart attack? or heart arrest or cardiovascular stroke or myocard* infarct*).ab,kw,ti.	210122
12	or/8-11 [mortality outcomes]	2291704
13	agranulocytosis/	7762
14	(agranulocytosis or Granulocytopenia).ab,kf,ti.	6870
15	myocarditis/	13738
16	(myocarditis or inflammatory cardiomyopathy).ab,kf,ti.	14042
17	or/13-16 [relevant disorders]	29334
18	incidence.sh. or exp mortality/ or follow-up studies.sh.	1058202
19	prognos:.tw.	493762
20	predict:.tw.	1279624
21	course:.tw.	551140
22	or/18-21 [Haynes' prognosis filter max sensitivity]	2972761
23	or/12,17,22	4445527

24	and/3,7,23	2013
25	3 and 12 and antipsychot*.mp.	1916
26	24 or 25	3513
27	remove duplicates from 26	3365

	Embase Classic+Embase 1947 to 2017 June 28. Ovid interface. Search date: 27 June 2017	
1	exp *schizophrenia/	115500
2	(schizophreni* or severe mental illness).ab,jx,kw,ti.	160760
3	or/1-2 [schizophrenia]	172755
4	clozapine/	29755
5	(Alemoxan or Azaleptine or Azaleptol or Cloment or Clonex or Clopin or Clopine or Clopsine or Clorazem or Cloril or Clorilex or Clozamed or Clozapex or Clozapin or Clozapina or Clozapine or Clozapinum or Clozapyl or Clozarem or Clozaril or Denzapine or Dicomex or Elcrit or Excloza or FazaClo or Froidir or Ihope or Klozapol or Lanolept or Lapenax or Leponex or Lodux or Lozapin or Lozapine or Lozatric or Luften or Medazepine or Mezapin or Nemea or Nirva or Ozadep or Ozapim or Refract or Refraxol or Refraxol or Schizonex or Sensipin or Sequax or Sicozapina or Sizopin or Sizopril or Sizoril or Syclop or Syzopin or Tanyl or Uspen or Versacloz or Xenopal or Zaclo or Zapen or Zapenia or Zapine or Zaponex or Zaporil or Ziproc or Zopin).ab,kw,ti,tn.	15637
6	"5786-21-0".ab,kw,rn,ti.	27835
7	or/4-6 [clozapine]	31084
8	*mortality/ or *cancer mortality/ or *cardiovascular mortality/ or *premature mortality/ or *standardized mortality ratio/ or *survival/ or *long term survival/ or *overall survival/ or *post treatment survival/ or *short term survival/ or *survival factor/ or *survival prediction/ or *survival rate/ or *survival time/ or *suicide/ or exp *heart arrest/	203638
9	(mortalit* or death* or (fatal adj3 outcome?) or fatality or "years of life lost" or suicide or Kaplan* or survival or surviving or survivor?).ab,kw,ti.	2653663
10	(cardiac arrest or cardiac infarct* or heart attack? or heart arrest or cardiovascular stroke or myocard* infarct*).ab,kw,ti.	300077
11	or/8-10 [mortality outcomes]	2852271
12	agranulocytosis/	12127
13	(agranulocytosis or Granulocytopenia).ab,kw,ti.	8993
14	myocarditis/	23380
15	(myocarditis or inflammatory cardiomyopathy).ab,kw,ti.	20353

Table continues on the next page

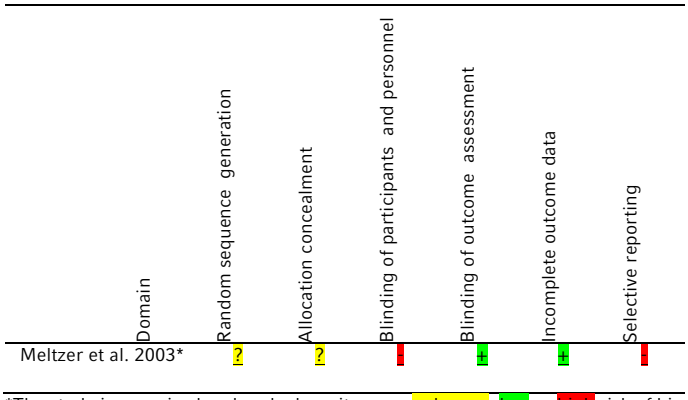
Supplement 1. Continued

16	or/12-15 [relevant disorders]	43849
17	(prognos* or course or longitudinal or follow up or predict*).ab,kw,sh,ti.	4366351
18	limit 17 to medline	694438
19	17 not 18 [longitudinal studies]	3671913
20	or/11,16,19	5668408
21	and/3,7,20	4519
22	3 and 11 and antipsychot*.mp.	2022
23	21 or 22	5850
24	remove duplicates from 23	5708

	PsycINFO <1806 to June Week 3 2017>. Ovid interface. Search date: 27 June 2017	
1	schizophrenia/ or acute schizophrenia/ or catatonic schizophrenia/ or paranoid schizophrenia/ or process schizophrenia/ or "schizophrenia (disorganized type)"/ or schizophreniform disorder/ or undifferentiated schizophrenia/	81656
2	(schizophreni* or severe mental illness).ab,jx,id,ti.	116812
3	"3213".cc.	51665
4	or/1-3 [schizophrenia]	123266
5	clozapine/	4415
6	(Alemoxan or Azaleptine or Azaleptol or Cloment or Clonex or Clopin or Clopine or Clopsine or Clorazem or Cloril or Clorilex or Clozamed or Clozapex or Clozapin or Clozapina or Clozapine or Clozapinum or Clozapyl or Clozarem or Clozaril or Denzapine or Dicomex or Elcrit or Excloza or FazaClo or Froidir or Ihope or Klozapol or Lanolept or Lapenax or Leponex or Lodux or Lozapin or Lozapine or Lozatric or Luften or Medazepine or Mezapin or Nemea or Nirva or Ozadep or Ozapim or Refract or Refraxol or Refraxol or Schizonex or Sensipin or Sequax or Sicozapina or Sizopin or Sizopril or Sizoril or Syclop or Syzopin or Tanyl or Uspen or Versacloz or Xenopal or Zaclo or Zapen or Zapenia or Zapine or Zaponex or Zaporil or Ziproc or Zopin).ab,id,ti.	7272
7	"5786-21-0".ab,id,ti.	0
8	or/5-7 [clozapine]	7298
9	"death and dying"/ or exp suicide/	50997
10	(mortalit* or death* or (fatal adj3 outcome?) or fatality or "years of life lost" or suicide or Kaplan* or survival or surviving or survivor?).ab,id,ti.	190623

11	(cardiac arrest or cardiac infarct* or heart attack? or heart arrest or cardiovascular stroke or myocard* infarct*).ab,id,ti.	5511
12	or/9-11 [mortality outcomes]	199072
13	(agranulocytosis or Granulocytopenia).ab,id,ti.	504
14	(myocarditis or inflammatory cardiomyopathy).ab,id,ti.	149
15	13 or 14 [relevant disorders]	629
16	(prognos* or course or longitudinal or follow up or predict* or long term).ab,id,sh,ti. [longitudinal studies]	739664
17	or/12,15-16	890741
18	and/4,8,17	1519
19	4 and 12 and antipsychot*.mp.	901
20	18 or 19	2215
21	remove duplicates from 20	2211

Supplement 2. Risk of bias assessment of study with randomized design



*The study is appraised and ranked per items as unknown, low or high risk of bias.

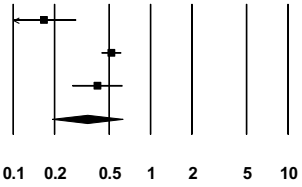
Supplement 3. Risk of bias assessment of observational studies

Domain	Selection (out of 4)	Comparability (out of 2)	Outcome (out of 3)	Total number of stars (out of 9 for cohort/case-control studies and 6 for convenience samples)
Studies with a cohort design				
Girgis et al. 2011	***		*	4
Hayes et al. 2014	****	**	**	8
Hennessy et al. 2002	****	**	***	9
Kelly et al. 2010	****	**	**	8
Modai et al. 2000	****		**	6
Pridan et al. 2014	***		**	5
Ringbäck et al. 2014	****	**	**	8
Taipale et al. 2017	****	**	***	9
Tiihonen et al. 2009	****	**	***	9
Walker et al. 1997	****	**	**	8
Wimberley et al 2017	****	**	**	8
Studies with a case-control design				
Mela et al. 2016	**	**	*	5
Studies with a convenience sample				
Gaertner et al. 2001	***		*	4
Khan et al. 2017	**		*	3
Lee et al. 2015	***		**	5
Munro et al. 1999	***		*	4
Srivastava et al. 2002	**		*	3
Davis et al. 2014	*		**	3
Dickson et al. 1998†	***		***	6
Lindström et al. 1989	***		*	4
Rimon et al. 1994	***		**	5
Schulte et al. 2016†	***		**	5
Taylor et al. 2009†	***		**	5

Each star represents a positive score in that particular domain
Case-control, but descriptive design for our study outcome

Supplement 4. Meta-analysis of mortality rate ratios of clozapine compared to no antipsychotics

Study name	Rate ratio	Lower limit	Upper limit	p-Value
Hayes et al. 2015	0.17	0.10	0.29	0.000
Taipale et al. 2017	0.52	0.44	0.62	0.000
Wimberley et al. 2017	0.41	0.27	0.63	0.000
	0.34	0.19	0.62	0.000



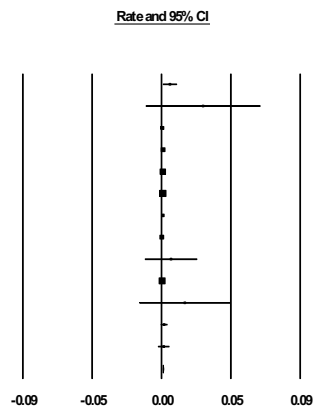
Heterogeneity: Q=15.38, *p*-value=<.001, I^2=87.0

Supplement 5. Adjusted all-cause mortality ratios for patients exposed to clozapine compared to other antipsychotics

Study	Adjusted Ratio (95%CI)	Type of ratio	Reference group
Hennessy et al. 2002	0.80 (0.5-1.2)	Rate ratio	Clozapine versus Haloperidol (reference)
Ringbäck et al. 2014	0.92 (0.70-1.22)	Odds ratio	Clozapine versus Haloperidol (reference)
Tiihonen et al. 2009	0.74 (0.60-0.91)	Hazard ratio	Clozapine versus Perphenazine (reference)
Wimberley et al. 2017	0.69 (0.41-1.16)	Hazard ratio	Clozapine versus non-clozapine antipsychotics (reference)

Supplement 6. Meta-analysis of death due to suicide rates of patients who continuously or ever used clozapine

Study name	Total	Rate	Lower limit	Upper limit	Z-Value	p-Value
Meltzer et al. 2003	5 / 913	0.0055	0.001	0.010	2.236	0.025
Dickson et al. 1998	2 / 74	0.0270	-0.010	0.064	1.414	0.157
Modai et al. 2000	2 / 3725	0.0005	-0.000	0.001	1.414	0.157
Ringbäck et al. 2014	13 / 12288	0.0011	0.000	0.002	3.606	0.000
Tiihonen et al. 2009	27 / 32000	0.0008	0.001	0.001	5.196	0.000
Walker et al. 1997	75 / 85399	0.0009	0.001	0.001	8.660	0.000
Wimberley et al. 2017	4 / 4492	0.0009	0.000	0.002	2.000	0.046
Taylor et al. 2009	0 / 2471	0.0002	-0.000	0.001	0.707	0.480
Gaertner et al. 2001	0 / 80	0.0062	-0.011	0.023	0.707	0.480
Munro et al. 1999	13 / 30973	0.0004	0.000	0.001	3.606	0.000
Srivastava et al. 2002	1 / 66	0.0152	-0.015	0.045	1.000	0.317
Lindström et al. 1989	2 / 1156	0.0017	-0.001	0.004	1.414	0.157
Rimon et al. 1994	0 / 350	0.0014	-0.003	0.005	0.707	0.480
		0.0007	0.000	0.001	5.748	0.000

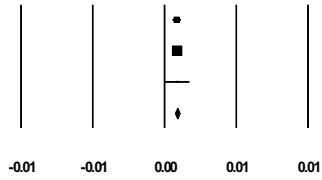


Heterogeneity: Q=22.38, *p*-value=0.033, I^2=46.4

Total= number of deaths/number of patient years.

Supplement 7. Meta-analysis of suicide rates of patients who continuously used clozapine

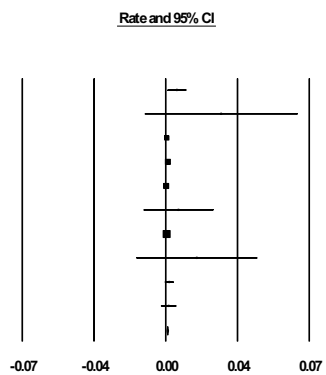
Studyname	Total	Rate	Lower limit	Upper limit	Z-Value	p-Value
Tiihonen et al. 2009	27 / 32000	0.0008	0.001	0.001	5.196	0.000
Walker et al. 1997	75 / 85399	0.0009	0.001	0.001	8.660	0.000
Wimberley et al. 2017	4 / 4492	0.0009	0.000	0.002	2.000	0.046
		0.0009	0.001	0.001	10.294	0.000



Heterogeneity: Q=0.035, *p*-value=0.983, I^2=0.0.
Total= number of deaths/number of patient years.

Supplement 8. Meta-analysis of death due to suicide rates of patients who ever used clozapine

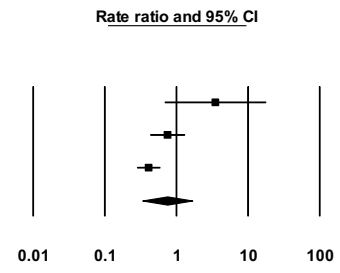
Studyname	Total	Rate	Lower limit	Upper limit	Z-Value	p-Value
Meltzer et al. 2003	5 / 913	0.0055	0.001	0.010	2.236	0.025
Dickson et al. 1998	2 / 74	0.0270	-0.010	0.064	1.414	0.157
Modai et al. 2000	2 / 3725	0.0005	-0.000	0.001	1.414	0.157
Ringbäck et al. 2014	13 / 12288	0.0011	0.000	0.002	3.606	0.000
Taylor et al. 2009	0 / 2471	0.0002	-0.000	0.001	0.707	0.480
Gaertner et al. 2001	0 / 80	0.0062	-0.011	0.023	0.707	0.480
Munro et al. 1999	13 / 30973	0.0004	0.000	0.001	3.606	0.000
Srivastava et al. 2002	1 / 66	0.0152	-0.015	0.045	1.000	0.317
Lindström et al. 1989	2 / 1156	0.0017	-0.001	0.004	1.414	0.157
Rimon et al. 1994	0 / 350	0.0014	-0.003	0.005	0.707	0.480
		0.0006	0.000	0.001	3.095	0.002



Heterogeneity: Q=13.81, *p*-value=0.129, I^2=34.8.
Total= number of deaths/number of patient years.

Supplement 9. Meta-analysis of rate ratios of death due to suicide clozapine compared to other antipsychotics

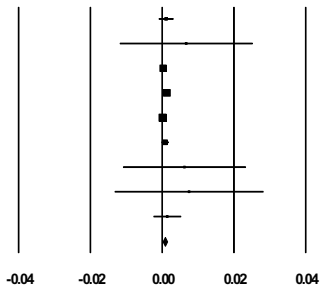
Study name	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Modai et al. 2000	3.50	0.68	18.04	1.50	0.134
Ringbäck et al. 2014	0.75	0.43	1.33	-0.98	0.328
Tiihonen et al. 2009	0.41	0.28	0.60	-4.54	0.000
	0.74	0.33	1.64	-0.75	0.455



Heterogeneity: Q=8.25, *p*-value=0.016, I^2=75.8.

Supplement 10. Meta-analysis of mortality rates due to ischemic heart disease of patients who ever or continuously used clozapine

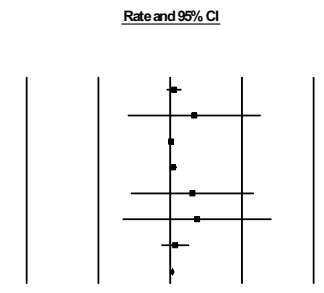
Studyname	Total	Rate	Lower limit	Upper limit	Z-Value	p-Value
Meltzer et al. 2003	1 / 913	0.0011	-0.001	0.003	1.000	0.317
Dickson et al. 1998	0 / 74	0.0067	-0.012	0.025	0.707	0.480
Modai et al. 2000	1 / 3725	0.0003	-0.000	0.001	1.000	0.317
Tiihonen et al. 2009	42 / 32000	0.0013	0.001	0.002	6.481	0.000
Walker et al. 1997	11 / 85399	0.0001	0.000	0.000	3.317	0.001
Taylor et al. 2009	2 / 2471	0.0008	-0.000	0.002	1.414	0.157
Gaertner et al. 2001	0 / 80	0.0062	-0.011	0.023	0.707	0.480
Srivastava et al. 2002	0 / 66	0.0075	-0.013	0.028	0.707	0.480
Rimon et al. 1994	0 / 350	0.0014	-0.003	0.005	0.707	0.480
		0.0007	0.000	0.001	2.126	0.033



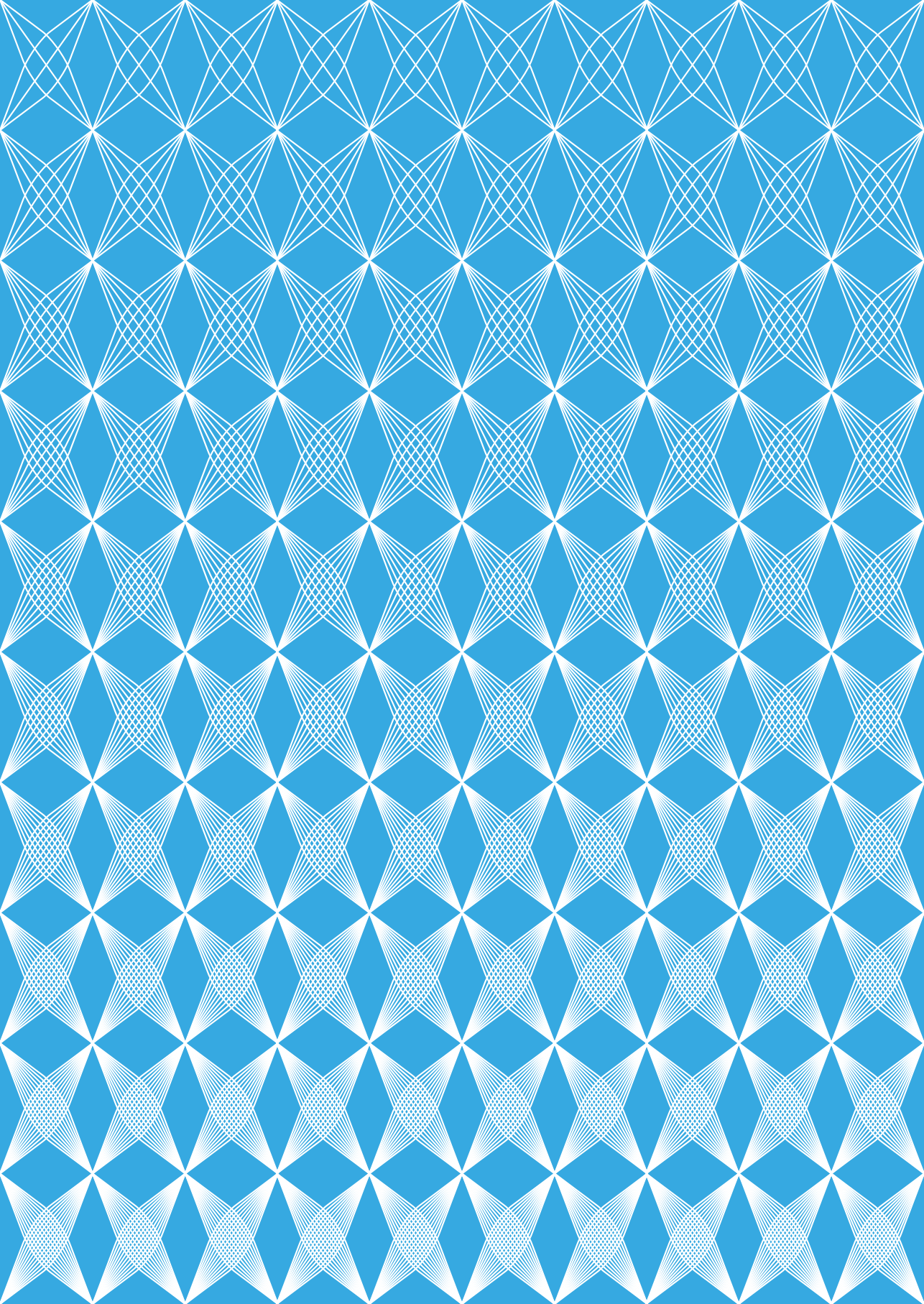
Heterogeneity: Q=36.8, *p*-value=<.001, I^2=78.3.
Total= number of deaths/number of patient years.

Supplement 11. Meta-analysis of mortality rates due to ischemic heart disease of patients who ever used clozapine

Studyname	Total	Rate	Lower limit	Upper limit	Z-Value	p-Value
Meltzer et al. 2003	1 / 913	0.0011	-0.001	0.003	1.000	0.317
Dickson et al. 1998	0 / 74	0.0067	-0.012	0.025	0.707	0.480
Modai et al. 2000	1 / 3725	0.0003	-0.000	0.001	1.000	0.317
Taylor et al. 2009	2 / 2471	0.0008	-0.000	0.002	1.414	0.157
Gaertner et al. 2001	0 / 80	0.0062	-0.011	0.023	0.707	0.480
Srivastava et al. 2002	0 / 66	0.0075	-0.013	0.028	0.707	0.480
Rimon et al. 1994	0 / 350	0.0014	-0.003	0.005	0.707	0.480
		0.0004	-0.000	0.001	1.808	0.071



Heterogeneity: Q=2.7, *p*-value=0.842, I^2=0.0.
Total= number of deaths/number of patient years.



APPENDICES

SUMMARY AND GENERAL DISCUSSION

1. OBJECTIVES

This thesis consists of three parts: in part one (Part I), the interactions between symptoms in patients with schizophrenia were examined by applying a network approach. Additionally, the influence of remission-status on network topology was explored by comparing remitted and non-remitted psychotic patients. In both network studies there was a focus on the association between depressive and positive symptoms. In the second part of this thesis (Part II) neuronal correlates of depressive symptomatology were reviewed by discussing findings of neuroimaging studies investigating emotion regulation in patients with a major depressive disorder (MDD). In the last part (Part III) various studies concerning the outcome of patients with schizophrenia were presented. This part starts with a study investigating the influence of depressive symptoms on quality of life (QoL). Thereafter, a new approach for measuring the quality of provided care to patients diagnosed with a non-affective psychosis is described. Finally, this thesis ends with three manuscripts concerning various aspects of schizophrenia treatment. We conducted a narrative review on treatment approaches for treating depressive symptoms and episodes in schizophrenia. Thereafter, two meta-analyses are presented: the first concerns the association between mortality risk and the long-term use (i.e., > 52 weeks) of antipsychotics compared to no antipsychotic use, and the second, the association between mortality risk and the long-term use of the antipsychotic clozapine.

The present chapter provides a summary of the main findings, discusses these findings within a broader perspective and mentions possible directions for future research.

2. MAIN FINDINGS PART I (CHAPTER 2 - 3): INVESTIGATING SCHIZOPHRENIA WITH A NETWORK APPROACH

In Part I, two studies are presented that applied the network approach to investigate the reciprocal influence of symptoms within patients diagnosed with a non-affective psychosis. In chapter 2 a symptom network was constructed based on data assessed with the Comprehensive Assessment of Symptoms and History (CASH)[1] in male patients diagnosed with non-affective psychosis. In the generated symptom network the most central symptoms were 'loss of interest', 'chaotic speech', 'inability to enjoy recreational interest in activities', 'inability to form or maintain relationships with friends' and 'poverty of content of speech'. These central symptoms reflect the importance of core depressive symptoms and the relevance of social participation and communication in patients with schizophrenia. Centrality analyses are thought to disentangle the most important symptoms within a network. It is proposed that intervening on these central symptoms might be the most effective way of treating patients as a decrease in the severity of central symptoms might lead to a decrease in the severity of other connected symptoms as well. It should be

noted that current network analyses (chapter 2 and 3) were cross-sectional of nature and therefore additional research is needed before conclusions regarding causality can be made. Additionally, specific 'symptom-symptom interactions' were explored, which might be of particular clinical relevance. For example, 'recurrent thoughts of death/suicide' appeared to be strongly connected to other depressive symptoms without direct connections to psychotic symptoms (or domains). This finding was considered important as earlier studies showed strong influence of psychotic symptoms on suicidality (e.g., acoustic hallucinations that incite to self-damaging behavior), consequently, this association was further investigated in a second network study in which a better measure of the severity of depressive symptoms was used.

The validity of the CASH in assessing depressive symptoms in patients with schizophrenia is considered limited, due to a restricted distinction between depressive and (secondary) negative symptoms and/or extrapyramidal side effects. Therefore, in chapter 3, symptom networks of depressive symptoms were further investigated by using the Calgary Depression Rating Scale for Schizophrenia (CDSS).[2] The CDSS is specifically designed to assess depressive symptoms in patients diagnosed with schizophrenia.[3] The constructed symptom network including the CDSS and the positive and negative symptoms (as part of the Positive and Negative Symptom Scale (PANSS))[4] showed comparable findings regarding the association between suicidality, depressive and positive symptoms; there was only one connection between the symptoms 'suspiciousness' and 'suicide', while there were several connections between depressive symptoms and 'suicide'. In line with a previous study by Bornheimer and colleagues,[5] it was hypothesized that depressive symptoms are directly associated with suicidality, whereas positive symptoms may influence depressive symptoms and through this pathway influence suicidality. However, it is important to mention that our results, both in chapter 2 and 3, are solely based on cross-sectional, group-level data and we were not able to make interferences about causality. Neither is it possible to draw conclusions regarding symptom interaction on an individual level. Nevertheless, our findings suggest that, in general, depressive symptoms are the most important moderating factor leading to suicidality in patients with non-affective psychotic disorders.

Additionally, potential differences in network connectivity between remitted and non-remitted psychotic patients were investigated showing a similar network structure; however, the networks varied significantly in terms of global strength. This significant difference between both networks is probably due to *more* connections in the network of the non-remitted psychotic patients, which suggested that the overall strength of connections within the networks was dependent on remission status. These findings are in line with the 'hysteresis principal' of the network approach.[6] The hysteresis principle assumes that activation of a network is easier in strongly connected networks (i.e., with more and/or stronger connections). Activation of symptom networks occurs through an external trigger (i.e., a traumatic or stressful life event) outside the symptom network. Once the network is activated, activation spreads through the symptom networks causing feedback loops. These feedback loops result in ongoing symptomatology (recognizable as psychiatric syndromes), also when the external trigger is no longer present.[6] The finding of more connections in the network of non-remitted patients may reflect the presence of such potential feedback loops, resulting in maintenance of non-remission. In other words, connections between the symptoms, which were more present in the non-remitted psychotic patients, and hereby keep on activating each other and result in the maintenance of a non-remission status.

2.1 Our findings in the light of earlier network studies

The empirical grounds for the network approach was established only recently.[7] In a review on this topic, Fried and collegaeus[8] summarized current evidence derived from network studies investigating psychopathology by focusing on three themes: comorbidity, prediction and clinical intervention. Regarding 'comorbidity', the network approach contributed by unravelling 'bridge symptoms' (i.e., symptoms that connect different symptom clusters with each other), which might explain the high rates of comorbidity between disorders (e.g., between depression and anxiety disorders). Indeed, different empirical studies, found bridge symptoms in different disorders.[9–13] Nevertheless, to date, studies pinpointing bridge symptoms in patients with non-affective psychotic disorder are scare.[14–16] In both network studies included in this thesis (chapter **2** and **3**) preliminary evidence for bridge symptoms was found (for instance, in our network 'grandiose delusion' connected the symptom domain 'delusions' to the 'manic' symptom domain). Moreover, widespread connections between individual symptoms were visible. Based on this analysis, one could argue that the network approach offers a more fine-grained conceptualisation of psychopathology than a categorical, more static conceptualisation of mental illness.

Additionally, with respect to the second theme 'prediction': network studies focusing on this topic can be divided in two, related, subthemes namely I) 'early warning signals' (i.e., changes to individual networks suggesting a forthcoming onset of psychopathology) and II) describing specific features of networks which predict the development of psychopathology.[8] The current studies added relevant knowledge to this second subtheme as the stability of the network structure in patients with non-affective psychosis was investigated (chapter **3**). Stability of network structure is needed to be able to further explore the different courses of patients within the psychosis spectrum. In sum, networks did not differ significantly regarding the structure of the connections between symptoms, but differed significantly with respect to the strength of the connections between patients in remission of their psychotic episode and patients who had not remitted (i.e., the networks of the group with a non-remitted psychotic episode was more densely connected). It would be of great interest to further explore how the connections of this state-independent network structure changes towards the more connected networks (i.e., the active psychotic status) and when symptoms start to increase.

Lastly, network studies focusing on the last theme 'clinical intervention' tried to identify symptoms with high centrality measures. In both network studies centrality measures were calculated and when combining the findings of both studies, high centrality of depressive symptoms and symptoms reflecting the social participation and communication of patients was found. Additionally, with respect to depressive symptoms (which are the most frequently studied in network studies)[7,8,10,17] 'depressed mood', 'loss of interest/pleasure', 'energy/fatigue' have consistently been found as central symptoms in different network studies. Interestingly, this first symptom (i.e., 'depressed mood') is also in line with the results in chapter **3**, suggesting that 'depressed mood' has an important role both in affective and psychotic disorders. This suggests that 'depressed mood' could be a transdiagnostic target for treatment interventions.

2.2 Future network studies

Most network studies to date focused on the interaction between symptoms. As pointed out by Fried and colleagues,[8] there are also authors who moved beyond symptom-interactions.[15,16,18] As an example, Isvoranu and colleagues[15] included childhood trauma in a cross-sectional network of psychotic and general symptoms in patients with non-affective psychosis. They constructed a network including schizophrenia symptoms (positive, negative and general psychopathology symptoms) assessed with the PANSS and the five different types of childhood trauma as *nodes*. This study did not support that there was a direct relationship between psychotic symptoms and childhood trauma. Instead, general psychopathology symptoms (such as anxiety and depression) mediated the relationship between childhood trauma and psychotic symptoms. Despite the cross-sectional nature of their data the authors concluded that their findings corroborated 'an affective pathway to psychosis after exposure to childhood trauma' (i.e., patients exposed to childhood trauma may first develop affective symptoms and as a result might develop psychotic symptoms).[15] In line with our finding that social participation and communication are central, a recent network study in patients diagnosed with schizophrenia showed that functional capacity and everyday life skills were the most central symptoms within the network and stresses the importance of 'recovery-oriented' treatment within schizophrenia.[16]

As pointed it out by Wichers and colleagues,[19] these approaches are very interesting as they make it feasible to investigate protective, factors that influence network-sensitivity and clarify questions like "*How does psychopathology develop differently within individuals?*" and "*How might psychopathology improve within individuals?*".[19] Coping mechanisms, medications and/or environmental factors that influence networks of patients to switch to an 'illness- state' could be studied, preferably in longitudinal designs. Only one cross-sectional network study explicitly investigated protective factors, however, in remitted formerly depressed patients.[8,18] This study[18] showed that of the five included risk- and protective factors (i.e., cognitive control, adaptive and maladaptive emotion regulation, residual symptomatology and resilience) resilience was the most central in the constructed networks. Resilience was measured with a 25-item scale and higher scores on this scale were negatively associated with lower residual symptomatology and memory complaints. Based on these findings, the authors suggested an important role that resilience may have had in the remission in the included remitted depressed patients.[18]

A disadvantage of current network studies in general is it cross-sectional nature and therefore the inability to study causality. A method that allows to study temporal dynamics is the experience sampling method (ESM).[20] ESM is a structured diary method by means of self-assessment at random time points during the day. ESM has already proved its value in patients diagnosed with schizophrenia[21] and in clinical settings.[22–25] By using ESM, dynamic temporal relations between different mood states and, for example, contextual factors can be studied in detail.[8,25–27]

The network approach argues that symptoms might be able to influence each other, which may result in (continuously interacting symptoms of) psychopathology, which might be a contributing factor to the maintenance of mental disorders. Different alternatives to study psychopathology have been proposed, such as the investigation of observable behaviour

processes in the form of the Research Domain Criteria (RDoC),[28–30] the addition of a dimensional assessment,[31,32] and the dynamical system theory.[33,34] The National Institute of Mental Health (NIMH) launched the RDoC:[29] a classification system initially for research purposes only in which five different dimensions are described based on "observable behaviour and neurobiological measures".[35] Although, dividing symptoms into subprocesses is sometimes difficult, the RDoc is a promising research method whose added value has to be proven.[36] Also interestingly in this field, is the work by Looijesteijn and colleagues,[37] which postulated a 'Integrated Network Model of Psychotic Symptoms (INMOPS)'. In their proposed network different levels exist: a microscale level represented by individual neurons, a mesoscale level represented by structural and functional alterations in the brain and a macroscale level represented by the social interactions between human beings. At each of these levels, the authors integrate current knowledge regarding alterations that occur at the time of psychotic (positive) symptoms, into functional networks and follow the basic assumptions of network analyses. The work of Looijesteijn and colleagues is an example of the possibilities of network theory to ingrate knowledge on different levels. Hereby, the network theory describes a new way of thinking of psychopathology.

Overall, the assumption underlying these different approaches is that psychiatric illnesses should not be considered as static entities, but as dynamic systems that change from moment to moment.[33] This basic assumption encourages clinicians to take associations between symptoms into consideration, both during the diagnostic phase but also during treatment. We propose that the network approach may be part of every day practice in which an inventory is made of which symptoms maintain each other and which symptoms are the 'core problem' (e.g., suppose there is insomnia that provides serious limitations in daily functioning and causes a depressed/flat mood, treatment will focus on the restoration of sleep) and it underlines the importance of symptoms interactions. Earlier and current network studies suggest that the network approach is indeed promising regarding a more dynamic way of investigating psychopathology, including co-morbidity and clinical implications for interventions (i.e., centrality of symptoms) and prediction. Network studies included in this thesis contribute to our current knowledge by emphasizing that a categorization of psychotic disorders might be artificial (given the fact that all symptoms within the networks were connected), stressed the importance of symptoms reflecting the social participation, suggested the transdiagnostic importance of the symptom 'depressed mood' and lastly showed the state-independence of the network structure in psychotic patients. The network approach, as used in this thesis, can be considered as one of the initiatives that offers an alternative way of thinking about the current diagnostic systems and indirectly forces clinicians to re-think about current categorization of psychiatric disorders.[19]

3. MAIN FINDINGS PART II (CHAPTER 4): NEURAL CORRELATES OF DEPRESSIVE SYMPTOMS IN MAJOR DEPRESSIVE DISORDER

In chapter 4, emotion regulation as a disturbed process underlying depressive symptomatology was reviewed. Emotion regulation is highly essential in daily life, as we are constantly exposed to emotional salient stimuli from our environment. Consequently, difficulties within this process might be responsible for clinical symptoms in different

major psychiatric disorders.[38,39] For example, patients with major depressive disorder (MDD) are known to have a bias towards negative emotions[40] and experience difficulties in altering aversive emotions leading to a sad mood, while patients with schizophrenia suffer from – amongst others – difficulties in the perception of facial emotions and interpretation of intentions of others, possibly underlying psychotic symptoms and difficulties within social functioning.

Summarized evidence, showed that overall the heterogeneity in neuronal alterations during emotion regulation tasks between the different neuroimaging studies was noteworthy. Nevertheless, the literature reviewed in chapter 4 suggests that, when compared to healthy controls, MDD subjects are able to achieve successful automatic emotion regulation (i.e., regulation of emotions that are not expressed in an explicit way, for example, because you are not aware of the emotional stimuli) by recruiting additional neuronal resources (i.e., lateral prefrontal cortex). The involvement of these additional resources is needed to cope with the strong influences of limbic hyperactivity. Nevertheless, this strategy of recruiting additional neuronal resources seems to fail during the voluntary phase of emotion regulation as the lateral prefrontal areas, normally involved in voluntary emotion regulation, showed (relatively) reduced activity in depressed patients when compared to healthy controls. It was suggested that patients with MDD are not able to voluntarily regulate emotions, i.e., once an emotion has already kept their attention. In depressed patients, voluntary regulations of emotions that you are aware of is apparently more difficult than regulating an emotion that you are not conscious of. In depressed patients, being aware of the emotions disables the capacity to actively apply emotion regulation strategies and consequently, relevant brain areas are not activated when compared to healthy controls. Although, more research is needed to test this hypothesis, these results might have clinical consequences. Effective voluntary emotion regulation might be partly dependent on intact automatic emotion regulation. When this is true, treatments based on the voluntary regulation of emotions by means of cognitive behavioural therapy (CBT) might be more successful when automatic emotion regulation is functioning sufficiently. However, more research is needed to confirm this hypothesis.

3.1 Emotion regulation in schizophrenia

The next paragraph will describe hypotheses regarding neuronal alterations during emotional regulation in patients with schizophrenia (with and without depressive symptoms). Moreover, these findings are compared to the results in MDD subjects.

To start, neuroimaging studies investigating structural alterations patients with schizophrenia (or within the psychotic spectrum) are abundant. In short, a meta-analysis reported brain volume decrease in gray matter structures (effect size ranging from -0.22 to -0.58), with volume decreases comparable in antipsychotic-naïve albeit to a lesser extent.[41] These findings are corroborated largely by longitudinal analyses.[42,43] The current view on structural alterations in patients diagnosed with schizophrenia is that alterations in white matter already exist before treatment onset, while reduction in gray matter and subcortical structures becomes more prominent during illness progression.[43–46] Additionally, consortiums collaborating and hereby including large sample sizes are showing widespread white matter abnormalities in patients with schizophrenia, also in line with

the 'dysconnectivity hypothesis' (i.e., inefficient communication between different brain regions).[47] In sum, the neuronal alterations found in schizophrenia patients are widespread and consequently, the pathophysiology of schizophrenia is only partly understood.

Nevertheless, in an earlier review[39] Phillips and colleagues reviewed emotion processing abnormalities in different major psychiatric disorders, including schizophrenia. Summarized evidence in patients with schizophrenia, showed difficulties in processes needed for adequate emotion regulation, including cognitive deficits, problems in the perception of facial emotions and identification of emotionally salient stimuli, reduced ability to form an idea of the perspective of another (i.e., theory of mind) and a limited regulation of own beliefs and emotional behaviour. Taken together, these abnormalities might be responsible for the difficulties during social interactions and specific symptoms (such as delusions) that patients with schizophrenia encounter.[39] Additionally, in the same review Phillips and colleagues described neuronal alternations in regions normally involved in emotion regulation in patients with schizophrenia. In short, patients with schizophrenia showed structural and functional abnormalities in both the ventral and dorsal systems: abnormalities in the ventral system (including amygdala, anterior insula and ventral striatum) might be responsible for the reduced ability to the (automatic) recognition of emotions (which causes a restricted range of distinguishable emotions), a reduced theory of mind and limited abilities to regulate affective states and behaviours. In the same line, dorsal abnormalities (including dorsal prefrontal cortex, dorsal anterior cingulate gyrus and hippocampus) might be responsible for problems during the voluntary regulation of emotions.

Despites its relevance, there are - to the best of our knowledge - neither systematic reviews nor meta-analyses investigating neuronal alterations in patients with schizophrenia by applying the postulated model - including the six subprocesses of emotion regulation - by Phillips and colleagues.[38] As difficulties with emotion regulation are considered to be an important feature of schizophrenia, there are some meta-analyses[48–51] investigating specific aspects of emotion regulation. Most of the included studies in these meta-analyses used tasks that, when integrated in the model by Phillips and colleagues,[38,39] involved the subprocess 'attentional control' (voluntary or automatic). Attentional control describes the capacity to engage or disengage of emotional stimuli.

For instance, Delvecchio and colleagues[48] showed a decreased likelihood of activation in among others frontal, limbic, paralimbic, occipital regions, the basal ganglia in patients with schizophrenia compared to healthy controls. However, they pooled automatic and voluntary tasks making the division into the subprocesses of Phillips and colleagues difficult. More recent, Dong and colleagues[51] performed a meta-analysis in which they pooled studies investigating neuronal changes after viewing threatening facial expression. Dong and colleagues[51] performed subgroup analyses in which they pooled neuronal changes during implicit (i.e., gender identification which should be considered as automatic attentional control) and more explicit processing tasks (e.g., matching emotions but also passive viewing of emotions and should therefore only partly be considered as voluntary attentional control), while focusing on threatening faces (including angry and fearful faces). When considering the results during implicit threatening facial tasks, they found reduced

activity in the hippocampus and parahippocampal gyrus, bilateral amygdala (with activity extending to the putamen) and fusiform gyrus (extending to the cerebellum lobule IV) in patients with schizophrenia compared to healthy controls. Results during explicit tasks were comparable: decreased activation in the inferior frontal gyrus, right cerebellum lobule VI, left fusiform gyrus and thalamus (which extended to the right amygdala). At the same time there was hyperactivity in the medial prefrontal gyrus.

Partly overlapping findings were shown in two meta-analysis,[52,53] which pooled results of tasks including facial emotion perception containing different emotions. For instance, Li and colleagues[52] showed reduced limbic activity (i.e., bilateral amygdala as well as under-activity of the parahippocampal- and fusiform gyrus, right superior frontal gyrus and lentiform nucleus) in patients with schizophrenia compared to healthy controls. In subgroup analyses where tasks were divided into explicit (which can be partly classified into voluntary attentional control, given that the passive viewing of faces without a regulation or cognitive component were also included) and implicit (i.e., automatic attentional control) the inability to recruit the amygdala was still present. In contrast to the study by Dong and colleagues[51] in this study an under-activation of the prefrontal cortex was noted, which could be explained by the specific involvement of the medial prefrontal cortex in threat related stimuli as used in the latter study.

In sum, there are currently neither systematic reviews nor meta-analyses investigating all aspects of emotion regulation in patients with schizophrenia. To date, most studies concerned the subproccess attentional control during threatening or fearful emotions when integrated in the model by Phillips et al.[54] Although the findings show inconsistencies, fronto-limbic alterations seem to be present during emotion regulation in patients with schizophrenia when compared to healthy controls. A lower activity in the limbic regions, which was present in both aforementioned meta-analyses,[48,51] might reflect a less alert state for (potentially threatening) stimuli in patients diagnosed with schizophrenia, resulting in impaired sensory processing in case of important (particular threatening) stimuli. The hyperactivity in medial prefrontal cortex, in the study by Dong and colleagues,[51] might reflect a compensatory recruitment to enhance top-down regulation in case of threat. However, possibly due to a reduced coordination within the limbic-prefrontal circuits, this regulation process fails.

Of note, the reduced activation of the amygdala in patients with schizophrenia compared to healthy controls might be depending on task contrast, as pointed out in a meta-analysis by Anticevic and colleagues.[50] Patients diagnosed with schizophrenia showed elevated activity in the amygdala as response to neutral faces but when neutral versus aversive emotion contrast was used, activation in the amygdala appeared as relatively "under-recruitment". Interestingly, when healthy controls versus patients were compared, the difference regarding amygdala activation was only present in studies that used a neutral versus aversive emotion interaction contrast, while this difference in amygdala activation disappeared in studies that directly compared patients to healthy controls during negative emotional stimuli. This finding questions the earlier findings regarding hypoactivation of limbic regions during aversive emotional stimuli. Therefore, the most consistent finding in patients with schizophrenia might indeed be a hyperactivity of the amygdala to neutral stimuli, which points towards a deviant response to non-salient stimuli.

3.2 Comparison with depression

Most of the emotion regulation studies that have been conducted in patients with schizophrenia concerned passive emotion processing without regulation and/or the subprocess attentional control. Given this lack of studies in patients with schizophrenia it is difficult to compare the results of our review regarding MDD subjects (chapter **4**) with the aforementioned meta-analyses. Nevertheless, when we compare findings during attentional control summarized evidence suggests that during automatic attentional control MDD subjects recruit parietal and lateral prefrontal cortices and showed non-significant differences in limbic areas when compared to healthy controls. MDD subjects seem to recruit these additional areas to overcome the strong bottom-up influence and succeed in this, as reflected by the equal activity in limbic regions when compared to healthy controls. At the same time, patients with schizophrenia showed amygdala over-activity to neutral stimuli and conflicting results with respect to prefrontal cortex (showing under-activity[53,55] respectively over-activity).[51] With respect to voluntary attentional control, the results are even more inconclusive. MDD subjects failed to recruit additional prefrontal areas, where patients with schizophrenia showed indecisive findings with respect to prefrontal regions.

Despite the lack of studies and heterogeneity in findings in both patients groups (i.e., depression and schizophrenia) the limbic-prefrontal cortex circuits seem to be involved in the difficulties during emotion processing: MDD subjects experience most difficulties during voluntary attentional control, when the emotion already took their attention they failed in the voluntary regulation of already ongoing process of negative valence stimuli. At the same time, current literature suggests that patients with schizophrenia show hyperactivation to neutral stimuli, in which the prefrontal cortices seem to fail in regulating this strong bottom-up influence. In sum, difficulties in emotion regulation are present in depression as well as in schizophrenia and might be responsible for clinical symptoms in both groups; however, the underlying deficits appear to differ between both groups.

Of note, one should bear in mind that most of the included studies in meta-analyses concerning schizophrenia consisted of medicated patients making it difficult to elucidate treatment effects, also when comparing patients with depression that are regularly treated with antidepressants (and other medications) compared to patients with schizophrenia usually treated with antipsychotics.

3.3 Emotion regulation in patients with schizophrenia and comorbid depression

Ultimately, it would be of great interest to gain knowledge regarding the neuronal alterations in patients with schizophrenia with and without depressive symptoms. Unfortunately, studies of emotion regulation tasks investigating depressive episodes (or symptoms) in schizophrenia are scare. We are aware of a study by Kumari and colleagues[56] (n=63) who investigated the (passive) viewing of emotional faces (including anxious, angry, happy and neutral faces) in patients with schizophrenia or a schizo-affective disorder. They showed a positive association between the levels of depression and the activity in the left thalamus (with activity extending to the putamen, globus pallidus, insula, inferior frontal gyrus and post-para-precentral gyrus). Patients with higher scores on a depression rating scale showed more activity in those regions compared to patients with lower (up to mild) scores

on the depression rating scale when viewing anxious faces. Most interestingly, previous neuroimaging studies investigating patients with a depressive episode showed amygdala hyperactivity when viewing anxious faces,[40] but almost no activation of the thalamus. In the study of Kumari[56] no amygdala activation was found, which may be an effect of the (often long-term) use of antipsychotics by patients in this study and/or the used contrasts. In sum, considering the lack of studies investigating neuronal differences between schizophrenia patients with or without depressive symptoms or episodes it is, currently, impossible to draw conclusions regarding the neuronal effects of depressive symptoms in patients with schizophrenia. Considering the clinical consequences of emotion dysregulation and its transdiagnostic nature, it would be of great interest to examine emotion regulation in schizophrenia patients with and without depressive symptoms.

Interestingly, a meta-analysis by Goodkind and colleagues[36] (n=15.892) included 193 studies investigating structural alterations in patients diagnosed with different psychiatric disorders (among others schizophrenia, bipolar disorder, depression, addiction, obsessive compulsive disorder and anxiety). Most of the findings were not diagnosis specific, with gray matter decrease in the dorsal anterior cingulate and bilateral insula across diagnosis compared to healthy controls. Although, this meta-analysis did not include emotion regulation or emotional processing tasks, the involvement of the aforementioned regions in emotional processing highlights the relevance of a transdiagnostic disturbance of emotion regulation, as pointed it out by the authors. Given its transdiagnostic involvement Fernandez and colleagues[57] even argued the expansion of RDoC domains by including emotion regulation as sixth domain. Taking these findings together, it seems most plausible to investigate emotion regulation transdiagnostic.

4. MAIN FINDINGS PART III (CHAPTER 5-9): TREATMENT AND OUTCOMES IN SCHIZOPHRENIA

In Part III different treatment aspects and outcomes in patients diagnosed with schizophrenia were studied. Considering the importance of depressive symptoms in the aforementioned network studies, in chapter **5**, the role of depressive symptoms and other clinical variables on QoL was further investigated. Of note, previous cross-sectional studies[58–61] already showed the undisputed negative influence of, in particular, depressive symptoms on QoL. However, due to the cross-sectional nature and the used statistical techniques of these studies it is impossible to make assumptions regarding the causality of these associations (i.e., causes a depressive episode a lower QoL or *vice versa*). Considering the construct of QoL, it is plausible that multiple variables play a role in the associations between depression and QoL (e.g., the level of social functioning and neurocognition might also be involved). By using *Structural Equation modelling* (SEM) Alessandrini and colleagues[62] investigated, cross-sectionally, the associations between different variables (i.e., the level of social functioning, neurocognition psychotic and depressive symptoms on QoL). They found a negative influence of depressive symptoms on QoL while psychotic symptoms and neurocognition indirectly influenced QoL through functioning. SEM is a statistical methodology that provide an opportunity to investigate in which order and to what extent multiple variables influence each other.[63] Studies investigating the long-term association between different variables that may act

on QoL are limited.[58,64] Despite, the relevance of the model proposed by Alessandrini and colleagues,[62] the longitudinal validity of this model was not yet investigated. Also, retesting in a larger sample, would enhance the validity and replicability of the original model of Alessandrini and colleagues.[62]

Both SEM-models (i.e., cross-sectional and longitudinal) in the GROUP sample showed good measures of fit. More specific, in the cross-sectional model, depression as well as social functioning was associated with QoL, while the severity of psychotic symptoms was strongly correlated with social functioning. Most important, in the longitudinal model, depression was prospectively associated with QoL during follow-up. The good fit of longitudinal model corroborated the validity and generalizability of the proposed model by Alessandrini and colleagues.[62] The negative, long-term influence of depressive symptoms on QoL, is considered as an important outcome measure in the long-term treatment of patients diagnosed with schizophrenia, which underlines the importance of treating depressive symptoms.

In the next chapter, chapter **6**, the quality of the treatment provided to patients diagnosed with a psychotic disorder was evaluated in a large group of admitted group of patients. Evaluating the safety and the quality of the care provided is important. However, reports investigating the quality of care in admitted psychiatric patients are lacking. Therefore, a quality assessment of provided care for patients admitted to psychiatric wards was performed. For this, process measures (defined as what was done *for* the patients, such as somatic screening and intervention to change unhealthy behaviour) and outcome measures, expressed as adverse events (defined as what happened *to* the patients) were combined. The most striking finding concerning the process measures was the fact that more than halve of the patients were smokers but only 1% received a smoking-cessation intervention. This is an important omission since the effectiveness of smoking cessation interventions in patients with schizophrenia has been proven.[65] Moreover, basic physical exam was only assessed in three-quarters of the patients and results regarding laboratory tests were also present in the same proportion of patients. Regarding adverse events; adverse drug reactions were the most frequently reported, however, patient elopements (i.e., patients who are unauthorized absent) and patient assaults (i.e., forcible physical contact) were also common. Overall, this study stresses that psychiatric patients are prone for adverse events and specifically to adverse drug reactions. In general, these findings underline the need for quality assessments of the care provided in psychiatry as these assessments could offer a solid basis to start improving treatment. For example, the findings underscore the importance of introducing evidence-based smoking interventions during admission of psychotic patients.

Interestingly, based on findings of this study, recently a new study started to investigate the effectiveness of offering smoking cessation to staff and patients admitted to the psychiatry ward of the Academic Medical Centre. More in general, chapter **6** provides an example of measuring the quality of the care that was provided. A measure of the quality of the care provided is useful for clinicians and policy makers. The use of patient reported outcome measurements (PROMs) is part of daily practice for clinicians in the Netherlands. Interestingly, despite the administrative burden for clinicians, there is no evidence that the

use of those measurements improved the quality of care provided in the past years, neither are they integrated into treatment plans.[66] In other words, further research is still needed to improve the measurement of clinically relevant measures to further improve the quality of care for patients with schizophrenia.

Part III of this thesis ends with three reviews concerning treatment. At first, the available treatment options for treating co-occurring depressive symptoms and episodes in patients with schizophrenia were summarized in a narrative review (chapter **7**). Based on the available studies a practical treatment approach for treating depressive symptoms and episodes in patients with schizophrenia was presented. Notwithstanding the high prevalence rates of depressive symptoms and episodes in patients with schizophrenia and its clinical relevance (among others the association between depressive symptoms and suicidality, reduced treatment adherence and lower QoL in patients diagnosed with schizophrenia, as described in this thesis) the available treatment studies investigating depressive symptoms as primary outcome was remarkable low. The available current evidence points out that the treatment of depressive symptoms and episodes should include the following steps: evaluating current antipsychotic medication, considering switching or lowering the dosages of current antipsychotic medication and motivating for physical activity. In the case of a persistent clinically relevant depressive episode, a subsequent therapeutic step is indicated. Unfortunately, current literature is inconclusive regarding the most effective treatment step, clinicians and patients can therefore choose between the start of cognitive behavioural therapy or to add an antidepressant to the current antipsychotic medication. Overall, this review stresses that more research is needed to expand our knowledge concerning the treatment of comorbid depressive symptoms or episodes in patients with schizophrenia.

Second, in chapter **8** further treatment aspects of schizophrenia were investigated: by systematically reviewing the literature and performing a meta-analysis on the relationship between long-term mortality risk (i.e., > 52weeks) and the use of different antipsychotics in patients with schizophrenia.This is of clinical relevance, as patients with schizophrenia have a 25-years shorter life expectancy compared to the general population. Strikingly, it is currently unclear what the role of antipsychotics is in this reduced life expectancy. Antipsychotics are known for inducing the metabolic syndrome, potentially leading to an increased mortality risk. At the same time, antipsychotic use leads to a decrease in psychopathology, causing a reduced risk of suicidality and/or other risky behaviour, which may result in a lower mortality risk. Twenty studies met the inclusion criteria, however, due to a great variation in study designs and clinical characteristics, it was only possible to pool results of four studies. Based on these pooled results, an elevated long-term mortality risk for patients not using antipsychotics compared to patients exposed to antipsychotics was found. Different reasons might explain this lower mortality risk in patients treated with antipsychotic medication. For instance, it has been suggested that patients not using antipsychotics should be considered as the most seriously ill patients, and, as a group, they underuse mental and somatic health care. Consequently, these patients may have an increased mortality risk.

Of note, most studies did not report dosages or used inconvertible measures and consequently it was utterly impossible to perform a meta-analysis on the relationship between cumulative exposure and mortality. Nevertheless, based on large included cohort studies,[67,68] it is likely that a low and medium cumulative exposure to antipsychotics, or short-term (0-0.5years) and long-term treatment (5-7 years) is correlated with a lower mortality risk. Overall, the results of this study suggest that antipsychotic treatment (and adherence to it) is important, given the higher mortality risk of patients not taking antipsychotics.

Further, the association between the long-term mortality (i.e., >52weeks) and the use of the antipsychotic clozapine was investigated, and compared to the use of other antipsychotics or no-antipsychotic medication (chapter **9**). Given the superior efficiency of clozapine in treating treatment resistant schizophrenia and its use in preventing suicide in patients diagnosed with schizophrenia, the associated mortality risk of clozapine was considered as clinically relevant.

Overall, 23 studies were included and in a median follow-up duration of 5 years, the unadjusted mortality rate of clozapine use was 6.69 per 1,000 patient years. Based on earlier literature and theory-driven we divided the use of clozapine in 'ever' users (i.e., those exposed to clozapine sometime during follow-up) and 'continuous' users (i.e., those exposed to clozapine during the complete follow-up). Remarkably, a significant lower pooled mortality rate of patients continuously treated with clozapine was found, compared to the patients continuously treated with other antipsychotics (mortality rate ratio=0.47). Non-significant differences were found when patients 'ever' treated with clozapine were compared to patients 'ever' treated with other antipsychotics. These findings suggest an exposure-response relationship in which continuous use of clozapine is associated with beneficial effects on life expectancy, but this effect is reduced when clozapine use is discontinued.

Different reasons can explain the overall lower mortality rates in patients treated with clozapine continuously: for instance, due to the frequent somatic controls during clozapine use there is more contact with clinicians (known as performance bias), which might have caused a closer monitoring of somatic risk factors and psychiatric symptoms. Another reason might be that clozapine most effectively treats psychopathology, which eventually results in a healthier lifestyle and health care use resulting in lower risk of mortality. Overall, the lower mortality risk in patients continuously treated with clozapine, stress that a re-evaluation of the restricted use and the hesitation of clinicians to prescribe clozapine is warranted.

4.1 Future studies regarding treatment and outcome in schizophrenia

4.1.1 Depressive symptoms

In line with previous research, this thesis underlined the importance of a comorbid depressive episode or depressive symptoms and its clinical associations in patients with schizophrenia. In chapter **5** the negative influence of depressive symptoms on the QoL was shown in a cross-sectional design, but in addition to previous studies, also in a prospective follow-up design. Moreover, in both network studies (**2** and **3**) the specific influence of depressive symptoms on suicidality (within the absence of a direct link between suicidality and positive symptoms) and a central role of depressive symptoms in both networks was shown. Given these findings but also the findings in earlier studies, the lack of knowledge

regarding the treatment of this comorbidity was striking (chapter **7**). Nevertheless, there is evidence that evaluating current antipsychotic medication, considering switching, motivating for physical activity, starting CBT and/or the augmentation with an antidepressant to current antipsychotic medication might be effective.

4.1.2 Augmentation with antidepressants

Nowadays, new studies are published every day, with on average even 11 new meta-analyses published daily.[69,70] Indeed, new studies emerged after publication of the review regarding the treatment of depressive symptoms and episodes in patients diagnosed with schizophrenia (chapter **7**). In this paragraph findings of two recent published meta-analyses[71,72] will be discussed with respect to the suggested treatment approach in chapter **7**. Of note, we argued in our review that despite the lack of studies investigating the augmentation with antidepressants for distinct depressive episodes and the possible introduction of interactions, the cautious augmentation with an antidepressant is advisable in case of a persistent, distinctive depressive episode that did not respond to other treatment approaches.

However, contradictory findings were reported by Galling and colleagues:[71] in this meta-analysis the augmentation with antidepressant in patients already treated with antipsychotics was investigated. Antidepressant augmentation did not result in a significant improvement of depressive symptoms compared to placebo (*p*-value= 0.19). In contrast, another recent published meta-analysis by Gregory and colleagues[72] showed a benefit for the augmentation with antidepressant with a ≥50% reduction on a depression scale. Based on this result, the authors reported a number needed to treat of 5 for augmentation with an antidepressant. However, with respect to a continuous outcome measure: improvement of depression score during follow-up showed non-significant differences for all antidepressants compared to placebo. Although when only trials were included that used the CDSS as outcome measure, a significant effect was reported, favouring antidepressant treatment (i.e., standardized mean difference of -0.47, 95%CI -0.92 to -0.02). Different factors might explain the differences in findings between these meta-analyses, as pointed out by Galling and colleagues:[71] for instance, there is a difference regarding the inclusion of studies that investigated the with antidepressants instead of the 'co-initiation' (i.e., in which antidepressant and antipsychotics are started at the same time). Additionally, differences in findings might also be due to pooling of studies that included patients who used second or first generation antipsychotics as 'base' agent, as the serotonergic effects of antidepressants might be limited in patients already using second generation antipsychotics.[71] Lastly, it is questionable whether the results of improving depressive symptoms can be extrapolated to treating a depressive episode. In sum, findings are contradictory with respect to the augmentation with antidepressants and future studies should elaborate on findings by including homogenous samples,[71] using questionnaires validated to assess depressive symptoms in patients with schizophrenia and should make a difference between depressive symptoms or episodes. Nevertheless, given the major consequences of depressive episode in patients with schizophrenia combined with the positive reported results regarding the augmentation with antidepressants, one cycle of antidepressant treatment in appropriate dosages is still recommended. This is especially the case when a patient is treated with a first generation antipsychotic: in this situation antidepressants can be seen as a serotonergic supplementation to the antipsychotic treatment.

4.1.3 Treatment with antipsychotic medication

In chapter **8** and **9** the effect of antipsychotics on mortality in patients diagnosed with schizophrenia was investigated. In the first meta-analysis it was shown that the use of antipsychotics was associated with a lower long-term all-cause mortality risk compared to no antipsychotic use. In a second meta-analysis clozapine was compared to other antipsychotics or no antipsychotic use and a lower long-term mortality risk was found in continuous clozapine users compared to other antipsychotics. These findings are clinically relevant and may motivate clinicians and patients to use antipsychotics and particularly clozapine (after non-responsiveness to two different antipsychotics).

Unfortunately, the use of antipsychotics is associated with high-rates of discontinuation. For example, in a large clinical trial (n= 1493) 74% of the patients discontinued antipsychotics within 18 months.[73] These high discontinuation rates might be due to adverse effects. Antipsychotics are known for a hazardous balance between effectiveness and adverse effects. Adverse effects are (partly) due to dopamine D2 receptor occupancy and high dosages of neuroleptics lead to increased blockage of this dopamine receptor leading to increased (extrapyramidal) side effects, which in turn could contribute to decreased treatment adherence. A lower dosage of antipsychotics medication could be effective to enhance treatment adherence but also to reduce adverse effect, but is challenging for clinicians because of the threat of a psychotic relapse. Results of upcoming randomized controlled trials (e.g., the Dutch multicentre Handling Antipsychotic Medication Long-term Evaluation of Targeted Treatment (HAMLETT) study,[74] which investigates the reduction or discontinuation of antipsychotic medication, will provide valuable information for clinicians regarding this issue.

5. METHODOLOGICAL CONSIDERATIONS

Different methodological considerations are related to the various chapters of this thesis, which are more extensively discussed in the limitation sections of each chapter. In general, the methodological consideration of the GROUP – study[75] are applicable for the chapters **2, 3** and **5**. At first, the GROUP – study is an observational cohort study with a large sample size, which provides a realistic reflection of a clinically ill population diagnosed within the psychosis spectrum. However, this study design also has some difficulties. For example, due to its naturalistic design it was considered impossible to investigate the influence of medication use on the symptom networks as presented in chapter **2**, **3** or the influence of medication on QoL (chapter **5**). Due to the wide variation in the use of types of medication, dosages, duration and other treatments it was unfeasible to model this in the symptoms networks and/or SEM-model. Furthermore, the GROUP study consisted of an extensive battery of questionnaires and neurocognitive tasks. The patients, who were willing and able to participate, probably consisted of a relatively well-functioning sample. Moreover, it is likely that the most serious-ill patients tend to drop out more frequently than patients with less severe illness. In other words selection bias reduces the generalizability of results obtained from the GROUP study. This selection bias is especially relevant in chapter **5**, where only those patients were included of whom follow-up data was available in our longitudinal analyses.

In general, the network approach has been applied in different areas of science, however, it is until recent that is has been applied in psychiatry. As a result, there are several methodological issues of debate (chapter **2** and **3**). First, symptom interactions were studied in cross-sectional design and as such, claims regarding causality cannot be made. This cross-sectional design is an important limitation, which requires cautiousness in the interpretation of our results. Nevertheless, findings of (cross-sectional) network studies underline the importance of interconnectedness between symptoms, which can serve as a hypothesis for future research (e.g., interventions in these hypothesized pathways). Second, despite the promise (of the value) of identifying central symptoms, there are no studies to date demonstrating that targeting central symptoms will indeed lead to better outcomes. Randomized controlled trails are needed to demonstrate whether targeting symptoms with high centrality will cause better outcomes compared to treatment as usual.[19] Fortunately, the network approach is developing rapidly and improvements of statistical techniques are emerging. For example, most recently an article was published regarding the 'predictability of central symptoms'.[76] An improvement of 'predictability' compared to the standard centrality analysis is its ability to provide an absolute measure (current centrality analysis offer only relative measures). The use of an absolute centrality measure will make it feasible to compare centrality symptoms between networks. Third, in the interpretation of results (including centrality measures) from network studies, one should bear in mind that results are based on group level and it is currently unknown to what level group-level results overlap with networks in individuals, most often obtained via repeated measurements or time-series.[8] Fourth, to enhance the robustness of the generated networks the number of participants needs to be sufficient in relation the number of included symptoms. Including too many symptoms will diminish the robustness of the network, while only including a few symptoms might lead to omission of important correlations. However, it is unclear which symptoms are most important. Therefore, current networks are based on the questionnaires used, which frequently include the symptoms as described in classifications systems (such as the Diagnostic Diagnostic and Statistical Manual of Mental Disorders: DSM). In other words, the networks are constructed based on existing questionnaires, and using other questionnaires might lead to other networks. Currently, it is up to researches to determine the 'right' variables (i.e., symptoms). As described in our network studies, symptoms from the CASH, CDSS and PANSS were retrieved, which are widely, used instruments and show symptomatic overlap. There are several developments to improve this approach, such as the incorporation of beyond-symptom variables (e.g., childhood trauma)[15] and or a more systematic integration of different levels as postulated by Looijesteijn.[37]

Regarding the systematic review describing the neuronal alterations during emotion regulations: the applied model by Phillips and colleagues[38,39] suggests that all subprocesses of emotion regulation are distinguishable, which is questionable as most strategies of emotion regulation will consist of different subprocesses. Of note, the model enables to study emotion regulation with more precision and with respect to corresponding neuronal alterations. In addition, this model describes two brain systems involved in emotion regulation (i.e., ventral and dorsal system), while there are probably many more brain-networks involved (such as the default mode network (DMN), frontoparietal and salience network) which are not considered.

With respect to the treatment and outcome studies: at first, the analyses performed in chapter **6** were based on retrospective data and consequently the figures we found could be an underestimation as clinicians could have forgotten to report adverse events in the used medical records. Additionally, with respect to chapter **7**, this review is a narrative review. Considering the different treatment interventions (antipsychotics, augmentation with antidepressants, CBT, physical exercise etc.) a systematic review or meta-analysis for all these outcomes was not performed. However, by integrating different areas of research this review added to current clinical knowledge by integrating several treatment approaches to guide every day practice.

Subsequently, when interpreting the meta-analysis regarding the use of antipsychotics and clozapine in particular, one should bear in mind that most of the included studies were cohort studies. Cohort studies are known for the potential of selection bias. Moreover, due to the lack of detailed reporting in most of the included studies it was impossible in both meta-analyses to correct for important confounders such as ethnicity, smoking behaviour, duration of illness, number of previous hospitalizations, history of suicidal behaviour or physical illness.

6. CONCLUSION

This thesis has two main aims. First, to review and increase knowledge concerning symptom interaction in patients with schizophrenia, with a specific focus on co-occurring depressive symptoms and its neural correlates in major depressive disorder (Part I and II). Second, to review and investigate different treatment aspects and outcomes in schizophrenia (quality of life, depressive symptoms and mortality) (Part III).

In sum, both network studies showed the importance of depressive symptoms in the symptom networks of patients with schizophrenia and showed the stability of such a network structure. Although the network approaches has several issues of debate, it is a promising new way of thinking about psychopathology. The network approach is an example of a new conceptualisation of psychopathology as dynamic systems that change over time. Additionally, this view on mental illness facilitates a more transdiagnostic approach, in which emotion regulation should be an important target for future studies.

Given the frequent co-occurrence of depressive symptoms in patients with schizophrenia, its centrality, its correlations with suicidality and influence on QoL, it is highly important to adequately treat co-occurring depressive symptoms and episodes. Systematically following the provided treatment guide to treat depressive symptoms or episodes might be useful.

Additionally, meta-analyses showed that schizophrenia patients who do not use antipsychotics have a higher mortality risk compared to patients that use antipsychotics. In a similar way, continuous use of clozapine was related to a lower mortality risk compared to patients using other antipsychotics.

Hopefully, reading this thesis will help clinicians to be more concerned about the importance of symptom interaction and the possible development of depressive symptoms in patients with schizophrenia, regardless if these symptoms meet the DSM depression criteria. In addition to recognizing and diagnosing a possible depressive episode, the treatment of this co-morbidity consists of several options that need to be considered because improvement of depressive symptoms will lead to improvement of other symptoms. Moreover, treating depressive symptoms will possibly not only lead to an improvement of quality of life at a certain time-point but also during follow-up.

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DUTCH SUMMARY / NEDERLANDSE SAMENVATTING

Dit proefschrift getiteld 'Depressive and psychotic symptoms in schizophrenia: focus on networks and treatment' had twee belangrijke doelstellingen. Ten eerste was het doel om de kennis te vergroten over interacties tussen symptomen bij patiënten met schizofrenie. In dit deel stonden depressieve symptomen in interactie met andere symptomen en de onderliggende neurologische veranderingen die geassocieerd zijn met depressieve symptomen centraal (deel I en II van dit proefschrift). Het tweede doel was om onze kennis van verschillende aspecten van de behandeling van patiënten met schizofrenie te vergroten (deel III van dit proefschrift). In dit hoofdstuk wordt een samenvatting gegeven van onze bevindingen.

In hoofdstuk **1** wordt een algemene introductie gegeven over symptomen en de behandeling van schizofrenie. Schizofrenie is een relatief zeldzame chronische aandoening die wordt gekenmerkt door een kwetsbaarheid voor psychotische episodes. Tijdens een psychotische episode staan wanen en/of hallucinaties op de voorgrond. De behandeling van schizofrenie bestaat uit meerdere onderdelen, waaronder een medicamenteuze behandeling (vaak met antipsychotica), psycho- en gedragstherapie en de ondersteuning in sociale zaken zoals huisvesting en het vinden van een baan. Gelet op de psychotische kwetsbaarheid van deze patiëntengroep is er in veel gevallen een noodzaak tot een langdurige behandeling met antipsychotica.

Naast psychotische episoden hebben patiënten met schizofrenie vaak andere klachten, zoals negatieve en depressieve symptomen. Negatieve symptomen betreffen gedragingen en/of verschijnselen die verminderd of helemaal niet meer aanwezig zijn. Voorbeelden van negatieve symptomen zijn onder andere een afvlakking van het gevoelsleven, moeite om dingen vol te houden, een gebrek aan initiatief en verminderde behoefte aan sociale contacten. Daarnaast rapporteren veel patiënten met schizofrenie ook depressieve symptomen.

Hoe vaak depressieve episoden of depressieve symptomen voorkomen bij patiënten met schizofrenie is onduidelijk. De studies die dit onderzochten rapporteren uiteenlopende uitkomsten, maar over het algemeen wordt ervan uit gegaan dat de mediane prevalentie van een depressieve episode in deze patiëntengroep 25% is. Dit betekent dat 25% van alle patiënten met schizofrenie op een zeker moment een depressieve episode doormaken. De depressieve symptomen hebben verregaande consequenties zoals een verhoogd risico op suïcide, een slechtere therapietrouw en meer middelenmisbruik. Met andere woorden: gelet op deze gevolgen moeten clinici alert zijn op het ontwikkelen van een depressieve episode en zo nodig de behandeling hierop afstemmen.

DEEL I (HOOFDSTUK 2 - 3) ONDERZOEK NAAR SCHIZOFRENIE MET EEN NETWERKBENADERING

Het eerste doel van dit proefschrift was om meer inzicht te krijgen in de interacties tussen symptomen bij patiënten met schizofrenie. In de huidige psychiatrische classificatie systemen (waaronder de *Diagnostic and Statistical Manual of Mental Disorders* (DSM)) worden symptomen bij elkaar gegroepeerd omdat ze voorkomen bij dezelfde psychiatrische stoornis. Deze classificerende benadering werkt in de hand dat er grote verschillen bestaan binnen de groep van patiënten gediagnosticeerd met dezelfde psychiatrische stoornis en aan de hoge mate van co-morbiditeit tussen psychiatrische stoornissen.

Een relatief nieuwe methode, de netwerk benadering, maakt het mogelijk om op een andere wijze te kijken naar symptomen die voorkomen bij een bepaalde stoornis: namelijk door het bestuderen van interacties tussen individuele of clusters van symptomen. De netwerk benadering gaat er namelijk van uit dat psychiatrische stoornissen niet simpelweg de 'optelsom' zijn van (psychiatrische) symptomen, maar stelt dat symptomen op betekenisvolle wijze samenhangen en met elkaar interacteren. Psychiatrische stoornissen zijn volgens de netwerk benadering het gevolg van een wederzijdse interactie tussen symptomen.

In hoofdstuk **2** is op grond van een uitgebreide symptoom inventarisatie met behulp van de *Comprehensive Assessment of Symptoms and History* (CASH) een symptoom netwerk gemaakt. De CASH is een diagnostisch, gestructureerd interview welke een breed scala aan symptomen meet en die kan worden gebruikt om te diagnosticeren binnen de schizofrenie-spectrum stoornissen. Voor de netwerkanalyse werden van de CASH 79 symptomen gebruikt, gemeten bij 408 (mannelijke) patiënten. Deze patiënten hadden alle deelgenomen aan het *Genetic Risk and Outcome of Psychosis* (GROUP) - project, een longitudinale observationele studie waarin patiënten, gediagnostiseerd met een non-affectieve psychose, 6 jaar lang zijn gevolgd.

Het symptoom netwerk liet zien dat de verbindingen tussen symptomen die onderdeel waren van a-priori, door de CASH, gedefinieerde domeinen sterker waren dan tussen symptomen uit andere symptoom domeinen. Enkele specifieke verbindingen tussen symptomen leverden betekenisvolle informatie op. Bijvoorbeeld 'terugkerende gedachten aan de dood / suïcide' was wel verbonden met andere depressieve symptomen en niet direct met psychotische symptomen (zoals wanen of hallucinaties). Dit was anders dan op basis van eerdere studies werd verwacht. Een andere bevinding was dat het symptoom 'grootheidswanen' niet alleen verbonden was met waanachtige symptomen maar ook met manische symptomen. Dit zou kunnen betekenen dat patiënten met manische symptomen die daarbij grootheidswanen krijgen, meer kans hebben om ook andere wanen te ontwikkelen (of *vice versa*).

Naast het observeren van specifieke verbindingen is het met de netwerk benadering ook mogelijk om de zogenaamde 'kortste route' tussen symptomen en symptoomdomeinen te verkennen. De 'kortste route analyse' is een relatief nieuwe hypothese-genererende techniek binnen de netwerk benadering die - alhoewel er meerdere routes zijn tussen verschillende symptomen - de kortste route visualiseert tussen symptomen en symptoomdomeinen.

Er wordt vanuit gegaan dat de interacties tussen symptomen vaker zal verlopen via deze 'kortste route'. Uit deze 'kortste route analyse' bleek dat het symptoom cluster 'anhedonie - antisocialiteit' samen met 'achtervolgingswanen' een belangrijke rol hebben in de verbinding tussen de symptoomdomeinen wanen en depressie. Een interpretatie van deze resultaten kan zijn dat patiënten die aan achtervolgingswanen lijden, meer geneigd zijn om daarnaast symptomen van anhedonie te ondervinden, welke gevolgd kunnen worden door depressieve symptomen of *vice versa*.

Tevens hebben we gekeken welke symptomen het meest 'centraal' zijn in het symptoom netwerk. Alhoewel de analyses in onze studies zijn gebaseerd op bevindingen op groepsniveau, wordt ervan uit gegaan dat de centrale symptomen het meest belangrijk zijn en mogelijk kunnen dienen als aangrijpingspunten voor behandeling van een individu. Deze assumptie wordt onderbouwd door het theoretische principe dat met het beïnvloeden van deze centrale symptomen, die sterk verbonden zijn met andere symptomen in het netwerk, ook andere symptomen zullen veranderen. Met andere woorden: behandelinterventies gericht op centrale symptomen zullen ook leiden tot een verbetering in andere symptomen. In het door ons onderzochte netwerk bleek dat de symptomen 'verlies van interesse en plezier', 'onvermogen om te genieten van activiteiten', 'onvermogen om relaties met vrienden te vormen of te onderhouden', 'gedachtenarmoede' en 'ongeorganiseerde spraak' centraal en dus belangrijk waren in het symptoom netwerk. Deze symptomen hebben gemeenschappelijke dat ze interfereren met de sociale participatie en communicatie van patiënten.

Gebaseerd op de resultaten uit hoofdstuk **2** wilden we de associaties tussen depressieve en positieve symptomen verder onderzoeken. Hoewel de CASH een breed palet aan symptomen beslaat is dit instrument niet optimaal voor het differentiëren tussen depressieve symptomen en negatieve symptomen in patiënten met schizofrenie. Daarom zijn in hoofdstuk **3** de associaties van depressieve symptomen verder onderzocht door gebruik te maken van de *Calgary Depression Rating Scale for Schizophrenia* (CDSS). De CDSS is een gevalideerde vragenlijst om een depressieve episode en symptomen in patiënten met schizofrenie vast te stellen.

Voor het construeren van een symptoom netwerk werden naast de symptomen van de CDSS ook positieve en negatieve symptomen, die onderdeel zijn van de *Positive and Negative Syndrome Scale* (PANSS), gebruikt. Voor dit netwerk werd data gebruikt van 470 mannelijke patiënten, allen gediagnosticeerd met een non-affectieve psychose. Ook hier betrof het deelnemers aan het eerder genoemde GROUP-project. In lijn met de resultaten uit hoofdstuk **2** was het symptoom 'suïcidaliteit' ook in dit symptoom netwerk verbonden met verschillende depressieve symptomen en was er slechts één verbinding met het positieve symptoom 'achterdocht'.

Hoewel de resultaten van deze studie replicatie behoeven, suggereren de bevindingen uit beide netwerk studies (hoofdstuk **2** en **3**) dat het vooral symptomen van depressie zijn die suïcidale gedachten beïnvloeden. Dat is bijzonder omdat suïcidaliteit dus minder direct samenhangt met psychotische symptomen dan eerder werd gedacht. Eerder studies onderstreepten dat het vooral akoestische hallucinaties zijn die patiënten aan kunnen

zetten tot suïcidaliteit. Terwijl de symptoom netwerken suggereren dat wanen sterk samenhangen met symptomen van depressie en mogelijkerwijs via deze route suïcidale gedachten kunnen induceren, in plaats van een direct invloed van wanen op suïcidale gedachten (of *vice versa*). Hierbij moet gezegd worden dat beide netwerk studies gebaseerd zijn op cross-sectionele data en dat er daardoor geen uitspraken gedaan kunnen worden te aanzien van causaliteit.

Verder bleek dat de symptomen 'depressieve stemming', 'geobserveerde depressie', 'contactgestoordheid', 'stereotype manier van denken' en 'wanen' centrale symptomen waren in dit netwerk. Het feit dat 'contactgestoordheid' een centraal symptoom was, komt overeen met de gevonden centrale symptomen zoals beschreven in hoofdstuk 2. Deze bevindingen komen ook overeen met die in netwerkstudies naar depressieve patiënten, welke vonden dat de symptomen 'depressieve stemming' en 'verlies van interesse' het meest frequent de centrale symptomen waren in deze netwerken. Dit suggereert dat het symptoom 'depressieve stemming' een transdiagnostisch centraal symptoom is.

Daarnaast is er onderzocht wat de verschillen waren tussen het netwerk van patiënten die op het moment van onderzoek niet psychotische waren (ook wel 'in remissie' genoemd) ten opzichte van patiënten die *wel* psychotisch waren. Tussen de beide symptoom netwerken werden er geen significante verschillen gevonden met betrekking tot de 'netwerkstructuur'. Wel werden er significante verschillen gevonden in de 'globale sterkte' van de verbindingen tussen symptomen. Het significante verschil met betrekking tot de globale sterkte is meest waarschijnlijk het gevolg van een groter aantal verbindingen in het symptoom netwerk van patiënten die op dat moment *wel* psychotisch waren. Dit duidt op de mogelijke aanwezigheid van 'vicieuze cirkels' van symptomen, waarbij symptomen niet alleen samen voorkomen maar elkaar blijven versterken in de netwerken van patiënten die een psychose hebben. Al met al, zouden deze vicieuze cirkels een verklaring kunnen zijn waarom symptomen blijven bestaan.

Over het geheel genomen, onderstreepten de resultaten uit de hoofdstukken 2 en 3 dat de netwerkbenadering een bijdrage kan leveren om onze kennis van psychopathologie te verbeteren. Specifieke symptoom interacties kunnen bijvoorbeeld inzicht geven in het ontstaan van psychopathologie en/of het instant houden van symptomen. Van daaruit kunnen er mogelijke nieuwe aangrijpingspunten voor behandelingen worden gevonden.

DEEL II (HOOFDSTUK 4) NEURONALE VERANDERINGEN VAN DEPRESSIEVE SYMPTOMEN IN PATIËNTEN MET EEN DEPRESSIEVE STOORNIS

In hoofdstuk 4 worden de resultaten van verschillende neuroimaging studies beschreven waarin emotieregulatie bij patiënten met een depressieve stoornis is onderzocht. Emotieregulatie beschrijft een proces dat het waarnemen, reageren en reguleren van emotionele stimuli beslaat. Het niet goed kunnen reguleren van emoties wordt beschouwd als een belangrijk kenmerk voor psychopathologie omdat emotieregulatie zo'n essentieel onderdeel uitmaakt van het dagelijks leven. Problemen in het reguleren van emoties worden als kernprobleem gezien bij patiënten met een depressieve stoornis.

Om het onderzoek naar emotieregulatie te vergemakkelijken hebben Phillips en collega's een model ontwikkeld waarin verschillende deelprocessen van emotieregulatie zijn opgenomen. Als eerste wordt er een onderscheid gemaakt tussen het automatisch (of bijna onbewust) reguleren van emoties en door inspanning vereiste (bewust) reguleren van emoties. Daarnaast zijn er drie verschillende 'strategieën' om emoties te reguleren (zoals het aanpassen van gedrag, het veranderen van de aandacht en/of gedachten). Op deze manier worden in totaal 6 verschillende deelprocessen onderscheiden om emoties te reguleren. Om een voorbeeld te noemen, iemand kan zijn emoties reguleren door bewust te denken aan iets plezierigs tijdens bijvoorbeeld een droevige situatie (op deze manier wordt er gebruikt gemaakt van een bewuste manier om de aandacht op iets anders te richten).

Eerdere neuroimaging studies hebben verschillende hersengebieden vastgesteld welke bij gezonde personen betrokken zijn in de verschillende deelprocessen van emotieregulatie. In hoofdstuk **4** wordt een overzicht gegeven van de gevonden verschillen in hersenactiviteit tussen patiënten met een depressieve stoornis in vergelijking met gezonde personen. De bevindingen van de geïncludeerde studies suggereren dat patiënten met een depressie tijdens het automatische reguleren van emoties extra neuronale gebieden activeren. Dit betreft met name de gebieden aan de buitenzijde van de voorkant van de hersenen (te weten: de laterale prefrontale gebieden). Dit betrekken van extra gebieden lijkt nodig te zijn om de sterke invloeden uit het 'overactieve' limbische systeem aan te kunnen. Door het activeren van deze extra gebieden wordt het voor patiënten met een depressie mogelijk om op een adequate wijze, door middel van automatische processen hun emoties te reguleren. Echter in de meeste studies die onderzoek deden naar bewuste emotie regulatie hadden depressieve patiënten tijdens het bewust reguleren van emoties een vergelijkbare of een afgenomen activiteit in de gebieden aan de voorkant van de hersenen, in vergelijking met gezonde controles. Op basis van de huidige literatuur werd er gesuggereerd dat het depressieve patiënten mogelijk onvoldoende lukt om bewust emoties te reguleren, als de emotie al hun aandacht heeft. Het bewust reguleren van een emotie waar je je al bewust van bent is blijkbaar moeilijker dan het reguleren van een emotie waar je je nog niet van bewust bent. Bij depressieve patiënten zorgt het bewust zijn van de emoties er dan voor dat het niet lukt om actief emotie regulatie toe te passen en worden de betreffende hersengebieden onvoldoende geactiveerd. Een mogelijke klinische implicatie van deze bevinding zou kunnen zijn dat behandelinterventies waar iemand bewuste emotie regulatie voor moet kunnen toepassen (zoals cognitieve gedragstherapie), pas zal moeten worden gestart als men weet of een patiënt in staat is om automatische emoties regulatie toe te passen. Echter meer onderzoek zal nodig moeten zijn om deze hypothese en toepassing te testen.

DEEL III (HOOFDSTUK 5-9) BEHANDELING EN UITKOMSTEN IN SCHIZOFRENIE

Aangezien depressieve symptomen centraal bleken te staan in de uitgevoerde netwerk-analyses is er in hoofdstuk **5** gekeken naar de associatie tussen depressieve symptomen en de kwaliteit van leven van patiënten met schizofrenie. Nationale en internationale richtlijnen benoemen kwaliteit van leven als één van de belangrijke uitkomstmaten in de langdurige behandeling van de patiënt met schizofrenie. Door het onderzoeken en identificeren van variabelen die geassocieerd zijn met de kwaliteit van leven, kunnen behandelinterventies gericht worden op die variabelen die bijdragen aan kwaliteit van leven.

Hoe en welke variabelen samenhangen met kwaliteit van leven is al vaker ondergezocht en deze cross-sectionele studies laten onder andere zien dat met name depressieve symptomen zorgen voor een slechtere kwaliteit van leven. Echter, op basis van cross-sectionele studies kunnen er geen conclusies worden getrokken over de richting van deze verbanden: krijgt men door een depressie een slechtere kwaliteit van leven krijgt of juist andersom? Daarnaast is het waarschijnlijk dat er meerdere variabelen betrokken zijn bij de associatie tussen depressie en kwaliteit van leven: een depressie leidt tot beperkingen in het sociaal functioneren en zou op deze wijze ook kunnen bijdragen aan een slechtere kwaliteit van leven. Recent werd er een studie door Alessandrini en collega's gepubliceerd, waarin gebruik gemaakt werd van *Structural Equation Modeling* (SEM). Deze studie liet zien dat depressieve symptomen zorgden voor een slechtere kwaliteit van leven. Daarnaast waren neurocognitief functioneren, sociaal functioneren en psychotische symptomen ook van (indirecte) invloed op de kwaliteit van leven. SEM maakt het mogelijk om niet alleen meerdere voorspellers te includeren maar ook om uitspraken te doen over de volgorde waarop en in welke mate deze interacteren.

Wij onderzochten in hoofdstuk **5** of het model van Alessandrini ook kon worden gerepliceerd in deelnemers aan het GROUP-project. Tevens werd gekeken of dit SEM-model behulpzaam was in het voorspellen van de kwaliteit van leven na 3 jaar. Specifiek onderzochten wij of de variabelen neurocognitief functioneren, sociaal functioneren, depressie en psychotische symptomen voorspellend zijn voor de kwaliteit van leven 3 jaar later en in welke mate ze dat doen. Uit deze studie bleek dat deze variabelen zowel de kwaliteit van leven op hetzelfde moment als 3 jaar later beïnvloeden. In beide modellen hadden depressie en sociaal functioneren een negatieve invloed op de kwaliteit van leven. Daarbij was de ernst van de psychotische symptomen sterk geassocieerd met sociaal functioneren. Het feit dat depressie een negatieve, langdurige impact had op de kwaliteit van leven onderstreept het belang van adequate behandeling van depressie bij mensen met een schizofrenie.

In hoofdstuk **6** werd een nieuwe benaderingswijze geïntroduceerd om de kwaliteit van zorg voor patiënten met een psychose te meten. In de huidige literatuur wordt de kwaliteit van zorg van patiënten die zijn opgenomen op psychiatrische afdelingen weinig onderzocht. Dit is opvallend mede gelet op het dramatische sterftecijfer in deze groep (patiënten met schizofrenie leven gemiddeld 25 jaar korter ten opzichte van de algemene bevolking). Dit vroegtijdig overlijden wordt met name veroorzaakt door hart- en vaatziekten en het optimaliseren van deze behandelbare aandoening is in deze groep patiënten essentieel.

In dit hoofdstuk hebben we 'proces maten' (dat wil zeggen wat *voor* de patiënt is gedaan om de gezondheid te verbeteren zoals bijvoorbeeld lichamelijk en aanvullend bloed onderzoek) gecombineerd met uitkomstmaten (gedefinieerd als gebeurtenissen die de patiënt zijn overkomen ten tijde van de behandeling zoals bijwerkingen van medicatie). Deze proces – en uitkomstmaten werden retrospectief gedestilleerd uit de medische dossiers van patiënten die werden ontslagen na opname op een psychiatrische afdeling. Uit deze studie bleek dat een aantal basale, doch essentiële onderdelen van een lichamelijk onderzoek (zoals gewicht- of bloeddrukmetingen) niet was uitgevoerd in een derde van de opgenomen patiënten. Opmerkelijk was ook het feit dat slechts 1% van alle patiënten die rookten een interventie kregen aangeboden om te stoppen met roken. Op basis van deze gegevens werd er geconcludeerd dat er veel ruimte was voor verbetering in de behandeling van patiënten met schizofrenie.

Dit is vooral van belang omdat een klinische opname moet worden gezien als een moment in de langdurige behandeling van deze patiëntengroep: het verrichten van een basaal somatische screenend onderzoek, het aanbieden van interventies om te stoppen met roken en systematisch evalueren van bijwerkingen op medicatie zijn hierin van groot belang om de uitkomsten van patiënten met schizofrenie te verbeteren.

Deel III van dit proefschrift eindigt met drie studies die verschillende behandelaspecten beschrijven van schizofrenie. In hoofdstuk 7 beschreven we op basis van literatuurstudie verschillende behandelopties voor de behandeling van depressieve symptomen en episoden in patiënten met schizofrenie. Zoals eerder genoemd krijgen veel patiënten met schizofrenie gedurende hun leven te maken met depressieve symptomen of een episode(n). Het probleem is echter dat er op dit moment geen studies zijn die alle relevante behandelopties voor deze co-morbiditeit bespreken, waardoor het voor clinici onvoldoende helder is wat de meest effectieve stappen zijn in de behandeling van depressieve symptomen of episode bij patiënten met schizofrenie en in welke volgorde deze – idealiter – zouden moeten plaatsvinden.

Over het geheel genomen was zowel het aantal als de kwaliteit van studies naar het effect van verschillende behandelinterventies gericht op een depressieve episode of symptomen in schizofrenie bijzonder laag. Dit is opmerkelijk gezien de hoge prevalentie van depressieve episoden en symptomen in schizofrenie. Op dit moment is er het meeste evidentie om bij een depressieve episode of symptomen de volgende stappen te ondernemen: nagaan of er sprake is van middelengebruik, overwegen of er sprake kan zijn van een psychotische exacerbatie (en zo ja, deze adequaat te behandelen middels antipsychotica), het evalueren en eventueel verminderen van de dosering van de antipsychotica, overwegen te switchen tussen antipsychotica en daarnaast motiveren tot bewegen. Wanneer bovenstaande interventies niet effectief zijn en er daadwerkelijk sprake is van een duidelijke depressieve episode wordt er geadviseerd te starten met een antidepressivum dan wel cognitieve gedragstherapie. Vooralsnog is onduidelijk welke van deze twee laatste behandelopties de voorkeur heeft en in welke volgorde ze zouden moeten worden ingezet.

In hoofdstuk 8 werd de associatie onderzocht tussen het gebruik van antipsychotica en de kans op sterfte bij patiënten gediagnosticeerd met schizofrenie. Antipsychotica zijn redelijk effectief gebleken voor het behandelen van psychotische symptomen. Echter, het langdurig gebruik van antipsychotica gaat gepaard met het risico op diverse bijwerkingen, zoals gewichtstoename, een risico om suikerziekte te ontwikkelen en een verstoring van het lipidenspectrum; dit zijn allen factoren die het risico op cardiovasculaire sterfte verhogen. Zoals eerder genoemd, is de levensverwachting van patiënten met schizofrenie gemiddeld 25 jaar korter dan de gezonde populatie. Het is tot op heden onvoldoende duidelijk wat de rol van antipsychotica is in dit vervroegde overlijden. In hoofdstuk 8 werd een systematische review en meta-analyse uitgevoerd om hier meer inzicht over te krijgen.

We concludeerden dat het risico op sterfte op de lange termijn in patiënten die geen antipsychotica gebruikten hoger was dan in de groep die wel antipsychotica gebruikte. Het is onbekend waardoor de groep patiënten die geen antipsychotica gebruikte een hoger

risico heeft om te overlijden. Mogelijk representeert deze groep patiënten een ernstig zieke groep die weinig tot geen gebruik maakt van de gezondheidszorg waarbij sprake is van slechtere zelfzorg, lichamelijke risicofactoren en onbehandelde psychiatrische klachten (waardoor er meer kan is op suïcide en ander risicovol gedrag).

Omdat er in veel studies geen details werden vermeld over de dosering en de lengte van het gebruik van de antipsychotica konden er helaas geen conclusies getrokken worden over het effect van de hoogte en de duur van blootstelling aan antipsychotica. Tevens ontbraken in veel studies de reden van overlijden waardoor er geen uitspraken kan worden gedaan of de redenen van overlijden verschilden tussen patiënten die wel of niet langdurig antipsychotica gebruikte. Kort samengevat: het gebruik van antipsychotica is op de lange termijn niet geassocieerd met een verhoogd risico op overlijden ten opzichte van het niet gebruiken van antipsychotica.

Ten slotte is er in hoofdstuk 9 een tweede meta-analyse uitgevoerd waarin werd gekeken naar het effect van het gebruik van clozapine en de kans op overlijden op de lange termijn. Clozapine is een antipsychoticum, welke door zijn superieure effectiviteit een bijzondere plek heeft in de groep van antipsychotica. Echter door de ernstige, doch zeldzame bijwerkingen als een ontsteking van de hartspier (myocarditis) en een acute daling in afweercellen (agranulocytose) wordt geadviseerd in de meeste richtlijnen clozapine alleen voor te schrijven als een patiënt met schizofrenie geen afname in symptomen laat zien op twee andere antipsychotica. Clozapine is een antipsychoticum die het sterkst geassocieerd is met bijwerkingen die kunnen leiden tot een verhoogd risico op hart- en vaatziekten (onder andere door de forse gewichtstoename bij het gebruik van clozapine). Door de bijzondere plek die clozapine inneemt is de vraag of patiënten op de langer termijn eerder overlijden bij het gebruik van clozapine ten opzichte van het gebruik van andere antipsychotica of geen antipsychotica.

Op basis van de huidige literatuur werd er geconcludeerd dat er bij langere tijd en continu gebruik van clozapine een lagere kans was op overlijden ten opzichte van de langdurige continu blootstelling aan andere antipsychotica. Het risico op overlijden op de lange termijn was niet significant hoger wanneer er werd gekeken naar het verschil tussen het in het verleden gebruiken van clozapine ten opzichte van het in het verleden gebruiken van andere antipsychotica. Dit suggereert mogelijk een blootstellings-respons relatie, waarbij het continu blootgesteld zijn aan clozapine geassocieerd is met positieve effecten die zorgen voor een verlengde levensverwachting. Dit effect gaat echter verloren als clozapine gestopt wordt. Anderzijds, zouden deze bevindingen ook verklaard kunnen worden door kenmerken van de groep die stopt met clozapine. Mogelijk zijn deze kenmerken (zoals een gebrek aan respons of ernstige bijwerkingen op clozapine of therapieontrouw) op zichzelf geassocieerd met een hogere mortaliteitsrisico.

Er zijn meerdere verklaringen te bedenken waarom clozapine geassocieerd is met een lagere sterftekans. Mogelijk zorgt clozapine voor het effectiever behandelen van psychiatrische symptomen waardoor patiënten beter functioneren, er een grotere kans is op het onderhouden van een gezondere levensstijl en daardoor een lagere kans hebben op

overlijden. Een andere mogelijkheid kan zijn dat medische controles (die noodzakelijk zijn bij gebruik van clozapine) ervoor zorgen dat hun lichamelijke en geestelijke toestand beter kan worden gemonitord. Al met al wijzen de bevindingen van deze meta-analyse erop, dat clozapine de mortaliteit niet verhoogd.

Hoofdstuk **10** geeft tenslotte een bespreking van de belangrijkste bevindingen van de hoofdstukken **2-9**, beschrijft de klinische implicaties van deze bevindingen. Ook worden er aanbevelingen gedaan voor toekomstig onderzoek.

PHD PORTFOLIO AND PUBLICATION LIST

Name:	Geeske van Rooijen
PhD period:	January 2015 – May 2018
Promotor:	Prof. dr. L. de Haan
Copromotores:	Dr. H.G. Ruhé, Dr. C.J. Meijer

LIST OF PEER REVIEWED PUBLICATIONS

Accepted

A state-independent network of depressive, negative and positive symptoms in male patients with schizophrenia spectrum disorders. van Rooijen G, Isvoranu AM, Kruijt OH, van Borkulo CD, Meijer CJ, Wigman JTW, Ruhé HG, de Haan L, GROUP investigators. *Schizophr Res* 2018;193:232-239.

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(* Authors shared senior authorship; ** Authors shared first authorship; *** All authors contributed equally)

Submitted / Under review:

Longitudinal evidence for a relation between depressive symptoms and Quality of Life in Schizophrenia using Structural Equation Modeling. van Rooijen G, van Rooijen M, Maat A, Vermeulen JM, Meijer CJ, Ruhé HG, de Haan L, GROUP investigators.

Measuring process indicators and adverse events to assess the quality of care for inpatients with psychosis. Vermeulen JM, van Rooijen G, van Dijk M, van Tricht MJ, de Haan L.

Book chapter

Schizofrenie en depressie. van Rooijen G, Ruhé HG, de Haan L. Handboek Schizofrenie. Uitgeverij de Tijdstroom *[In Press].*

TEACHING

Supervising

Marita van de Kerkhof – *Master thesis: Clozapine and long-term mortality risk in patients with schizophrenia; a systematic review and meta-analysis*	2017

General Courses

Groepsdynamica, basiscursus	2017
Psylearning, e-learning over de DSM-5	2017
Cochrane Systematic Reviews	2010
SCID training	2008

Scientific writing in English 2007
Oral presentation in English 2007

Specific courses

Psychological Networks Amsterdam Summer School 2016
MRI scanning course 3-Tesla scanner, AMC, Amsterdam 2008

(Inter)national conferences

Schizophrenia International Research Society Conference
Florence, Italy 2018
American Psychiatric Association (APA), Annual Meeting.
Toronto, Canada. 2015

Poster presentation

Six weeks of paroxetine treatment improves dorsolateral prefrontal brain activity. An fMRI study using the Tower of London
International Society of Affective Disorders, Vancouver, Canada 2010

Oral presentations

Netwerkanalyses van affectieve symptomen
Masterclass NVP 'Stemming en slaap bij psychose', Utrecht 2018

Clinical work/ Studies

Medical school,
University of Amsterdam 2005 – 2012

Medical doctor, department of psychiatry
Medisch Centrum Haaglanden, The Hague. 2013 – 2014

Resident Psychiatry,
AMC, Amsterdam 2014 – 2018

Resident psychiatry,
Arkin, Amsterdam 2017 – 2018

ACKNOWLEDGEMENTS / DANKWOORD

Er is een (zeer beperkt) aantal voordelen van het combineren van een opleiding – en promotietraject, één daarvan is dat je de kans krijgt om mensen te bedanken die bij één van deze onderdelen een belangrijke rol hebben gespeeld. Bij deze.

Als eerste, promotor prof. dr. de Haan, beste Lieuwe, bedankt voor het begeleiden van dit promotietraject. Jouw visie op schizofrenie, het "grotere plaatje" en de immer terugkerende "So what?" vraag bewaakte de grote lijnen van dit proefschrift. Jouw praktische inslag zorgde ervoor dat ik de basis voor dit proefschrift kon leggen ten tijden van mijn klinische opleiding. Dit alles gecombineerd met jouw relativerende visie op de wetenschap en humor heb ik enorm gewaardeerd (met hierin voorop staande jouw de Freek de Jonge sketch en mijn à terme indicatie voor metformine).

Copromotor Dr. Ruhé, beste Eric, het begin van onze samenwerking in onderzoek doen gaat lang terug. Ik was (pas) derdejaars geneeskunde student toen jij mij enthousiast maakte en de noodzaak liet inzien van wetenschappelijk onderzoek. Bedankt voor jouw roestvaste vertrouwen in mij, ondanks dat ik niet meteen enthousiast was over een promotietraject. Ik realiseer me dat door deze promotie, je uiteindelijk toch gelijk hebt gehad (al moet je dat nooit te vaak toegeven, toch?). Jouw ijver om altijd verder de blijven zoeken en het beste uit papers te halen, vind ik bewonderenswaardig.

Copromotor Dr. Meijer, beste Carin, jouw enthousiasme en humor hebben er voor gezorgd dat deze promotie leuk bleef. Jouw no-nonsense houding, je betrokkenheid (ook op persoonlijke vlak en met name de adviezen t.a.v. het *niet* strijken van de hydrofiele luiers) heb ik enorm gewaardeerd. Dank voor de vele telefoontjes op de juiste momenten. Tussen ons zijn er wat kleine verschillen in de behoefte naar controle en overzicht: ik realiseer me dat je mijn overzichtstabellen en mijn (door jouw gevreesde) laptop (die ik altijd in de aanslag had) louter belachelijk hebt gemaakt. Dank hiervoor.

Dank ook aan de leden van de promotiecommissie voor het kritisch lezen van dit proefschrift: Prof. dr. Lindauer, Prof. dr. Cahn, Prof. dr. Bockting, Dr. Lok en Dr. Wigman.

Ook veel dank aan mijn collega-onderzoekers: Thijs, Olle, Isidoor, Melisse, Roel, Anna, Ellen, Nathalie, Iris, Paul (mijn gevoel zegt dat we beter samen kunnen publiceren dan samen dienst hebben) en Arjen (dank voor het inzicht dat je neurotische conflicten het beste oplost met wijn op een terras in Florence, onafhankelijk van de uitkomst). Dear Adela, thank you for helping me with statistics regarding the network analysis. Beste Claudia, dank voor je kritische commentaar op de artikelen. Zelf benoemde je in jouw feedback dat het verbeteren van komma's mogelijk getuigt van autisme; ik denk dat dit wel meevalt, waarschijnlijk wel enige mate van perfectionisme...;-). Arija: de basis voor onze samenwerking was een 'draak van een dienst' (waarin jij overigens een zeer fijne achterwacht was). Gelukkig

stond je mij ook bij de verwerking daarvan (iets met tequila, toch?). Desalniettemin tijdens dit project, waren jouw enthousiasme en ideeën om weer anders naar de data te kijken inspirerend. Floor en Marije: alles voor de wetenschap, ook als dat betekent om op vrije dagen te werken! Lieve Frederike, dank voor het beantwoorden van mijn talloze vragen en je nuchtere visie op de wetenschap; je bent de 'moeder Gans' van de afdeling! Lieve Maaik, ook onze onderzoekers samenwerking gaat al lang terug: ik bewonder je vastberadenheid en doorzettingsvermogen als dingen tegenzitten. Lieve Nicole, dank voor jouw administratieve ondersteuning van deze promotie.

Alle psychiaters, arts – assistenten, verpleegkundigen, secretaresses, psychologen en onderzoekers van het AMC dank voor jullie bijdrage in een leerzame promotie – en opleidingstijd. In het bijzonder, Prof. dr. Denys, Dr. Storosum en Dr. de Koning, veel dank gaat uit naar jullie voor het creëren van het opleidingsklimaat waarbij kwaliteit hoog in het vaandel staat en er ruimte is voor persoonlijke ontwikkeling en onderzoekstijd. Alle AMC-psychiaters: dank voor het overbrengen van jullie kennis in de afgelopen jaren, ik kijk ernaar uit om te blijven samenwerken. Marloes, mijn eerste supervisor in het AMC, wat was ik blij met jou! Laten we het erop houden dat onze neuroses goed bij elkaar aansluiten. De borrel komt er (ooit!). En alle supervisoren die hierop volgden en bijdroegen aan mijn leerschool om steeds een beetje meer psychiater te worden: Laura, Dominique, Jara, Eefje & Rianne (ik denk nog vaak terug aan de spoedcursus 'verdragen') en als laatste de combinatie Pelle & Nienke & Ati (dank ook voor jullie vertrouwen in mij als jonge collega). Ook dank aan de arts –assistenten met wie ik intensief heb samengewerkt: Maarten, Hester, Joosje, Floor, Rianne, Carlijn, Yasmin, Lotje, Angela, Nienke, Jytte, Wieke, Willem, Karel en Koen. Lieve collega's van de angst, wat zijn jullie een gemotiveerde afdeling, die volop openstaat voor vernieuwingen en waar nimmer de discussie wordt geschuwd. Beste intervisie groep: jullie inzichten van de afgelopen jaren zijn zeer leerzaam.

Iets verder terug in het verleden, oud – collega's vanuit het Westeinde: jullie dwongen me als groep om psychiater te worden, waar ik toen zeer over twijfelde. Daar ben ik jullie dankbaar voor, met name omdat jullie gelijk hadden. Beste Ferdi, jij leerde me als jonge dokter om altijd (en in alle situaties) naast een patiënt te gaan staan. Lieve Roos, kunnen we niet nog een keer visite lopen waarbij jij plaatsneemt in een rolstoel? We waren een goed team samen en bovenal familie (en dat zegt soms veel). Hierbij ook niet te vergeten: De Drie musketiers! Lieve Nien en Justien: wat hebben wij intensief samengewerkt bij onze eerste baan, wat was dat fijn en wat kennen jullie me goed. Desalniettemin, ik wil nog steeds in het Ford Feestje naar *Duinroosje* (maar wie wil dat niet?).

Niet te vergeten mijn vrienden: Undara (en in het bijzonder lichting 2006), dank voor jullie jarenlange vriendschap en ontelbare woensdagavond etentjes. Zo lang jullie me niet dwingen om liedjes te zingen, is het gezellig. Club Mamba (inclusief aanhang): er gaat niets boven de Plan C. Beste Zeeuwen, wat is een relativerende Zeeuwse visie op veel dingen toch verhelderend! Lieve Fed, je bent een voorbeeld van ambitie en moederschap en de kunde om in korte tijd veel gin te drinken (en met name na nachtdiensten op zaterdagochtend in de Watergraafsmeer). Mirte, in het verre verleden een collega, maar nu zo veel meer: laten we blijven filosoferen! Lieve Eef, ons eerste huisje op het Rembrandtplein was een feest (van te veel rosé, te veel series kijken en te veel bezoeken aan de 'Kroon') maar bovenal van

onbezonnenheid. Er zijn er weinig van wie ik de mening zo hoog heb zitten, jouw eerlijkheid en je scherpte waardeer ik enorm. Ik heb bewondering voor je doorzettingsvermogen en je positivisme in de afgelopen maanden. Lieve Lien, ons eerste project op vierjarige leeftijd was een minder groot succes (ik ben nog steeds furieus dat jij de politiepet op mocht en dat je de piepers te vroeg uit de oven haalde). Maar onze vriendschap is nu zo veel meer. Dank dat je er altijd bent als het (bij vlagen) tegenzit en je betrokkenheid bij *Toena*. Zo lang we niet samen koken maar Besta's in elkaar zetten, hebben we het fantastisch. Thanks to Ted, we now drink more wine and order pizza instead of being busy with Besta's or cooking at all; leading to the better Lebanese versions of ourselves.

Mijn paranimf Jentien (a.k.a. dokter Gerrie & collegaaa), een goede kamergenoot *lies on the roots* van een succesvolle promotie. Zonder de 'sniffy sticks' was het een groot feest van sloten koffie, eierkoeken, gedagdroom over IJ-witjes, mijn gewauwel over Prof T. en jouw verhalen over je karate –aspiratie. Dit werd afgewisseld met inhoudelijke discussies en analyses van Rigoletti. We zijn een ijzersterke combinatie. Dank voor je ontembare enthousiasme en inzichten m.b.t. (met name) Anna Karenina en dat je op de grote dag naast me staat. Aangezien er een sterke correlatie is tussen rapkwaliteiten en promoveren, en een nog sterkere tussen danskwaliteiten op Sean P. en promoveren, worden jouw laatste maanden een eitje. Ik kijk er naar uit om (klinisch) te blijven samenwerken.

Mijn tweede paranimf, lieve Maaik: jij leerde me van kinds af aan schrijven (hoeveel werkstukken heb jij wel niet nagekeken en ja 'd's' en 't's' zijn uitermate complex op die leeftijd, het woord 'Toetanchamon' overigens ook). In de jaren ben je langzaam van grote zus, mijn zusje geworden (louter ten gevolge van jouw achterblijvende groei en mijn reuzengroei, om in jouw terminologie, te spreken). In werkelijkheid zijn we langzaam vriendinnen geworden, waarbij we reizen ondernemen, sparren over onderzoekideeën en wijn drinken op een terras. Je bent een geweldige tante, veel dank dat je naast me staat op de grote dag.

Beste Familie van Rooijen, ik koester onze momenten samen: 'het hele stel bij elkaar', zoals oma zou zeggen. Ome Knor, je bent ons te vroeg ontvallen, wat had ik je hier graag bijgehad! Tijmen, dank voor je relativerende, technische visie tijdens de gesprekken (inderdaad 'de hechtingstheorie' is het juiste antwoord op alle vragen). Beste schoonfamilie, een betere (met een vergelijkbare Bourgondische smaak) kan ik me niet wensen. Ad en Ellen, dank voor jullie betrokkenheid bij jullie kleinzoon. Fem en Jes, we komen te weinig toe aan borrelen en goed eten, maar laten we het blijven doen. Marg en Jur, dank voor de altijd aanwezig facilitaire ondersteuning. Moreover the Dutchies in the USA: Rick (a.k.a. the ghost writer; for once, I hate and – despite several psychoanalytic sessions from your side - am still afraid of alligators and I know that's normal!), Anke (a.k.a. the German lady, *never* to be under estimated), Catherine (can you have too much New York Fire-fighters in life?) and (oxford comma) Ricky.

Pap en mam, jullie hebben het je vaak afgevraagd: hoe jullie me 'zo ambitieus hebben afgeleverd'. Gedurende dit traject, heb ik jullie wel eens zien afvragen of het allemaal wel samen kon. Ondertussen weten we dat dit kan, mede dankzij jullie hulp. Daarbij verliezen jullie nooit je vertrouwen en nimmer jullie belangstelling en betrokkenheid (en al die keren op Schiphol als ik - weer uit budget overwegingen - op 1ste kerstdag besloot te vliegen). Jullie zijn een prachtige opa en oma, dank voor jullie gedrevenheid hierin.

Ten slotte de allerbelangrijksten: Jop en Teun. Lieverd, ik weet dat je het onzin vindt om hier iets over jou of ons op te schrijven. Maar eerlijkheidshalve en kort gezegd (op jouw manier) komt het hier op neer: dank voor je relativerende humor, je loyaliteit aan ons, je nuchtere Zeeuwse (?) visie op het leven maar bovenal dank voor je liefde. Onze zoon is het mooiste wat daaruit voortgekomen is. Lieve Teun, als allerlaatste: jouw komst was qua planning ideaal voor deze promotie (dank daarvoor!) maar bovendien was je aanwezigheid de meest relativerende en leukste afleiding die ik me kon wensen tijdens deze promotie.

CURRICULUM VITAE

The author of this dissertation was born on April 22, 1987 in Alkmaar. In September 2005 she started her medical studies at the Academic Medical Center (AMC) of the University of Amsterdam (UvA), where she was allocated by a decentralized selection procedure. She received her medical doctor degree (with '*cum laude*') in October 2012. During her medical studies, she was selected to participate in the honours-program: a three-year program consisting of supplementary interdisciplinary courses on top of the regular programme. As part of this course she followed a minor on ethics at the UvA. During this period she worked as a research assistant at the department of mood disorders at the Academical Medical Center (AMC) in Amsterdam, supervised by Prof. dr. Schene and Dr. Ruhé.

After obtaining her medical degree, she was first employed as a medical doctor at Medisch Centrum Haaglanden, in The Hague. In April 2014, she started as a resident in psychiatry at the AMC, under the supervision of Dr. Storosum and Dr. de Koning. During her residency she started her PhD-research under the supervision of Prof. dr. de Haan, Dr. Meijer and Dr. Ruhé. She did research on the application of network analyses in psychotic disorders and later on she investigated different treatment aspects and outcomes in patients with schizophrenia. In January 2019 she is expecting to complete her residency and she will continue to work as a psychiatrist at the Department of Anxiety Disorders of the AMC.