The impact, assessment, and longitudinal course of negative symptoms of schizophrenia.

Savill, Mark

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Submitted in partial fulfilment of the requirements of the Degree of Doctor of Philosophy

I. Contents

II. Statement of originality

I, Mark Savill, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material. I accept that the College has the right to use plagiarism detection software to check the electronic version of the thesis. I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university. The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without the prior written consent of the author.

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Details of collaboration and publications:

The main findings of chapter 3 and chapter 7 have been published. In all chapters I was responsible for study design, analysis, interpretation, and manuscript preparation. Aspects of study design, interpretation, and presentation of the findings was supported by my primary supervisor Professor Stefan Priebe. Dr Stephen Bremner provided statistical advice for chapters 3 and 7, and Dr Ceire Costelloe provided statistical advice for chapter 4.In chapter 3 I completed all aspects the systematic search, study selection and data extraction procedure. For purposes of reliability, Ciara Banks duplicated 25% of the abstract screening and 50% of the full paper screening, whilst Husnara Khanom duplicated the remaining 50% of the full paper screen. In chapter 4, the original data was obtained from a previously published trial evaluating the effectiveness of a structured communication intervention (Priebe et al., 2007). The data analysed in chapters 5 and 6 was obtained from a trial evaluating the effectiveness of body psychotherapy as a treatment for negative symptoms of schizophrenia (Priebe et al.,

2013), for which I have been the Trial Manager for the entire duration of the study. In this role I was involved in study design, and the management of participant recruitment and data collection. In chapter 7, a pooled analysis of data from three previous studies was completed (Kallert et al., 2005; Kallert et al., 2007; Priebe et al., 2010)

Published findings:

Appendix I: Savill, M., C. Banks, H. Khanom, and S. Priebe (2014). Do negative symptoms of schizophrenia change over time? A meta-analysis of longitudinal data. *Psychological Medicine 45*, 1613-1627.

Appendix II: Savill, Mark, Jelena Jankovic, Christina Katsakou, Thomas Kallert, and Stefan Priebe (2012). Symptom levels and initial appraisal of hospital treatment in patients with schizophrenia. *Psychiatry Research* 199, 2, 79-83.

III. Acknowledgements

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IV. Abstract

The negative symptoms of schizophrenia include impoverished speech, affective blunting, an inability to anticipate pleasure, asociality, and amotivation. Current effective treatment options are limited, which is a significant issue given their strong association to functional impairment. The primary aims of this thesis are to explore areas which may inform the design of clinical trials addressing these symptoms, build upon recent advances in negative symptom assessment, and further understand the impact of negative symptoms on outcomes.

A meta-analysis examining the longitudinal course of negative symptoms demonstrated a consistent reduction in negative symptoms over the study period in all treatment conditions examined, including in studies which adopted different eligibility criteria to minimise the presence of secondary negative symptoms. A comparison of different eligibility criteria revealed that whilst these criteria reduce the association between negative and depressive symptoms, their association to positive symptoms remains largely unaffected, and can substantially reduce the proportion of available participants.

Given existing negative symptom assessment tools have been identified as a significant barrier in the development of new treatments, a comparison of assessment methods was performed. Results revealed the Clinical Assessment Interview for Negative Symptoms to be a more sensitive instrument, and a better predictor of functional impairments, relative to the negative subscale of the Positive and Negative Syndrome Scale. Findings described here also demonstrate that the link between negative symptoms and subjective quality of life may be stronger than previously assumed, relating exclusively to experiential deficits. Finally, manic and positive symptoms, rather than negative symptoms, were found to be associated with inpatient treatment appraisal, an important factor in treatment outcomes.

Overall, this thesis describes key findings which demonstrate the importance of the appropriate assessment of negative symptoms of schizophrenia, shine new light on symptom progression over time, and highlight a need to further refine clinical trial inclusion criteria.

V. List of Abbreviations

APA: American Psychiatric Association

ATC: Anatomical Therapeutic Chemical Classification

BDI: Beck Depression Inventory

BNSS: Brief Negative Symptom Scale

BPRS: Brief Psychiatric Rating Scale

BSA: Broad Spectrum Antipsychotics

CAINS: Clinical Assessment Interview for Negative Symptoms

CANSAS: Collaboration to Advance Negative Symptom Assessment in Schizophrenia

CAT: Client Assessment of Treatment scale

CFA: Confirmatory Factor Analysis

CGI-SCH: Clinical Global Impressions Scale - Schizophrenia

CI: Confidence Interval

CPRS: Comprehensive Psychopathological Rating Scale

DDD: Defined Daily Dose

DSM: Diagnostic and Statistical Manual of Mental Disorders

EFA: Exploratory Factor Analysis

EPS: Extrapyramidal Symptoms

ES: Effect Size

FGA: First Generation Antipsychotic

HDRS: Hamilton Depression Rating Scale

ICC: Intraclass Correlation Coefficient

ICD: International Classification of Diseases

LOCF: Last Observation Carried Forward

MANSA: Manchester Short Assessment of Quality of life

MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia

MCCB: MATRICS Consensus Cognitive Battery

NIMH: National Institute for Mental Health

NIHR: National Institute for Health Research

NSA: Negative Symptom Assessment Scale

OCCPI: Operational Criteria Checklist of Psychotic Illness

OQOL: Objective Quality of Life

PANSS: Positive and Negative Syndrome Scale

SANS: Scale to Assess Negative Symptoms

SAPS: Scale to Assess Positive Symptoms

SCID: Structured Clinical Interview for DSM Disorders

SD: Standard Deviation

SDS: Schedule for the Deficit Syndrome

SE: Standard Error

SGA: Second Generation Antipsychotics

SIR: Subjective Initial Response

SNS: Social Network Scale

SQOL: Subjective Quality of Life

TUS: Time Use Survey

WHO: World Health Organisation

Chapter 1. Introduction

1.1. Introducing schizophrenia

1.1.1. What is schizophrenia and why is it important?

Schizophrenia is a serious mental health disorder characterised by a disruption in thinking and emotional responses. Whilst the point incidence is relatively low (2-10/10,000), the prevalence is much higher due to the chronic nature of the illness (70/10,000) (Saha et al., 2005). Despite recent evidence which suggests that the long term negative impact of the illness may have been previously overestimated due to sample biases (Morgan et al., 2014), it is clear that schizophrenia is a highly disabling condition in terms of physical, social, and functional outcomes.

Mortality and suicide rates in those diagnosed with schizophrenia is disproportionately high relative to the general population (Hor and Taylor, 2010, McGrath et al., 2008, Reininghaus et al., 2015), and co-morbid disorders, particularly substance use disorders, are common (Buckley et al., 2009). Patients diagnosed with schizophrenia are more likely to suffer chronic physical conditions such as obesity, type II diabetes and coronary heart disease, and medications taken for schizophrenia have been associated with sexual dysfunction, obesity, movement-disorders, and cataracts (Marder et al., 2014). In the AESOP-10 study, almost three quarters of the participants assessed remained unemployed for at least 75% of the time over a period of ten years, and further psychiatric hospital admissions occurred in 88% of cases (Morgan et al., 2014). Impairments in work and academic performance, interpersonal relations, and self-care are so intrinsic to our current definition of schizophrenia that these features form part of the diagnostic criterion for the illness (APA, 2013). In a cohort study spanning 15 years, 80% of participants were found to have a persistent impairment in social functioning (Wiersma et al., 2000), and the disorder can result in substantial caregiver burden (McDonell et al., 2003). Following the first psychotic episode, only 13.7% of patients (95% CI= 6.4% - 20.9%) were found to meet criteria for full recovery for at least two of the following 5 years (Robinson et al., 2014).

In addition to the significant impact that the disorder can have on both the individual and caregivers, schizophrenia is also recognised to have a major economic cost. In 2012, the estimated annual cost of schizophrenia to English society was placed was £11.8 billion, £7.2

billion of which costed to the public sector (Andrew et al., 2012). In summary, schizophrenia is recognised to have a substantial negative impact on the individual, families and care givers, and to society at large, and therefore presents a need for future research to help alleviate the devastating impact of this disorder.

1.1.2. The typical course of schizophrenia

Prior to the onset of schizophrenia individuals typically experience a period known as the prodromal phase, which can last for a number years before acute psychotic symptoms surface (Häfner et al., 1999). In his stage, which usually occurs in late teens or early adulthood, it is common for people to experience a decline in global functioning. This can include various forms of cognitive impairments such as deficits in executive function, general intelligence, verbal and visual memory, verbal fluency, attention, working memory, and social cognition (Fusar-Poli et al., 2012), in addition to depressed mood or anxiety, infrequent or attenuated psychotic symptoms, or negative symptoms such as social withdrawal (Häfner et al., 1999). During this period it is also common for patients to experience a decline in social, occupational or academic performance (Cornblatt et al., 2007). In a longitudinal study following those that qualify for prodromal syndrome, 35% of cases were found to go on to develop psychosis within a period of 30 months (Cannon et al., 2008). In those that do go on to develop schizophrenia, patients typically experience acute psychotic symptoms such as delusions, hallucinations, thought disorder, and a further deterioration in cognitive and social functioning. Following treatment, most patients transition on to the chronic phase of the disorder where psychotic symptoms diminish, but significant impairments in functioning and negative symptoms remain. Approximately 80% of patients in the acute phase of the disorder go on to experience a substantial reduction in psychotic symptoms, although many (~70%) will go on to experience a relapse into the acute phase again within 5-7 years (Wiersma et al., 1998). The antecedents of regressing back to the acute phase of the disorder are not entirely clear, however non-adherence to mediation and social withdrawal have been found to be associated (Robinson et al., 1999). Other predictors identified include younger age, earlier illness onset, substance use disorder, and prior episodes of relapse (Ascher-Svanum et al., 2010). Whilst complete remission from the disorder is relatively rare (Jääskeläinen et al., 2013), in a more recent study there is evidence to suggest that periods of remission are more common than was previously believed (Morgan et al., 2014).

1.1.3. Factors associated with the development of schizophrenia

Whilst the causes of schizophrenia are undetermined, a number of risk factors have been identified. Of these, having a positive family history has been recognised as the most influential factor. Lifetime risk is 6.5 times higher in people who have first degree relatives diagnosed with the disorder (Kendler and Diehl, 1993). Twin studies suggest a strong genetic component for this association, with the risk factor as high as 40% in monozygotic twins where one has been diagnosed with the disorder (Cardno et al., 1999).

Two systematic reviews suggest that the incidence rate of schizophrenia is higher in males in comparison to females, with a male to female ratio of 1.4:1 (95% CI: 1.3 – 1.6) (Aleman et al., 2003, McGrath et al., 2008). In addition, males appear to have an earlier age of onset, experience more severe negative symptoms, and report a worse outcome (Jablensky, 2000). However, as described in a review by McGrath et al. (McGrath et al., 2008) this higher incidence rate did not appear to translate to a higher prevalence rate in males. The reason for this is not entirely clear, however it is possible that this could be explained at least in part by the higher mortality rates in male schizophrenia patients in comparison to females sufferers (standardized mortality ratio's, male=2.8, females=2.4) (Ösby et al., 2000).

Another factor associated with developing psychosis is migrant status, with both the incidence and prevalence of schizophrenia significantly higher in migrants relative to native-born individuals (Fearon et al., 2006, McGrath, 2006). This higher incidence rate of psychosis was found in both first and second generation immigrants, which suggests that the difference is not attributable to events which occurred prior to immigration (Bourque et al., 2011). In addition, this risk appears to be inversely related to the proportion of migrants within their local community (Boydell et al., 2001). In the UK, higher incidence rates of psychosis in Caribbean migrants have been consistently reported (Fearon et al., 2006, Sharpley et al., 2001). However, with rates not found to be higher in the countries of origin, this suggests that the issue is related to being an immigrant, rather than having any genetic predisposition towards the illness (Messias et al., 2007).

Despite the risk being relatively small, there has been consistent evidence which suggests that people that are born during the winter months are significantly more likely to develop psychosis (Davies et al., 2003). The reasons for this are not entirely clear, however a number of theories have been proposed. One hypothesis states that influenza infections during gestation may be related to increased rates of schizophrenia, however no evidence for this was found in a large epidemiological study (Morgan et al., 1997). Another theory proposes that this may be

associated with biometeorologic variables such as temperature, ultra-violet radiation and precipitation, which is supported by the finding that people born at higher latitudes have both higher prevalence and incidence rates (Saha et al., 2006). Related to this, McGrath went on to propose that low pre-natal vitamin D may be a risk modifying factor for schizophrenia (McGrath, 1999). To complicate the issue of birth seasonality and its impact on schizophrenia further, there is evidence to suggest that this effect is not consistent in all types of the illness. In a pooled analysis of 6 countries, patients diagnosed with the deficit syndrome of schizophrenia (see section 1.3.3 for a summary) were significantly more likely to have been born in the months of June-July, relative to non-deficit syndrome schizophrenia patients (Messias et al., 2004).

In addition to the season in which the gestational period occurs, prenatal and obstetric complications have also long been implicated in increase rates of schizophrenia (Kraepelin, 1971). In a systematic review by Geddes and colleagues (Geddes et al., 1999) the diagnosis of schizophrenia was associated with premature rupture of membranes, a gestational age below 37 weeks, and the use of resuscitation or an incubator. There was also evidence of a weak effect between low birth weight and a forceps delivery. In a review by Cannon and colleagues (Cannon et al., 2002), different risk complications were grouped into three different factors; complications in pregnancy, abnormal foetal growth and development; and delivery complications, all of which were significantly associated schizophrenia. Different reasons why these complications are associated with higher incidence of schizophrenia have been proposed, including the effect of hypoxia and or Ischemia (Geddes et al., 1999, Zornberg et al., 2000), malnutrition (Susser and Lin, 1992), or developmental impairments caused by premature birth (Nosarti et al., 2012).

Another possible risk factor is paternal age, where there is evidence to suggest that this is positively associated with an increased risk of schizophrenia (Brown et al., 2014, Zammit et al., 2003). In one cohort study an increase in relative risk by a factor of 2.96 (95% CI 1.60-5.47) was detected in the offspring of fathers over 55, in comparison to those aged 20-24 (Malaspina et al., 2001). Malaspina postulated that this effect may result from *de novo* mutations in sperm cells. In support of this argument, it has since been found that the positive association with paternal age is only significant among those without any family history of the disease (Sipos et al., 2004).

In addition to obstetric complications and the link between paternal age and schizophrenia, there is evidence of link between the mother experiencing traumatic event up to six months

before or during pregnancy and increased later incidence of schizophrenia in the child (Khashan et al., 2008). Following birth, Larssen (Larsson et al., 2013) found that 85% of people assessed with psychosis reported experiencing childhood trauma, with emotional abuse and neglect particularly common (63% and 67% respectively). In a review by Read (Read et al., 2005) the authors suggested a causal factor between childhood experience of abuse and schizophrenia, however Morgan and Fisher (Morgan and Fisher, 2007) urged caution in determining such a link based on the current evidence base.

Since the 1930's there has been evidence which suggests that the prevalence of schizophrenia is higher in urban, as opposed to semi-urban or rural sites (Faris and Dunham, 1939). Given the cross-sectional design of the analysis however it was argued that this difference may be attributable to a selection bias, where better access to healthcare in urban sites may result in improved illness detection, and encourage migration to major cities. In more recent studies this has been examined prospectively (Lewis et al., 1992, Marcelis et al., 1998), which again supported a higher prevalence in urban sites, leading to the conclusion that the higher prevalence is independent of selection (Krabbendam and Van Os, 2005). A number of possible reasons for this difference have been postulated, such as environmental pollutants (Pedersen and Mortensen, 2006) and overcrowding stresses (Cougnard et al., 2007). In the review by McGrath and colleagues (McGrath et al., 2008) a higher incidence of the disorder was detected, though no changes in prevalence were observed.

Finally, there is evidence to suggest a link between schizophrenia and smoking cannabis. In a large cohort study in Sweden, cannabis was associated with an increased risk of developing schizophrenia, with a dose response effect present (Zammit et al., 2002). In prospective longitudinal study, Arseneault and colleagues (Arseneault et al., 2002) also found a higher risk of developing psychosis with taking cannabis prior to experiencing psychotic symptoms, which suggests the association is not attributable to self-medicating against positive symptoms. In a meta-analysis examining overall effect size and consistency of the association between cannabis and psychosis, (Henquet et al., 2005) an effect was found to be consistent after controlling for any effects of self-medication, with a pooled odds ratio of 2.1 (95% CI 1.7-2.5). Finally, in an overview of 5 systematic reviews (Minozzi et al., 2010) a consistent association between cannabis use and psychotic symptoms was detected.

Overall, the evidence suggests that biological, psychological and societal factors all have a significant influence on the development of psychosis (Broome et al., 2005). Many of these factors are likely to be inter-related, and further work on the interaction between these

differing risk factors is needed. Such work may advance our understanding of how to detect those at most risk of developing the disorder, which is important given there is evidence to suggest early treatment of at-risk groups may help reduce the likelihood of transitioning to psychosis (Morrison et al., 2004). However, whilst such work may help reduce the proportion of people developing the disorder, a significant proportion of people at present still go on to develop the illness. Consequently, there is still an urgent need to develop new treatments, and to develop an appropriate framework in which therapeutics can be evaluated in the most efficient manner possible.

1.1.4. The current diagnostic criterion for schizophrenia and implications for research

In schizophrenia, diagnosis is determined by the presence of particular symptoms. Despite the existence of a number of diagnostic systems (for a review, see (Berner, 1983), the two most commonly implemented diagnostic tools at present are published by the ICD (International Classification of Diseases) and the DSM (Diagnostic and Statistical Manual of Mental Health Disorders). The DSM is the manual published periodically by the American Psychiatric Association (APA) and primarily adopted in the USA, whilst the ICD is the criterion adopted by the WHO and is most commonly used in the UK and throughout Europe. In both manuals, the concept of schizophrenia is defined as a spectrum disorder, including a number of variations of psychotic illnesses and different disorder subtypes. In order to qualify for a diagnosis of schizophrenia utilising the ICD-10 criteria, the following conditions must be met:

At least one of the following “first rank” symptoms must be present:

a) Thought echo, thought insertion or withdrawal, or thought broadcasting.

b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception.

c) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body.

d) Persistent delusions of a different kind which are culturally inappropriate and completely impossible (e.g. being able to control the weather, or being in communication with aliens from another world).

OR, at least two of the following “second rank” symptoms must be present:

e) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas.

f) Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech.

g) Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor.

h) "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses.

The symptoms should be present most of the time during an episode of psychotic illness, for a duration of at least one month. In addition, the symptoms must have occurred independently of a depressive or manic episode, and not be attributable to either an organic brain disease, or substance abuse withdrawal or intoxication.

In the ICD-10 the diagnosis of schizophrenia is broken down into different subtypes, including paranoid, hebephrenic, catatonic, residual, simple and undifferentiated schizophrenia. Between these subtypes, differences in the presentation of symptoms are evident. In paranoid schizophrenia, delusions and hallucinations must be prominent, and negative symptoms (see section 1.2.3.) must not dominate the clinical picture. In hebephrenic schizophrenia, thought disorder and negative symptoms are dominant, relative to hallucinations and delusions. In catatonic schizophrenia, extremes of behaviour must be prominent for at least two weeks. These can include severe rigidity, stupor, bizarre posturing, command automatism or negativism, or, at the other end of the spectrum, extreme excitement and constant motor activity. In residual schizophrenia, the general criteria must have been met at some point in the past, and negative symptoms must have been present continuously over the past 12 months. In simple schizophrenia a progressive deterioration of functioning and an increase in

negative symptoms must have occurred over at least 12 months, whilst delusions, thought disorder and hallucinations are absent. Lastly, in undifferentiated schizophrenia patients either meet none of the outlined subtypes, or would qualify for multiple subtypes.

In the DSM-V (APA, 2013), the criteria for the diagnosis of schizophrenia include:

At least two of the following symptoms (with at least one of them being A-C) being present for a significant proportion of time during a 1-month period.

a) Delusions
b) Hallucinations
c) Disorganised speech
d) Grossly disorganised or catatonic behaviour
e) Negative symptoms

In addition, some form of social or occupational dysfunction must be present for a significant portion of time since the onset of the disturbance, occurring over a period of at least 6 months. Prior to receiving a diagnosis of schizophrenia, both schizoaffective and mood disorder must be ruled out. Furthermore, the disturbance must not be due to physiological effects of substance abuse, withdrawal, or intoxication.

Whilst there is a significant degree of overlap between the diagnostic criteria for the DSM-V and the ICD-10, some differences do exist. In contrast to the ICD-10 criteria, in the DSM-V formulation no distinction between subtypes of the illness is made. In the DSM-V, evidence of social and occupational dysfunction from the point of disturbance onset is required. In the DSM-V, no distinction between Schneiderian first and second rank positive symptoms is made (see section 1.1.5 for a summary). Finally, in the DSM-V recent amendments to the criteria for schizophreniform disorder, schizoaffective disorder, and schizotypal disorder have implications on the specificity of the schizophrenia diagnosis. Given these differences are likely to have implications on who may and may not qualify for a diagnosis of schizophrenia, this may influence the characteristics of the sample evaluated. Consequently, specifying which criteria have been adopted for each part of the investigation should be considered important. In the meta-analysis completed in chapter 3 the aim was to pool a broad range of samples from as many countries as possible. As a result, patients diagnosed in accordance to either ICD or DSM criteria were considered. However in chapters 4-7, where all participants were recruited within Europe, all participants were diagnosed in accordance with ICD-10 criteria.

As specified previously, the ICD-10 criteria make distinctions between different subtypes of schizophrenia such as paranoid, hebephrenic, catatonic and residual schizophrenia. As a result, schizophrenia can either be evaluated as a single concept, or with the subtypes each evaluated separately. However, as reviewed by Tandon and colleagues (Tandon et al., 2013), a wealth of evidence exists which suggests that subtype classifications exhibit poor reliability, longitudinal stability, and poor prognostic value (Deister and Marneros, 1993) resulting in little distinction between subtypes (Linscott et al., 2010). Given these criticisms, subtypes were not considered in any of the analysis completed in this investigation. Whilst this is a divergence from the criterion from which all of the patients would have been diagnosed, this approach is reflective of current research practice, as indicated in a review by Braff (Braff et al., 2013).

Related to diagnosis it is important to consider whether schizophrenia alone should be evaluated (ICD-10 criteria F20.0-F20.9), or if other psychotic disorders such as schizotypal disorder (F21), delusional disorders (F22-24), or schizoaffective disorder (F25) should also be included. In the analysis which aimed evaluate negative symptoms in relatively stable outpatients over different timepoints (chapter 3-6) only patients with schizophrenia were included. In the analysis of acute patients at the point of hospital admission (chapter 7) participants with any psychotic disorder were included.

In schizotypal disorder (F21) negative and cognitive symptoms are typically less severe than in schizophrenia (Handest and Parnas, 2005), and patients are not required to exhibit any level of functional impairment to qualify for the diagnosis. In addition, the diagnosis of schizotypal disorder has been found to have relatively poor diagnostic stability over time (Shea et al., 2002). Therefore, patients with schizotypal disorders were excluded from samples evaluating stable outpatients order to avoid over-stating the variability of negative symptoms, and/or under-reporting their severity in clinical samples. In delusional disorders (F22-24), patients do not typically present with negative symptoms, and they are not included as part of the diagnostic criteria. Given these symptoms were the primary focus of the analysis in chapters 3-6, participants with this diagnosis were excluded. In chapter 7, other symptoms such as positive, depressive and manic symptoms were considered, therefore meriting the inclusion of other psychotic disorder as part of the investigation.

Schizoaffective disorder (F25) shares many of the features of schizophrenia and have been included in trials evaluating the effectiveness of negative symptom treatments, such as the CONSIST study (Buchanan et al., 2007). In addition, patients diagnosed with schizoaffective disorder have been included in studies which evaluate primary negative symptoms and the

"deficit syndrome" (Amador et al., 1999, Carpenter et al., 1988) which is an important feature of any investigation into negative symptoms. However, patients with schizoaffective disorder were omitted from all analyses evaluating stable outpatients (i.e. chapters 3-6) for a number of reasons. Firstly, there is evidence to suggest that there are a range of symptomatic, clinical and demographic differences between schizophrenic and schizoaffective clinical samples, with negative symptoms in particular more severe in patients with schizophrenia (Cheniaux et al., 2008). Secondly, schizoaffective disorder appears to follow a different longitudinal course, with significantly better long terms outcomes (Harrow et al., 1997). Thirdly, schizoaffective disorder has also been found to have poor diagnostic stability (Malhi et al., 2008), (Jäger et al., 2011). Consequently, patients with schizoaffective disorder were omitted from the analysis completed in chapters 3-6. In chapter 7 the stability of symptoms over time was not a feature of the analysis, and so therefore patients with schizoaffective disorder were included in this part of the investigation.

1.1.5. A history of the conceptual model of schizophrenia

With no diagnostic physiological markers found in schizophrenia, our concept of the disorder has been built up by the presence and absence of particular behaviours and experiences. Over the years this concept has been repeatedly revised. Given the extensive re-conceptualisations of the illness, providing a full historical account of the disorder is beyond the scope of this thesis. Instead, with the focus of this project limited to the deficient (or negative) features of the illness, the aim is to explore the evolution of how these symptoms have been considered as part of the wider schizophrenia complex. From negative symptoms being defined as the central feature of the disorder at the turn of the 20th century, greater emphasis has been placed on the positive psychotic symptoms of the illness over time. However, in recent years there has been an increasing focus on negative symptoms again due to their impact on various social and functional outcomes. Understanding the evolution of schizophrenia should be considered important of this investigation as a number of recent developments in negative symptoms are rooted in earlier conceptions of the illness.

In a review by Adityanjee and colleagues (Adityanjee et al., 1999), it was proposed that Phillippe Pinel drafted the first integrated description of schizophrenia in the medical literature (Pinel, 1806). Some 70 years later, Karl Kahlbaum (Kahlbaum, 1874) was one of the first to recognise the importance of course and outcome in the nosology of mental health disorders such as the "degenerative psychoses". Kahlbaums approach was adopted by Emil Kraepelin

(Kraepelin, 1971), whose work has since been recognised as amongst the most significant advances in the field of mental health, forming the basis of modern psychiatry (Eysenck, 1960).

Although not the first, Emil Kraeplin (1856-1926) was a major advocate of classifying mental health disorders into categories (Kraepelin, 1971). Central to his work was the distinction between manic depression, which would now be recognised as encompassing mood disorders, and 'dementia praecox', which forms the basis of what we recognise as schizophrenia today. Dementia praecox was characterised by a significant deterioration in attention, memory, and volition, starting during the individuals late teens or early twenties. In this conception of schizophrenia, symptoms relating to what would now be defined as cognitive and negative symptoms were recognised as central features of the disorder.

Kraepelin linked a number of biological abnormalities to the cause of schizophrenia, such as severe lesions in the cerebral cortex. Originally Kraepelin believed that these symptoms typically followed a course of prolonged and progressive deterioration, however in later work this position shifted to recognise that remission or improvement may be possible in at least some cases. Kraeplin went on to validate the existence of dementia praecox cross culturally, and postulated a number of antecedent factors including genetic factors, family history, and obstetric complications. In later work, Kraeplin integrated hebephrenia, catatonia, and paranoia into the dementia praecox classification, proposing that the subtypes are different expressions of a single disease entity.

Following Kraepelin, Eugene Bleuler (1857-1939) proposed an alternative, broader classification of the illness which focused more on the psychological aspects of the disorder (Bleuler, 1950). Bleuler rejected the idea that the illness follows a typically deteriorating course and so rejected the term dementia praecox, instead preferring schizophrenia, which literally translates to *split-mind*. This newly proposed name reflected the importance Bleuler gave to associative splitting as the central feature of the illness. For Bleuler, this splitting of associations gave rise to four features that he believed were central to the disorder, known as the "four A's". The four A's include the loosening of associations, affective flattening, autism, and ambivalence. Other symptoms of schizophrenia, such as hallucinations and delusions, were believed to be accessory symptoms resulting from an inability to manage the core "four A" symptoms. Therefore, similar to Kraepelin's definition of schizophrenia, Bleuler proposed that the primary features of the illness are related to a deficit in functioning, as opposed to the presence of symptoms such as hallucinations or delusions. Building on Kraepelin's work which incorporated different subtypes with the singular entity of schizophrenia, Bleuler proposed

two other subtypes known as 'latent' and 'simplex' forms of the disorder, in which the accessory features were not typically present. The strength of reconceptualising schizophrenia in this manner meant that the concept was better able to capture the heterogeneity of the disorder. However, this also led to criticism that the concept became too expansive (Van Praag, 1976).

Whilst the focus of his enquires were not specific to schizophrenia, the work of neurologist John Hughlings Jackson (1835-1911) was also highly influential to later conceptualisations of the illness (Jackson, 1958). Hughlings Jackson has been credited with developing the conceptual framework for clinical neurophysiology (York and Steinberg, 2011), framing the nervous system as an exclusively sensorimotor mechanism and rejecting metaphysical input. Hughlings Jackson proposed that the nervous system comprises of three levels; the highest level situated in the pre-frontal region, the mid-levels in the cortex, and lowest, least complex functions situated in the medulla and spinal cord. The higher levels were believed to control and inhibit the lower levels, meaning that cortical disease could potentially result in two distinct types of symptoms; the loss of function of the cortex itself, and/or the loss of the ability to inhibit lower nervous system levels. Following the work of John Russell Reynolds (Eadie, 2007) the loss of cortex function was believed to lead to "negative" symptoms, which reflect the loss of higher level functioning. Alternatively, "positive" symptoms were believed to result from an inability to inhibit lower cortical level functioning, and therefore consisted of the appearance of previously inhibited functions. This theory influenced a later distinction made between "positive" and "negative" symptoms of schizophrenia, and also "subtypes" of schizophrenia (Strauss et al., 1974) (see section 1.2.4).

As psychiatry moved towards the standardisation of diagnostic systems, the classification of different symptoms of schizophrenia proposed by Kurt Schneider (Schneider, 1959) became increasingly influential. Schneider proposed a hierarchy of symptoms based on the work of Karl Jaspers (Jaspers et al., 1997) which focused on the form, as opposed to the content of the symptom. In a departure from Kraepelin and Bleuler, greater emphasis was placed on particular positive symptoms of schizophrenia, such as command hallucinations and persistent delusions given they were easier to observe, and at the time were considered to be specific to psychotic disorders. These symptoms were defined as "first rank symptoms", whilst other symptoms such as negative symptoms, thought disorders and other hallucinations were considered "second rank symptoms". In the diagnostic criteria, fewer first rank symptoms were required to qualify for a diagnosis of schizophrenia, relative to second rank symptoms. At the time, it was thought that this distinction would improve the sensitivity and specificity of the schizophrenia diagnosis. This shift in emphasis towards positive symptoms was further

justified by the observed response of patients to the newly developed antipsychotic medications such as chlorpromazine, which were found to be particularly effective in the treatment of these particular symptoms.

While Schneider's conception of schizophrenia has underpinned the diagnostic criteria utilised over the past 50 years, the specificity of first rank symptoms to schizophrenia has been increasingly questioned (Crichton, 1996, Ihara et al., 2009, Nordgaard et al., 2008, Peralta and Cuesta, 1999a, Tanenberg-Karant et al., 1995). These limitations highlighted lead to the distinction being dropped in the most recent update of the DSM (APA, 2013), although to date it currently remains in the ICD formulation. In addition, with cognitive and negative symptoms being found to have a greater impact on functioning, relative to positive symptoms (Green et al., 2004a, Hunter and Barry, 2012), in recent years there has been there has been an increasing focus on the symptoms originally identified as the core features of the disorder by Kraepelin and Bleuler.

In 1974, Strauss and colleagues attempted to go beyond the categorisation of symptoms proposed by Schneider by outlining a model to explain the pathological mechanisms of the disorder. In doing so, the aim was to enhance the specificity of diagnostic criterion, provide a framework in which treatments can be evaluated, and account for the significant heterogeneity which has consistently been found in the presentation of the disorder (Strauss et al., 1974). In contrast to the theories proposed both by Kraeplin (1919), and Bleuler (1950), Strauss argued that the presentation of schizophrenia is a consequence of multiple processes, as opposed to a singular process. Drawing on the work by Hughlings Jackson (Jackson, 1958) see section 1.1.4.), Strauss postulated that positive symptoms, negative symptoms, and disorders of relating may represent three semi-autonomous processes with different antecedents. Positive symptoms were considered to be a consequence of biological, family environment, and psychological factors. Negative symptoms were considered either to be related to a loss of functioning of higher order cortical function, or the consequence of prolonged isolation and social stigma that patients with chronic schizophrenia typically experience. Negative symptoms could therefore represent core psychopathology, which may in turn lead to accessory positive symptoms (as proposed by both Hughlings Jackson and Bleuler), or be accessory symptoms themselves resulting from external factors. Finally, disorders of relating were considered to be somewhat different, representing dysfunctions in psychological processes that typically precede the onset of psychiatric symptoms.

Following the model outlined by Strauss and colleagues, Crow (Crow et al., 1980) built upon the idea of multiple processes existing within the schizophrenia complex and proposed the

existence of two syndromes of schizophrenia, called “type 1” and “type 2” schizophrenia. In type 1 schizophrenia patients primarily experienced positive symptoms, and was commonly seen in the acute phase of the disorder. Crow stated that type 1 schizophrenics exhibited a good response to neuroleptics, had a relatively good prognosis, and did not experience accompanying intellectual impairment. In contrast, type 2 schizophrenia was characterised by severe and chronic negative symptoms and intellectual impairment. Patients with type 2 schizophrenia were thought to respond poorly to neuroleptics, and had a much poorer long-term prognosis. Crow proposed differing pathological processes, attributing type I schizophrenia to increased dopamine receptor sensitivity, and type 2 schizophrenia to structural changes in the brain such as ventricular enlargement (Andreasen and Olsen, 1982). However, Crow also recognised that both syndromes can occur in the same patient, often at the same time, and suggested that the two dimensions may have the same aetiology (Crow, 1985). This conclusion was supported by Andreasen and colleagues, who found over that three quarters of participants evaluated were found to present with a mixture of positive and negative symptoms (Andreasen et al., 1990, Peralta et al., 1992b). In later work, many of the neurological differences between the positive and negative subtypes found in earlier studies were not reproduced. Finally, it was evident that the subtypes of schizophrenia were not typically stable over time (Marneros et al., 1992).

Following the work of Crow and Strauss (Crow, 1985, Strauss et al., 1974), a series of factor analytic studies were conducted in an attempt to validate the distinction between positive and negative symptoms as separate dimensions. Such work was conducted both as a means of model building (utilising explanatory factor analysis; EFA) and model validation (utilising confirmatory factor analysis; CFA). Whilst the majority of these studies supported a distinction between positive and negative symptoms, the majority of studies failed to uncover a 2-factor solution, with the positive symptom construct in particular being relatively unstable (Andreasen et al., 1990). As identified in a review of models (Peralta and Cuesta, 2001), a series of factor solutions were proposed, a summary of which is outlined in table 1. Whilst a large number of different factor solutions have been proposed, ranging from between 2-11 factors depending on the statistical methodology employed and sample evaluated, a distinction between positive, negative, and disorganised symptoms were consistently proposed (Bilder et al., 1985, Brekke et al., 1994, Liddle, 1987, Peralta et al., 1992a, Toomey et al., 1997), which was later supported in a meta-analytic confirmatory factor analysis (Smith et al., 1998). In some of the more complex models, such as the 11 factor model proposed by Peralta and Cuesta (Peralta and Cuesta, 1999b), they suggested that the different factors could be combined into 3 super-ordinate themes of positive, negative, disorganisation symptoms.

These findings led to the proposal that schizophrenia disorder is characterised by three separate dimensions of positive, negative and disorganised symptoms.

Whilst the distinction between positive, negative and disorganised symptom clusters were relatively consistent, a number of unresolved issues remained, not least the issue regarding the relative instability of the disorganisation symptom cluster (Peralta and Cuesta, 2001). In different factor analytic studies formal thought disorder, poverty of speech content, bizarre behaviour, alogia, inappropriate affect, conceptual disorganisation, difficulties in abstract thinking, disturbance of volition, stereotypical thinking and poor insight have all been included within the disorganization symptom construct (Hardy-Baylé et al., 2003). In an alternative approach to factor analytic studies, Hardy-Bayle instead proposed taking a pathogenic approach to understanding disorganisation in schizophrenia, suggesting that two distinct cognitive processes underpin the symptom dimension. These two processes included deficits in the integration of contextual information (Cohen et al., 1999, Widlöcher and Hardy-Bayle, 1989), and theory of mind deficits (Corcoran et al., 1995, Frith and Corcoran, 1996). Following this work, Harvey (Harvey et al., 2006) further emphasised the distinction between negative and cognitive symptoms.

The distinctions between cognitive, positive, and negative symptoms have now been consistently adopted in the literature, and this will provide the framework for how symptoms will be evaluated throughout this investigation. An outline of what symptoms these different dimensions are comprised of are presented in section 1.2.

Table 1: Summary of factor solutions conducted examining schizophrenia symptoms[a]

Study	N	Scale	Method of Analysis	No of factors	Factor loadings
Chronic patient sample					
(Lorr et al., 1962)	296	Inpatient Multi-dimensional Rating Scale	EFA	10	Mania, depression, negative, paranoid, hallucinations, catatonia, hostility, megalomania, mania, disorganisation
(Overall and Woodward, 1975)	2000	BPRS	Multi-response analysis of variance	11	Psychosis, disorganisation, hostility, anxiety, agitated, depression, depressive-withdrawal, excitement, positive
(Schuldberg et al., 1990)	399	SAPS-SANS	EFA	2	Positive, negative
(Shtasel et al., 1992)	107	SAPS-SANS, BPRS	EFA	4	Negative, disorganisation, psychotic, paranoid
(Minas et al., 1992)	114	SAPS-SANS	Multidimensional scaling	3	Psychosis, disorganisation, negative
(Malla et al., 1993)	155	SAPS-SANS	EFA	3	Psychosis, disorganisation, negative
(Thompson and Meltzer, 1993)	131	SADS and PSE	EFA	3	Psychosis, disorganisation, negative
(Minas et al., 1994)	114	SAPS-SANS	EFA	5	Negative, social dysfunction, delusions, hallucinations, thought disorder
(Lindenmayer et al., 1994)	240	PANSS	CFA	5	Negative, positive, excitement, cognitive, depression-anxiety
(Peralta et al., 1994)	253	SAPS-SANS	CFA	4	Psychosis, disorganisation, negative, social dysfunction
(Murphy et al., 1994)	169	SCID, SANS	EFA	3	Psychosis, disorganisation, negative
(Bell et al., 1994)	146	PANSS	EFA	5	Positive, negative, excitement, depressive, cognitive
(Andreasen et al., 1995)	243	SAPS-SANS	EFA	3	Psychosis, disorganisation, negative
(Maziade et al., 1995)	138	SAPS-SANS	EFA	3	Psychosis, disorganisation, negative
(Maziade et al., 1995)	131	SAPS-SANS	EFA	3	Psychosis/disorganisation, apathy/anhedonia, affective blunting/alogia
(Kitamura et al., 1995)	584	Checklist	EFA	5	Psychosis, negative, mania, depression, catatonia
(Johnstone and Frith, 1996)	329	Manchester scale	EFA	3	Psychosis, disorganisation, negative
(Mellers et al., 1996)	114	PSE	EFA	4	Hallucinations, delusions, negative, disorganisation
(Cardno et al., 1996)	102	OCCPI	EFA	5	Paranoid, disorganisation, negative, bizarre delusions, first-rank hallucinations
(Lenzenweger and Dworkin, 1996)	192	SANS, Phillips scales, Venables-O'Connor scale	CFA	4	Psychosis, disorganisation, negative, poor premorbid social adjustment

(Harvey et al., 1996)	404	Social Behaviour Schedule	EFA	4	Disorganisation, social withdrawal, depression, anti-social behaviour
(Serretti et al., 1996)	500	OCCPI	EFA	4	Excitement, depression, disorganisation, delusional
(Peralta et al., 1997)	314	SAPS-SANS	EFA	3	Psychosis, disorganisation, negative
(Toomey et al., 1997)	630	SAPS-SANS	EFA	5	Negative, disorganisation, social dysfunction, bizarre delusions, auditory hallucinations
(White et al., 1997)	1233	PANSS	CFA	5	Negative, psychosis, excitement, depression, autism
(Ratakonda et al., 1998)	221	SAPS-SANS	EFA	3	Psychosis, disorganisation, negative
(van Os et al., 1999)	706	CPRS	EFA	4	Depression, mania, psychosis, negative
(van Os et al., 1999)	706	OCCPI	EFA	5	Depression, mania, psychosis, negative, disorganisation
(Hori et al., 1999)	258	Manchester scale	EFA	3	Psychosis, disorganisation, negative
(Peralta and Cuesta, 1999b)	660	SAPS-SANS	EFA	11	Poverty of affect and speech, thought disorder/ inappropriate affect, bizarre delusions, social dysfunction, paranoid delusions, bizarre behaviour, auditory hallucinations, manic thought disorder, attention
Recent-onset of psychosis samples					
(Gureje et al., 1995)	60	SANS, BPRS	EFA	3	Psychosis, disorganisation, negative
(Vazquez-Barquero et al., 1996)	86	SAPS-SANS	EFA	4	negative, disorganisation, paranoid, nonparanoid
(Van Os et al., 1996)	166	OCCPI	EFA	7	Catatonia/ bizarre behaviour, bizarre delusions, mania, negative, depression, insight, other delusions
(McGorry et al., 1998)	509	Multidiagnostic instrument for Psychosis	EFA	4	Mania, depression, bleulerian, schneiderian
Follow-up studies <1 year[b]					
(Jackson et al., 1990)	53	Manchester scale	EFA	T0: 3	Depression, mixed, positive
				T1: 3	Negative, positive, depression-psychosis
(Addington and Addington, 1991)	41	SAPS-SANS	EFA	T0: 4	Avolition, disorganisation, poverty of affect and speech, psychosis
				T1: 3	Negative, psychosis, disorganisation
(Goldman et al., 1991)	40	BPRS, SANS	EFA	T0: 3	Negative, psychosis, excitement
				T1: 3	Negative, psychosis, excitement

(Dollfus and Petit, 1995a)	57	SAPS-SANS	EFA	T0: 3	Negative, disorganisation, psychosis
				T1: 3	Negative, disorganisation, psychosis
(Dollfus and Petit, 1995a)	57	PANSS	EFA	T0: 5	Negative, disorganisation, excitement, psychosis, anxiety
				T1: 5	Negative, excitement, psychosis, disorganisation, depression
(Nakaya et al., 1999)	86	PANSS	EFA	T0: 5	Negative, hostility, psychosis, disorganisation, stereotyped thinking
				T1: 3	Negative, mixed, abstraction
Follow-up studies >1 year[b]					
(Kulhara and Chandiramani, 1990)	89	SAPS-SANS	EFA	T0: 3	Negative, psychosis, disorganisation
				T1: 3	Negative, mixed, disorganisation
(Rey et al., 1994)	163	PSE, SANS, PIRS	EFA	T0: 5	Poverty of affect and speech, anhedonia, neurosis, positive symptoms, psychosis
				T1: 5	Poverty of affect and speech, anhedonia, neurosis, positive symptoms, psychosis
(Eaton et al., 1995)	90	PSE	EFA	T0: 3	Negative, psychosis, disorganisation
				T1: 3	Negative, mixed, disorganisation
(Van der Does et al., 1995)	65	BPRS-E	EFA	T0: 4	Manic, negative, psychosis, depression
				T1: 4	Disorganisation, negative, manic, depression
(Arndt et al., 1995)	65	SAPS-SANS	FA	T0: 3	Negative, disorganisation, psychosis
				T1: 3	Negative, disorganisation, psychosis
(Salokangas, 1997)	156	CPRS	EFA	T0: 5	Negative, delusions, anxiety, mania, hallucinations
				T1: 5	Depression, negative, disorganisation, psychosis, delusions

[a]Table adapted from Peralta and Cuesta, 2001

[b] In cases where multiple assessment points were evaluated, the first and last stage data are included.

CPRS= Comprehensive Psychopathological Rating Scale; SANS= Scale of Assessment for Negative Symptoms; SAPS= Scale for Assessment for Positive Symptoms; PSE= Present State Examination; PIRS= Psychological Impairments Rating Scale; PANSS= Positive and Negative Syndrome Scale; BPRS= Brief Psychiatric Rating Scale; FA= Factor analysis; EFA=Explanatory Factor Analysis; CFA= Confirmatory Factor Analysis; OCCPI, SCID= Structured Clinical Interview for DSM Disorders.

1.2. The symptoms of schizophrenia

The symptoms of schizophrenia as they are currently defined are separated into three distinct clusters, known as positive, negative and cognitive symptoms. The severity of these symptoms is defined by their frequency, persistence, and the degree to which they impact on functioning. An outline of what these different clusters constitute is summarised below.

1.2.1. Positive symptoms

The positive symptoms of schizophrenia include hallucinations, delusions, and thought disorders. These symptoms are known as "positive symptoms" due to the fact that their abnormality lies in their presence, as opposed to an absence, of typical human experience.

Hallucinations are defined as "a sensory perception that has the compelling sense of reality of a true perception, but that occurs without external stimulation of the relevant sensory organ" (APA, 2013). Hallucinations can present in auditory, visual, olfactory, haptic, or gustatory form, with the perceived origin being either internal ("pseudohallucinations") or external ("true hallucinations") in nature (Jaspers et al., 1997). Schneider (Schneider, 1959) made a distinction between different forms of auditory hallucinations, defining hallucinations of voices that communicate between themselves, provide a running commentary, or emanate from other parts of the body as specific to psychotic disorders, leading to an increased emphasis in these particular forms in some diagnostic criterion for schizophrenia (see section 1.1.3.). Approximately 70% of people diagnosed with schizophrenia are thought to experience hallucinations in the acute phase of their illness, with auditory hallucinations most common (Sartorius et al., 1974). In a review by Andreasen and Flaum (Andreasen and Flaum, 1991), the percentage of patients reporting experiencing audible thoughts of at least moderate severity ranged from 1.5% to 28% (Carpenter and Strauss, 1974, Koehler et al., 1977).

A number of factors have been thought to influence the occurrence of hallucinations in people with schizophrenia including stress, predisposing factors, environmental stimulation, and reinforcement (Bentall, 1990, Slade, 1976). In addition, a number of theories that underlie the formulation and maintenance of experiencing hallucinations have been postulated, summarised in a review by Bentall (Bentall, 1990). These included classical conditioning (Davies, 1974), the seepage of preconscious material into consciousness (Frith, 1979, West,

1975), a consequence of vivid mental imagery (Mintz and Alpert, 1972), and the link between sub-vocalisation and hallucinations.

Delusions are bizarre or irrational beliefs which are out of context from the society or culture from which they are part. In assessing the presence of delusions, Oltmanns (Oltmanns, 1988) suggested that six dimensions should be considered, including how implausible it is, how strongly it is held, what it is based upon, whether others also hold it, how pre-occupying it is, and the level of distress it causes. Delusions can take a number of forms, including somatic influence, thought withdrawal, thought insertion, thought broadcasting, projected feelings and impulses, delusions of control, and delusional perceptions. Of these, delusional perceptions relating to reference and persecution have been found to be amongst the most commonly reported psychotic symptoms (Sartorius et al., 1986), with persecutory delusions the most common type of delusion which people act upon (Wessely et al., 1993). The concept of persecutory delusions were operationalised by Freeman and Garety (Freeman and Garety, 2000), suggesting that in order for the delusion to be considered persecutory in nature the individual must believe that harm is either occurring, or else will occur to them (meaning harm to friends and or family and not the individual does not count), and that the persecutor has an intention to cause harm.

In addition to hallucinations and delusions, positive symptoms can take the form of thought disorder, the external manifestation of which presents itself in the form of disordered speech. In a review by Rule (Rule, 2005) a number of different terms were identified which cover the different expressions of disordered speech, with a significant degree of overlap and redundancy. Rule summarised the different terms used to define thought disorder symptoms into four overarching themes, including faults in descriptive terminology, mental processing, idiosyncrasy in the use of words, and intelligible speech.

Faults in descriptive terminology cover different symptoms all related to the formulation of the speech itself, and are not connected to underlying cognitive deficits. These include formal thought disorder, akataphasia, paralogia, alogia, laconic speech, poverty of thought, and bradyphasia. Poverty of thought content and empty speech both relate to the content of speech. Desultory thinking, loosening of associations, knights move thinking, and crowding of thought all relate in some form to a jumping from one theme to another without a logical connection. Derailment, tangentiality, “vorbeirden”, and loss of goal refer to an expected change in direction in a thought process. Transitory thinking is similar, albeit with additional words either added or omitted. Paragrammatism, and parasyntax are the inappropriate use of

words and sentence structure. Rule identified numerous terms to define of unintelligible speech including, drivelling, muddling, verbigeration, word salad, speech confusion, incoherence, aculalia glossolalia, catologia, cataphasia, jargon aphasia, and schiozophasia. With regards to the idiosyncratic use of words, Rule made a distinction between the use of words or phrases used in an unusual context, and the invention of new words. Neologisms and word approximations include either the unusual or invented use of words. Metonymy relates to the use of imprecise expressions. Paraphasia, paraphemia, pseudoagrammatism, paraphrasia all relate to the substitution of one word for another with similar form. The last theme identified by Rule included symptoms which imply faults in mental processing. The different terms that are used that relate to this theme include condensation, fusion, displacement, substitution, omission, thought blocking, incoordination, asyndesis, interpenetration, overinclusion, and fragmentation.

1.2.2. Cognitive symptoms

The cognitive symptoms of schizophrenia include impairments in memory, attention, executive functioning, verbal fluency, and psychomotor performance, and are experienced by the majority of those diagnosed with the illness (Marder and Fenton, 2004). Historically, cognitive deficits have been recognised as a key feature of schizophrenia (Kraepelin, 1971), consistently identified both in the acute phase (McGhie and Chapman, 1961), and during periods of remission (Wohlberg and Kornetsky, 1973).

Cognitive deficits are typically present during the prodromal period (Lencz et al., 2006), and unlike positive symptoms, are thought to be a highly stable feature of the disorder (Nopoulos et al., 1994, Rund, 1998). Whilst there is some evidence to suggest that second generation antipsychotics (SGA) may be a more effective treatment for cognitive symptoms, relative to first generation antipsychotics (FGA), their response to treatment is typically poor (Harvey and Keefe, 2001). This this lack of treatment efficacy is seen as an important issue, given cognitive symptoms have been found to be strongly associated with functional impairment (Green et al., 2000, Green et al., 2004a).

In light of the minimal progress in developing treatments for cognitive symptoms, the National Institute for Mental Health (NIMH) initiated the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) collaboration. Under the auspices of the MATRICS initiative a multi-stage programme was initiated to improve the assessment of

cognitive symptoms, with the aim of providing a more robust framework by which new treatments could be evaluated. This process led to a systematic review to identify different dimensions of the cognitive symptom construct that are independent, reliable, and underpinned by the neuropsychological and cognitive neuroscience literature (Nuechterlein et al., 2004). In total, 7 different dimensions of cognitive impairments in schizophrenia were identified, including speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and verbal comprehension. Whilst there was insufficient evidence at the time of the review, social cognition was added the list of constructs evaluated in the MCCB (MATRICS Consensus Cognitive Battery) (Kern et al., 2008, Nuechterlein et al., 2008), given its possible importance as a mediatory between neurocognitive deficits and functional outcomes (Brekke et al., 2005). Social cognition, whilst related to negative symptoms, appears to have a much stronger association with neurocognition and so was not considered part of the negative symptom construct (Kirkpatrick et al., 2006, Sergi et al., 2007). This construct is instead thought to contain 5 distinct domains, covering theory of mind, social perception, social knowledge, attributional bias, and emotional processing (Green et al., 2008).

1.2.3. Negative symptoms

Negative symptoms represent a pathological deficit in typical human experience and have been considered central to schizophrenia since the earliest conceptions of the disorder. Negative symptoms relate specifically to Bleuler's core symptoms of schizophrenia, known as the "4 A's" (loosening of associations, affective flattening, autism, and ambivalence) (Bleuler, 1950) and Kraepelin's "avolitional syndrome" (Kraepelin, 1971). At present, the negative symptoms of schizophrenia include alogia, asociality, anhedonia, avolition, and blunted affect (Kirkpatrick et al., 2006). Recent work suggests that these negative symptoms comprise of at least two distinct subdomains, with alogia and blunted affect representing expressive deficits; and asociality, anhedonia and amotivation representing experiential deficits (Blanchard and Cohen, 2006, Horan et al., 2011, Kring et al., 2013).

Negative symptoms have been found to be highly prevalent in clinical samples, with Bobes et al (Bobes et al., 2010) finding that 57.6% of patients treated for schizophrenia in routine outpatient care present with at least one negative symptom of moderate severity or worse. A summary of the five different types of negative symptoms are outlined below.

1.2.3.1. Alogia

Alogia relates to the reduction in the initiation and production of speech, and is distinct from irrelevant speech and incoherence which can either be attributable to thought disorder or cognitive deficits. In a recent meta-analysis significant deficits in speech production were found in patients with schizophrenia relative to healthy controls, particularly in regards to response latency (Cohen et al., 2014).

A number of different theories have been postulated as an explanation for poverty of speech in schizophrenia. Berenbaum and colleagues (Berenbaum et al., 2008) suggest that alogia is a result of impairments in generating ideas and planning disturbances (Kravariti et al., 2003, Morris et al., 1995), as opposed to impairments in working memory (Barch and Berenbaum, 1994), a general fluency disturbance (Stolar et al., 1994), or word finding difficulties (Alpert et al., 1994).

1.2.3.2. Blunted affect:

Blunted affect is the reduction in emotional expression, variation in vocal tone, and body movement. Different features identified include an unchanging expression, decreased movements, paucity of gestures, poor eye contact, affective non-responsivity, inappropriate affect, and lack of vocal inflection (Andreasen, 1983). This reduction in expressiveness is recognised to relate both to positive and negative emotion expression. In a meta-analysis comparing schizophrenia compared to healthy controls, schizophrenia patients were found to present with significant impairments in emotional expression (d=-1.11, 95% CI = -1.78 to -0.43) (Hoekert et al., 2007).

As summarised by Kring and colleagues (Kring et al., 1993) there are two main theories which explain the reduction of emotional expression in schizophrenia. Bleuler (Bleuler, 1950) proposed the inhibition hypothesis, which suggests that schizophrenia patients experience emotion at a level comparable to controls, but experience significant impairments in the ability to express emotions. Rado (Rado, 1953) suggested that low expressivity was a reflection a reduced ability to experience emotions, and positive emotions in particular. Whilst the terms are sometimes used interchangeably, the former is characterised as blunted affect, whilst the latter is known as emotional blunting. The current evidence base appears to support the

inhibition hypothesis, with a number of laboratory studies finding that patients report experiencing both positive and negative emotional experiences to the same degree as healthy controls (Kring et al., 1993, Berenbaum and Oltmanns, 1992, Cohen and Minor, 2010). In addition, there is evidence to suggest that these deficits may relate to impairments in the amplification of emotional expression of experienced emotions, as opposed to any expression of emotions experienced being suppressed (Henry et al., 2007).

Blunted affect in schizophrenia is associated with abnormalities in social behaviour, and are predicative of poor outcomes (Dworkin et al., 1998). Blunted effect has also been found to be associated in poorer premorbid adjustment, poorer quality of life, and worse outcome at 1-year follow up (Gur et al., 2006). However, blunted affect was not found to be associated with deficits in social skills (Salem and Kring, 1999) or social functioning (Sayers et al., 1996). This suggests that any impairments in outcomes experienced may either be attributable other factors, such as their association with other symptoms (notably amotivation; (Sayers et al., 1996), or the responses from people they are in contact with.

1.2.3.3. Asociality:

Asociality relates to reduced engagement with family members, partners, friends, and/or casual contacts (Blanchard et al., 2011). Asociality is a multifaceted concept in that it can relate both to a desire for relationships and or contact, and actual number of social activities conducted. Therefore, asociality can be evaluated both behaviourally (for example by counting up the amount and frequency of contacts over a specified period) or subjectively, by exploring the individuals interest in engaging with others. Given the fact that behavioural indicators of can be strongly influenced by extrinsic factors, Blanchard and colleagues (Blanchard et al., 2011) emphasise the importance of tapping into the subjective component of this symptom construct.

Understanding why patients with schizophrenia are more isolated appears to be somewhat complex, particularly given patients often report a desire to have friends, a vocation, and a family (Davidson and Stayner, 1997). Part of this is likely to be attributable to overlapping deficits in motivation, which explains why these symptoms are consistently reported to be part of the same overall construct in factor analytic studies (Blanchard and Cohen, 2006). In support of this hypothesis, Sayers and colleagues have found that amotivation is consistently positively associated with social dysfunction in patients with schizophrenia (Sayers et al., 1996).

However, increased asociality may also be attributable to other extrinsic factors, such as environmental under-stimulation and increased positive symptoms. Regarding the impact of positive symptoms on asociality, paranoid ideation has been found to be significantly associated with social anxiety (Rector, 2004), whilst formal thought disorder is linked to greater sensitivity to social rejection (Grant and Beck, 2009), both of which may result in patients being less engaged in their social environment.

Other possible antecedents of asociality include skill deficits and dysfunctional beliefs. There is evidence to suggest that patients with schizophrenia exhibit significant deficits in social skills which can contribute to social isolation (Bellack et al., 1990). Patients with schizophrenia often mistake other people's emotional states, which is associated with poorer social competence (Cramer et al., 1992, Mueser et al., 1996). People with schizophrenia have also been found to a report a greater number of asocial beliefs, which were found to be a strong predictor of asociality, both cross-sectionally and over time (Grant and Beck, 2010). In addition, Rector (Rector, 2004) found a significant association between negative symptoms and dysfunctional social performance beliefs.

1.2.3.4. Anhedonia:

Anhedonia is defined as the inability to experience pleasure from activities which are typically found to be enjoyable. In laboratory-based studies, schizophrenia patients appear to experience positive emotions as intensively as controls (Berenbaum and Oltmanns, 1992, Kring and Earnst, 1999, Kring and Neale, 1996). However, in both structured interviews and self-report questionnaires patients report experiencing significantly lower levels of social and physical pleasure in comparison to healthy subjects (Blanchard et al., 1994, Blanchard et al., 1998, Herbener and Harrow, 2002). In a review by Cohen and colleagues (Cohen et al., 2011), five different explanations for this apparent disconnect between state and trait experiences of anhedonia was proposed; a specific affective deficit in anticipatory hedonic experience; an affective regulation deficit; an encoding-retrieval deficit; a representational deficit; and a social-specific hedonic deficit.

Of the five theories, a deficit in anticipatory hedonic experience is arguably the one that has received the greatest attention. Gard and colleagues (Gard et al., 2007) suggested that people with schizophrenia may experience deficits exclusively in anticipatory, as opposed to consummatory pleasure. These deficits in anticipatory pleasure extend both to the prediction

of experiencing pleasure in the future, and the experience of pleasure in the moment through the anticipation of future events. In support of this theory, Heerey and colleagues (Heerey et al., 2007) found that patients with schizophrenia are significant more likely to choose smaller immediate rewards over greater, delayed rewards. In addition, there is evidence to suggest that different neural pathways are involved for experiencing anticipatory and consummatory pleasure, supporting a distinction between these different types of experience (Berridge and Robinson, 1998, Berridge and Robinson, 2003). In neurobiology, serotonin and opioid systems are primarily linked with the experience of consummatory pleasure (Schultz, 2002, Wise, 2002), whilst anticipatory pleasure has been found to be linked the dopamine system (Berridge and Robinson, 1998). This is significant, given dopamine dysregulation has long been implicated in the development and maintenance of psychosis and schizophrenia (Howes and Kapur, 2009).

In the second possible explanation, an affective regulation deficit relates to the inability to minimise unpleasant experiences and enhance pleasurable ones, which are automatic strategies people unconsciously employ to enhance psychological wellbeing (Gross, 1998, Westen et al., 1997). Support for this hypothesis comes from the field of neuropsychology, where areas which are implicated in the affective regulation process such as prefrontal and anterior cingulate cortex (Kross et al., 2009) have been found to be substantially impaired in individuals with schizophrenia (Barch et al., 2003, Heckers et al., 2004). In the third explanation, it is proposed that dysfunctional encoding or retrieval of experiences may lead to inaccurate representations, a theory supported by evidence which suggests that people with schizophrenia can experience significant impairments in memory recall (Gold et al., 1992). In the fourth, a representational deficit relates to a deficit in the ability to assign an appropriate value to a stimuli (Gold et al., 2008). The final theory outlined in the review by Cohen and Colleagues (Cohen et al., 2011) relates to a social-specific deficit, where they suggest that hedonic impairments relate only to social experiences, whereas consummatory experiences remain largely intact. In their conclusion, Cohen and colleagues proposed that there is likely to be a significant degree of overlap between the theories, and highlighted the importance of considering the different systems together as a way to develop a fuller understanding of the mechanism of anhedonia in schizophrenia.

Studies into the longitudinal course of symptoms of schizophrenia suggest that anhedonia is a relatively common feature of the disorder, with 76% of patients displaying at least mild anhedonia, and 23% showing marked or severe hedonic deficits (Fenton and McGlashan, 1991). Historically, both Rado (Rado, 1956) and Meehl (Meehl, 1962) identified anhedonia as

the central feature of schizophrenia, and a reliable prognostic indicator for later developing the illness. In support of this, college graduates with high social anhedonia were found to be 24 times more likely to be diagnosed with a schizophrenia-spectrum disorder within 10 years compared to participants who report low social anhedonia (Kwapil, 1998). In addition, family members of those diagnosed with schizophrenia have been found to experience significantly greater levels of trait anhedonia when compared with controls (Franke et al., 1994, Grove et al., 1991, Katsanis et al., 1990).

1.2.3.4. Avolition:

Avolition is defined as the lack of motivation to perform activities and pursue goals. According to Ryan and Deci (Ryan and Deci, 2000), motivation concerns "energy, direction, persistence, and equifinality". Avolition can be characterised into two different components, relating either to a deficit in the individuals internal will to action, or the behaviours they display. In recent review determining how negative symptoms may be assessed, Blanchard and colleagues identified four different areas were avolition may be relevant to schizophrenia patients, including social activity, work/vocation, recreation, and self-care (Blanchard et al., 2011).

Deficits in motivation have been seen as a core feature of schizophrenia since the earliest days of its conception. Emil Kraeplin identified avolition as the key feature of patients' long term decline, whilst Bleuler identified avolition as one of one of the "4-A's". More recently, Foussias and Remmington (Foussias and Remington, 2010) proposed that avolition results in the clinical presentation of negative symptoms, and is the principle driver of functional decline.

That patients with schizophrenia exhibit persistent deficits in goal-seeking behaviours have been recognised in the ealiest models of the disorder (Bleuler, 1950, Kraepelin, 1971). A number of theories have been proposed as to why such deficits occur. Gard and colleagues (Gard et al., 2014) found that schizophrenia patients experience difficulties in perceiving reward outcomes, which results in participants engaging in less effortful goals which earn lower rewards. Related to this, Heerey and Gold (Heerey and Gold, 2007) found that subjects show a deficit ability to associate their behaviour to motivational properties of a stimulus.

1.3. Primary and secondary negative symptoms of schizophrenia

In 1974 Strauss and colleagues (Strauss et al., 1974) proposed that negative symptoms have different antecedents, suggesting that they may either constitute a fundamental feature of the disorder itself, or else may arise as a consequence of dealing with institutionalisation, social stigma, and isolation which can result from the diagnosis. Carpenter and colleagues (Carpenter et al., 1985) further expanded upon the importance of identifying the antecedents of negative symptoms in order to explain the heterogeneity in treatment response. In addition to the primary negative symptoms of the disorder which were considered core psychopathology, Carpenter et al. suggested that negative symptoms can arise as a consequence secondary factors, including positive symptoms, the side-effects of antipsychotic medication, a response to under-stimulating environments (with particular reference to long term institutionalisation), and depressive symptoms. Whilst secondary negative symptoms usually improve relatively quickly once these factors are addressed, primary negative symptoms were considered to be highly stable, have a poor prognosis, and be largely non-responsive to treatment.

Differentiating between primary and secondary symptoms may be important for a number of reasons. Firstly, a distinction between these symptoms may explain the heterogeneity in longitudinal course and treatment response which has been recognised in respect to negative symptoms. Secondly, identifying the aetiology of the negative symptoms can inform the appropriate response with regards to treatment. Third, differentiating between these symptoms may be important with regards to evaluating therapeutics for core psychopathology. Finally, isolating symptoms specific to the core pathology of the disorder may help to uncover possible causes and risk factors of schizophrenia.

In a study of consecutively admitted inpatients, the existence of persistent primary negative symptoms was detected in 25.7% of cases with a diagnosis of schizophrenia (Peralta and Cuesta, 2004), suggesting a significant proportion of patients may experience such symptoms. A summary of the different factors identified to cause secondary negative symptoms are summarised below.

1.3.1. Factors that induce secondary negative symptoms

1.3.1.1. Environmental under-stimulation

The link between under-stimulating institutional care and negative symptoms such as decreased spontaneity, reduced drive, and blunted affect have been recognised in concepts such as “institutional neurosis” (Barton, 1959) and “social breakdown syndrome” (Gruenberg et al., 1966). In a study comparing different mental hospitals, Wing and Brown (Wing and Brown, 1970) found a strong association between the severity of the social environment with what they defined as “clinical poverty”, which included symptoms such as blunted affect, poverty of speech, and social withdrawal. In addition, they found that these symptoms reduced relatively quickly once their environment improved. In a replication of the study completed 30 years later (Curson et al., 1992), no association between length of stay and negative symptoms was detected, and only a weak association between environmental poverty and negative symptoms was found. Curson and colleagues attributed this weaker relationship to the improved hospital environment, supporting the conclusion that it is the environmental impoverishment, as opposed to incarceration itself, which exacerbates negative symptoms. In a cross-cultural validation of the original Wing and Brown study (Oshima et al., 2003), the link between environment and negative symptoms was evaluated in 139 Japanese hospitals, where deinstitutionalisation and rehabilitative practices had not been adopted at the time (Mino et al., 1990). Whilst no association was detected between length of stay and negative symptoms, a significant association between negative symptoms and an under-stimulating environment was found.

Overall, these findings support the link between environmental under-stimulation and negative symptoms, and the importance of providing stimulating environments in order to minimise secondary negative symptoms. However, given only a very low association was detected in the study by Curson (Curson et al., 1992) it suggests that the negative symptoms induced in hospitals with good social and rehabilitative provision may be lower than previously thought. Regardless, given the potential impact of hospitalisation, and the fact that it is beyond the scope of this investigation to evaluate the environmental poverty of each institution, these findings highlight another issue in disentangling primary and secondary negative symptoms in inpatient settings. Consequently, this investigation focuses exclusively on outpatients, apart from the analysis conducted in chapter 7 which considers the impact of symptoms specifically in the acute phase of treatment.

1.3.1.2. Antipsychotic medication side effects:

Since the discovery of antipsychotic medication in the 1950's it has been recognised that these compounds can cause extra-pyramidal side effects (EPS) (Rifkin, 1987). Common extra-pyramidal side effects include dystonia, parkinsonism, tardive dyskinesia, and akathisia. Other movement-disorders related to antipsychotic drugs include catatonia, and in very rare cases, neuroleptic malignant syndrome (Caroff, 1980). Akathisia is characterised by restlessness, anxiety, inner tension and the need to be in constant motion. Akathisia is thought to be relatively common, with prevalence estimated at between 20-35% of patients in routine practice (Kane et al., 2009). Dystonia is an acute involuntary movement disorder, characterised by prolonged muscle contractions causing twisting movements and abnormal postures (Berardelli et al., 1998). Drug-induced parkinsonism mimics Parkinson's disease, and can result in tremors, postural or gait disturbances, hypersalivation, rigidity, and bradykinesia (slowness in the execution of movement), and akinesia (loss of movement power). Tardive dyskinesia is characterised by repetitive hyperkinetic movements, which, unlike most EPS symptoms, can be irreversible (Caroff et al., 2011). Catatonic symptoms associated antipsychotic side-effects include stupor, and states where patients find themselves unable to move and/or speak (akinetic mutism). In rarer cases, patients can experience catalepsy (which is a state whereby patients are outwardly unresponsive to external stimuli) and waxy flexibility (which is a rigid maintenance of body position) (Gelenberg and Mandel, 1977). EPS are positively associated with medication non-compliance (Fenton et al., 1997), which in turn is associated with a higher risk of relapse (Gilbert et al., 1995). In a review by Fenton and colleagues (Fenton et al., 1997) it was found that between 25%-66% of patients cite medication side effects as the primary reason for treatment non-compliance in schizophrenia

When second generation antipsychotics (SGA's) first became available, it was believed that a lower risk of EPS was one of their major benefits over the older first generation antipsychotics (FGA's) (Kane et al., 1988, Safferman et al., 1991). However, in a meta-analysis comparing the side effects of typical and atypical antipsychotics (Leucht et al., 2009b) much of the difference previously reported was attributable to high potency FGA's being used in the control arm conditions. When different SGA's were compared to lower potency FGA's (defined as equipotent or less potent than chlorpromazine) the difference in EPS was less marked, and less consistent. In another study comparing EPS levels between atypical antipsychotics and a lower potency FGA (perphenazine), no differences were detected (Lieberman et al., 2005). These findings suggest that issues related to EPS have not been eliminated by the advent of second

generation antipsychotics, and remain an important consideration in the treatment and research of schizophrenia.

In addition to causing significant levels of distress to patients, EPS can mimic negative symptoms which can make assessing core psychopathology difficult (Carpenter et al., 1985). In animal studies, antipsychotic drugs have been found to be associated to behavioural changes comparable to negative symptoms such as apathy, and lack of spontaneity and affective arousal (McKinney et al., 1980, McKinney and Moran, 1981). In addition, both the dose and duration of antipsychotic medication received was found to be positively associated with negative symptoms (Perenyi et al., 1998). When individual negative symptoms were considered separately, Kelley found that medication effects appeared to be related primarily to expressive deficits such as blunted affect (Kelley et al., 1999).

Regarding particular types of EPS, significant overlaps between parkinsonian symptoms such as bradykinesia and akinesia and negative symptoms have been identified (Allan et al., 1998). In a study by Kane (Kane et al., 1994), a significant correlation between akinesia and anergia was detected, which persists even after a washout period of at least two weeks prior to the assessment taking place. Similarly, Prosser reported that negative symptoms have been found to be significantly correlated with the parkinsonian symptoms akinesia and tremor (Prosser et al., 1987). Regarding individual negative symptoms, Allen suggested that the link between facial bradykinesia and blunted affect, and akinesia to avolition may be a considered a particular issue (Allan et al., 1998).

In clinical practice, anticholinergic drugs have typically been prescribed to control or limit the impact of EPS (Ogino et al., 2014). In research, EPS can be measured using validated scales such as the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970) or Barnes Akathisia Rating Scale (BARS) (Barnes, 1989) to either to specify maximum EPS inclusion criteria, or else be included as covariates in the model. Given the content overlap between negative symptoms and akinetic parkinsonian symptoms such as bradykinesia and akinesia, Peralta and Cuesta suggest that focusing on the non-akinetic symptoms such as tremor and hypersalivation may be a more useful in distinguishing primary from drug-induced negative symptoms (Peralta and Cuesta, 1999c).

1.3.1.3 Depression

Depression is a state of low mood that can lead to changes in feelings, thoughts and behaviours. Symptoms include feelings of hopelessness, apathy, lethargy, changes in sleep patterns, guilt, suicidal thoughts and somatic complaints. Depression is considered to be relatively common in patients with schizophrenia. In a review by Siris (Siris, 1991), the prevalence of depression and prominent depressive symptoms ranged from 7%-70%, depending upon the criteria adopted and the sample evaluated. At the point of hospital admission for a first episode, 71% of participants presented with clinically meaningful depressive symptoms, and 23% fulfilled criteria for a diagnosed depressive episode (Häfner et al., 2005). Prior to onset, the lifetime prevalence of depressive mood for a period longer than 2 weeks was found to be particularly high (83%; (Häfner et al., 2005). Overall, depression and depressive symptomology is considered to be highly prevalent in patients with schizophrenia.

Whilst studies have consistently shown that negative and depressive symptoms are distinct constructs (Blanchard and Cohen, 2006), there is a significant degree of overlap with regards to their clinical presentation (Mulholland and Cooper, 2000). For example, both negative symptoms and depression can manifest as a lack of energy and drive, anhedonia, and social withdrawal. However, a number of differences are also apparent. As recognised in in section 1.2.3.4., anhedonic deficits in schizophrenia appear to be confined specifically to anticipatory pleasure (Gard et al., 2007), whilst in depression anhedonia relates to experiencing pleasure overall (Snaith, 1993). In addition, depressive symptoms appear to be more associated to positive, rather than negative symptoms (Lindenmayer et al., 1991). Other differences include the fact that patients with severe negative symptoms often report relatively high subjective quality of life and satisfaction scores (Fitzgerald et al., 2001, Priebe, 2007). This is in contrast with depression, where the negative association between depressive symptoms and subjective quality of life is well documented (Priebe et al., 2000, Reine et al., 2003).

Whilst a number of scales have been developed to measure depressive symptoms such as the Beck depression inventory (BDI) (Beck et al., 1988) and the Hamilton Depression Rating Scale (HRDS) (Hamilton, 1960), disentangling symptoms using these scales is considered problematic. Addington and colleagues (Addington et al., 1996) found significant correlations between the HRDS and assessments of negative symptoms in patients with schizophrenia. In a different study, the HRDS was found to contain a negative symptom factor which correlates strongly with the SANS (Goldman et al., 1992). In addition, there is evidence to suggest that global rating scales such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al.,

1987) are not to be able to distinguish between depression, negative symptoms, and EPS (Collins et al., 1996).

In an attempt to disentangle ratings of depression and negative symptoms, the Calgary Depression Scale for Schizophrenia Scale (CDSS) (Addington et al., 1993, Addington et al., 1992) was designed specifically for use in psychotic populations. In a study examining the divergent validity of the CDSS from negative symptomology (Addington et al., 1996), no significant associations were found both at hospital admission (r^2=.02, P=.67), or at three months follow-up (r^2=.06, P=.14). These findings are in contrast to an assessment of the relationship between the HDRS and negative symptoms, where significant associations were detected at both time points (r^2=.28, P<.01, and r^2=.23 P<.01 respectively). Overall, these findings highlight the importance and complexity of disentangling depressive and negative symptoms, and the importance of choosing appropriate methods to control for depressive symptoms when controlling for secondary negative symptoms.

1.3.1.4. Positive symptoms:

The positive symptoms of schizophrenia include hallucinations, delusions and thought disorder (for a detailed summary see 1.2.1.). In reformulations of the positive/negative symptoms dichotomy (Crow, 1980, Crow, 1985, Strauss et al., 1974) positive and negative symptoms were understood to be independent, with some studies suggesting they may even be inversely associated once general psychopathology is controlled for (Kay et al., 1987). However, later work has found positive correlations between the two symptom dimensions, both in the acute phase and during periods of remission (Addington and Addington, 1991).

In an evaluation of the positive and negative “subtypes” of schizophrenia, Angrist and colleagues (Angrist et al., 1980) examined the effects of prescribing antipsychotics and amphetamines to patients with schizophrenia. As hypothesised, amphetamines increased the severity of positive symptoms but, contrary to expectations, negative symptoms also increased. When this was examined at an item level, the increase was found to be exclusively attributable to elevated emotional withdrawal. Angrist postulated that the increase in emotional withdrawal may be attributable to autistic preoccupations with increased persecutory delusions or auditory hallucinations, as opposed to any change in core psychopathology. In a more recent study, (Kelley et al., 1999) found that increases in positive symptoms predicted more severe avolition but not blunted affect, supporting the theory that

positive symptoms appear to influence the experiential features of negative symptoms in particular.

Since the study by Angrist, a number of other researchers have reported on the improvement in negative symptoms being linked to improvements in positive symptoms (Tandon et al., 1990, Tandon et al., 1993, van Kammen et al., 1987). Whilst no such association was detected in studies by Brier or Serban (Breier et al., 1987, Serban et al., 1992), Tandon suggested this may be attributable to small sample sizes and insufficient positive symptoms present at baseline to drive changes in negative symptoms (Tandon et al., 1993). In an attempt to model for the impact of positive symptoms on negative symptoms in clinical trials, a number of path-analytical studies have been completed (Alvarez et al., 2006, Moller et al., 1995, Tollefson and Sanger, 1997). Whilst direct effects of atypical antipsychotics on negative symptoms were detected in all studies, significant improvements in these symptoms were also found to be attributable to improvements in positive symptoms. For example, in the study by Alvarez et al. 42.69% of the improvements detected in negative symptoms in patients prescribed with olanzapine over risperidone was found to be attributable in the improvement in positive symptoms (Alvarez et al., 2006). Such findings highlight the importance of either limiting, or controlling the severity of positive symptoms when attempting to evaluate core negative psychopathology.

1.3.3. Deficit syndrome and persistent negative symptoms

Following the distinction between primary and secondary negative symptoms, Carpenter and colleagues went on to suggest that those who experience primary negative symptoms may constitute a distinct subtype of schizophrenia, known as the “deficit syndrome” (Carpenter et al., 1988). As recognised in a review by Buchanan (Buchanan, 2007) the concept is based upon Kraepelin’s “avolitional syndrome” (Kraepelin, 1971). In a departure from the subtype definition proposed by Crow (Crow, 1980, Crow, 1985), a diagnosis of deficit syndrome is determined by the persistence of core psychopathology, as opposed to the presence of symptoms measured at a single time point. The operational criteria for the Deficit syndrome proposed by Carpenter (Carpenter et al., 1988) include:

1) At least 2 of the following 6 symptoms present at a clinically significant level: flattened affect, diminished emotional range, alogia, impaired interest, diminished sense of purpose, asociality.

2) 2+ symptoms present for minimum of 12 months, present during periods of clinical stability.
3) The above symptoms must not be a consequence of secondary factors
4) A diagnosis of schizophrenia

The distinction between deficit and non-deficit forms of schizophrenia has been found to be highly stable over time (Amador et al., 1999), with the diagnosis of deficit syndrome consistent in 83% of cases, and a non-diagnosis consistent in 88% of cases 3-4 years later. Over a longer period, Strauss and colleagues (Strauss et al., 2010), found that approximately 70% of deficit syndrome patients at baseline still qualified for the diagnosis 20 years later. The prevalence of the deficit syndrome has been estimated to be 20-30% of schizophrenia in clinical samples, and 14-17% in schizophrenia population samples (Kirkpatrick et al., 2006). The prevalence for the disorder appears to be significantly higher in older patient samples, with 37% of participants found to qualify for deficit syndrome in a sample of patients over 45 years old (Harris et al., 1991).

In a review of deficit syndrome by Kirkpatrick, it was proposed that differences in the signs and symptoms, longitudinal course, risk and antecedent factors, treatment response, and pathophysiological correlates between deficit and non-deficit subtypes all support the theory that they constitute distinct disorders (Kirkpatrick et al., 2001, Kirkpatrick and Galderisi, 2008). Patients diagnosed with deficit syndrome have been found to present with lower positive psychotic symptoms and less severe depression relative to non-deficit patients, in addition to lower rates of less drug abuse, suicidality, anxiety, guilt and hostility (Kirkpatrick et al., 1996a, Kirkpatrick et al., 1994). As identified in section 1.1.3., winter birth is associated with non-deficit schizophrenia, whilst deficit syndrome has a stronger association with summer birth (Messias et al., 2004). Deficit syndrome patients have been found to have a significantly lower age of onset relative to non-deficit patients (Kirkpatrick et al., 2000a). With regards to the course of the illness, the deficit syndrome has been found to be associated with poorer premorbid adjustment (Galderisi et al., 2002). Tek and colleagues found that patients diagnosed with deficit syndrome had a poorer quality of life, experienced a greater impairment in functioning, and had more severe negative symptoms 5 years later (Tek et al., 2001). In studies that compare the symptoms of family members of people with deficit and non-deficit schizophrenia, sub-clinical negative symptoms are more severe in the families of

people with deficit syndrome (Hong et al., 2003), whilst symptoms of dysphoria and positive symptoms are higher in family members of non-deficit patients (Kirkpatrick et al., 2000b).

Regarding any neurological differences between deficit and non-deficit syndrome there is evidence to suggest that non-deficit patients experience a greater reduction in frontal lobe white matter relative to both deficit patients and healthy controls (Buchanan et al., 1993), whilst there is also some evidence of electrophysiological differences between deficit and non-deficit patients (Mucci et al., 2007, Turetsky et al., 1998). In addition, there is evidence to suggest that eye-tracking dysfunction appears to be significantly more impaired in deficit patients, relative to non-deficit patients (Ross et al., 1997, Ross et al., 1996). Overall, there is a substantial (and still emerging) evidence base to suggest that deficit syndrome may represent a distinct subtype of schizophrenia which emphases the importance of considering this distinction in any investigation of negative symptoms.

1.3.4. Persistent negative symptoms as an alternative to the deficit syndrome

Whilst assessment tools such as the Schedule for the Deficit Syndrome (SDS) have been found to be a reliable tool for identifying deficit patients (Kirkpatrick et al., 1989), Buchanan suggested that making such a distinction may be problematic in the context of a clinical trial (Buchanan, 2007). Firstly, accurate information regarding the presentation of symptoms is required over a period of 12 months, which is likely to be difficult to obtain in the majority of cases. Secondly, determining the aetiology of negative symptoms (i.e. whether they are primary in origin or attributable to secondary factors) requires a high degree of clinical expertise that assessors in clinical trials may not typically have. As an alternative, Buchanan proposed that clinical trials designed to evaluate treatments for negative symptoms should instead include those that experience what he defined as “persistent negative symptoms”.

The criteria that Buchanan proposed to define what constitutes persistent negative symptoms differ from the criteria for deficit syndrome in two important respects. Firstly, the requirement that the negative symptoms considered must be present for 12 months is omitted. No predefined time period is specified, although 6 months is generally recommended. Secondly, patients with secondary negative symptoms may still qualify for eligibility so long as the negative symptoms experienced are persistent, and have failed to respond to usual treatments for causes of secondary symptoms which are adequately controlled for. To operationalise the

concept of persistent negative symptoms, Buchanan (Buchanan, 2007) proposed the following criteria:

1) At least moderate severity of negative symptoms, measured on a validated symptom rating scale
2) Demonstrated clinical stability for an extended period of time prior to the start of study
3) A defined maximum threshold of positive symptoms as measured on a validated symptom rating scale
4) No (or low level of) depressive symptoms, as measured on a validated rating scale
5) No (or low level of) extrapyramidal symptoms, as measured on a validated rating scale

(Buchanan, 2007)p.1016)

Adopting the criteria of persistent negative symptoms over deficit syndrome criteria has a number of advantages. By not having to disentangle the aetiology of the negative symptoms adopting persistent negative symptom criteria should be easier to implement, relative to deficit syndrome criteria. In addition, utilising the persistent negative symptom criteria should mean that a substantially larger pool of potential participants would be available, easing the challenge to recruit eligible participants. Related to this, with the eligible population being much closer to the clinical population, any subsequent findings could be considered to have greater ecological validity. As recognised in the NIMH-MATRICS consensus statement on negative symptoms (Kirkpatrick et al., 2006) symptoms that are highly persistent, irrespective of the aetiology, represent an unmet therapeutic need and so merit inclusion in clinical trials designed to treatment these symptoms.

Whilst it may appear attractive to adopt the criteria of persistent negative symptoms in clinical trials, further work on how these criteria should be implemented is required. At present the criteria are broad, and it is not clear how the different ways in which they can be implemented may influence the association between negative symptoms and causes of secondary negative symptoms such as depression, positive symptoms, and EPS. In addition, recent work has suggested that the manner in which these criteria are adopted can have a substantial impact on the size of the potential sample pool (Dunayevich et al., 2014, Rabinowitz et al., 2013),

which can impact both the validity of the findings and the ease of recruitment. This area will be explored in greater depth in chapter 4.

1.5. Longitudinal course of negative symptoms of schizophrenia

A number of different conceptual models of schizophrenia have suggested that negative symptoms are either highly stable, or get progressively more severe over time. Kraepelin (Kraepelin, 1971) defined schizophrenia as a degenerative disorder, with all symptoms getting more severe over time. In contrast, Bleuler (Bleuler, 1950) adopted a much broader conception of schizophrenia arguing that outcome can be much more heterogeneous, albeit with negative symptoms being more stable than the "accessory" positive symptoms. More recently, Crow (Crow, 1980, Crow, 1985) thought negative symptoms were permanent, believing they were a result of morphological changes in the brain.

In longitudinal assessments of symptoms over time, Pfhol and Winokur (Pfohl and Winokur, 1983) catalogued the presence and absence of symptoms over 25 years in 52 chronic institutionalised hebephrenic and catatonic schizophrenia patients. In this study they found that the prevalence of avolition, impaired social interaction and flat affect increased over time, whilst positive symptoms reduced. In a series of investigations as part of the Chestnut Lodge study, Fenton and McGlashan found that that negative symptoms "accrue severity, stability and prognostic weight over time" (Fenton and McGlashan, 1991, McGlashan and Fenton, 1992, McGlashan and Fenton, 1993). However, there is also a significant body of literature which suggests that negative symptoms are largely stable, with a minority of patients exhibiting small improvements over time. Pogue-Geile & Harrow (Pogue-Geile and Harrow, 1985) found that the severity of negative symptoms were largely stable over a period of 5 years, with a tendency towards remission. In a study spanning 4 years, Johnstone and colleagues (Johnstone et al., 1987) found that whilst negative are much more stable than positive symptoms, and that the deficits were not irreversible with all of features of negative symptoms improving in at least some cases. Over a period of 10 years, Eaton (Eaton et al., 1995) found that the prevalence of both positive and negative symptoms reduced in the year following first hospitalisation, and were then stable hereafter. In a sample of neuroleptic-naïve patients at admission, Arndt (Arndt et al., 1995) found that negative symptoms were prominent at the baseline stage, and remained largely stable over a period of 2 years. In an evaluation of community outpatients over a period of 2 years, Quinlan (Quinlan et al., 1995) found that negative symptoms significantly reduced, whilst positive symptoms increased.

More recently, Whitty (Whitty et al., 2008) reported significant improvements in both positive and negative symptoms over a period of 4 years from first presentation, suggesting that the outcome may not be as pessimistic as once thought.

In addition to examining the longitudinal course of negative symptoms as a singular construct, a number of studies have also examined the course of individual negative symptoms (Dollfus and Petit, 1995b, Eaton et al., 1995, Fenton and McGlashan, 1991, Pogue-Geile and Harrow, 1985). There is some evidence to suggest that alogia and blunted affect are more stable than other negative symptoms (Dollfus and Petit, 1995b, Johnstone et al., 1987, Kelley et al., 2008), which may be due to these symptoms being less influenced by improvements in positive symptoms (Kelley et al., 1999).

In the current investigation, the longitudinal course of negative symptoms will be examined by way of meta-analysis in an attempt to uncover broader trends regarding how these symptoms may change over time in chapter 3.

1.5.1. Longitudinal course of negative symptoms in patients with deficit syndrome

Whilst it is important to determine the longitudinal course of negative symptoms that patients typically experience irrespective of their aetiology, disentangling their origin may be helpful as a way to explain the heterogeneous findings highlighted in section 1.5. As stated previously, Carpenter (Carpenter et al., 1985) proposed that while secondary negative symptoms may fluctuate in accordance with the extrinsic factors which cause the symptoms change, primary negative symptoms should be considered a highly stable feature of the disorder. In order to evaluate the severity and stability of primary negative symptoms over time, a number of longitudinal studies have been completed in patients that qualify for the deficit syndrome.

In one of the earliest evaluations of negative symptoms in deficit and non-deficit schizophrenia patients, Fenton and McGlashan (Fenton and McGlashan, 1994) found that negative and cognitive symptoms get significantly worse in patients that qualify for deficit syndrome over a period of 5 years. In addition, periods of symptomatic remission were found to be a lot less frequent in patients in these patients, with 78% showing a continuing course of illness, relative to 28% of non-deficit patients. These findings were similar to those reported in a later study by Kirkpatrick and colleagues (Kirkpatrick et al., 1996b) who found that deficit patients presented with more severe negative symptoms two years later, in addition to reporting poorer psychosocial functioning and greater global impairment.

In a prospective study evaluating the longitudinal course of negative symptoms over a much longer period (20 years) (Strauss et al., 2010), the results were broadly consistent with earlier studies. Deficit syndrome patients were found to experience significantly fewer periods of global recovery, and a greater degree of social and occupational impairment. However, in contrast to previous studies negative symptoms were not found to get significantly worse over time. Instead, negative symptoms were found to follow a fluctuating course in a similar manner to non-deficit patients.

1.6. The impact of negative symptoms on quality of life

Considerable attention has been paid to the impact of negative symptoms of schizophrenia on quality of life, despite the fact that there is no precise definition of what constitutes quality of life in this context (Priebe et al., 2010b). For the purposes of this investigation, quality of life is defined to include subjective components such as wellbeing and satisfaction with life, and objective components including daily life functioning and external resources, both material and social (Katschnig, 2000, Lehman et al., 1982). Consequently, a number of studies which do not specifically mention quality of life, but do evaluate concepts such as functioning, wellbeing, and satisfaction have all been deemed as relevant to this area of interest.

With regards to the objective components of quality of life (OQOL), negative symptoms have been found to be significantly associated with less frequent social contacts, lower quality of social interaction, and poorer community participation (Lysaker and Davis, 2004). Hunter and Barry (Hunter and Barry, 2012) found a strong association between negative symptoms and impairments in various measures of functioning, including the quality of interpersonal relations, vocational role, intrapsychic foundations, and personal and social performance. In longitudinal studies, higher negative symptoms at baseline have been found to be associated with more substantial impairments in OQOL 2 to 7 years later in areas such as global functioning, psychosocial functioning, impairment in recreational activities and relationships, and work performance (Ho et al., 1998, Milev et al., 2005, Pogue-Geile and Harrow, 1985, Whitty et al., 2008). Such quality of life deficits have been found to be particularly severe in patients that qualify for deficit syndrome (Fenton and McGlashan, 1994, Tek et al., 2001). In an evaluation of individual symptoms, anhedonia in particular has been found to be a predictor of various features of lower quality of life, including psychological, social, and spiritual domains (Ritsner et al., 2011), whilst apathy has been found to be associated with poorer individual living skills (Kiang et al., 2003).

Whilst a strong association between various domains of OQOL and negative symptoms have been consistently detected, the association between negative symptoms and subjective quality of life (SQOL) is less clear. Somewhat counter-intuitively, patients with negative symptoms tend to report relatively high SQOL, despite experiencing a poor OQOL (Arns and Linney, 1993, Katschnig et al., 2006). As a result, the association between objective and subjective quality of life have been found to be only weak-to-moderate in schizophrenia, ranging from 0.04 to 0.57 (Priebe and Fakhoury, 2007). Fitzgerald and colleagues (Fitzgerald et al., 2001) found that whilst various observer-rated quality of life domains were found to be significantly associated to negative symptoms, subjective life satisfaction was not. In a meta-analysis examining the cross-sectional association between symptoms of schizophrenia and SQOL, only a weak association was detected with negative symptoms (Eack and Newhill, 2007). In an assessment of the association between the change in subjective quality of life and anergia symptoms over time only a weak association was detected, and this was not significant after controlling for other symptoms, notably depression (Priebe et al., 2011b).

Subjective quality of life can cover a number of concepts, such as ones satisfaction with their employment situation, finances, recreational activities, friendships, safety, housing, health, sex-life, family and overall life satisfaction (Priebe et al., 1999). Determining ones subjective appraisal of their life is thought to be influenced by three different factors, including a comparison between expectations and aspirations, a comparison with others, and adaptation over time (Priebe, 2007). As a result, Priebe suggested that patients may report relatively high levels of SQOL due to the fact that schizophrenia is a highly chronic illness, meaning patients may have had a long time to adapt to their present situation, in addition to peer comparison. However, an alternative explanation is that many scales which have been designed to measure negative symptoms focus primarily on behavioural referents (Blanchard et al., 2011), which may result in the association between SQOL and symptoms being under-reported. Regardless of the explanation, subjective quality of life reports are an important indicator of patients' views and experiences which cannot be disqualified by any external measure, and so should be respected (Priebe, 2007). This relationship is further explored in chapter 6.

1.7. The treatment of negative symptoms

Whilst negative symptoms have been found to improve as a result of antipsychotic treatment (Goldberg, 1985, Kane et al., 1988, Marder and Meibach, 1994), this is considered primarily to be a consequence of improvement in the causes of secondary negative symptoms, such as

positive symptoms (Buchanan, 2007, Tandon et al., 1993). To date, any advances in the treatment of schizophrenia have been found to provide only limited benefits to negative symptoms directly. In a meta-analysis by Leucht which examined the efficacy of individual second generation antipsychotics, most were found not to provide a significant improvement relative to first generation drugs, and in those that did the effect sizes found were small (Leucht et al., 2009a). Meta-analyses into the efficacy of adjuntive medications such as alpha-2 receptor antagonists (Hecht and Landy, 2012) and glutamatergic compounds (Tuominen et al., 2005) show some promise, although since these publications a large-scale trial found no impact of either glycine or D-cycloserine (Buchanan et al., 2007). There is some evidence to suggest that adjunctive antidepressant medication may have some limited benefit (Singh et al., 2010). In a broader review evaluating the different pharmacological approaches in treating negative symptoms (Arango et al., 2013), promising new drugs that act on the NMDA and alpha-7 nicotinic receptors are highlighted, but further work is required.

In evaluations of psychotherapeutic approaches, a meta-analysis of CBT reported a small effect on negative symptoms (Jauhar et al., 2014), a meta-analysis on social skills training reported a moderate effect size (Kurtz and Mueser, 2008), whilst a meta-analysis on social cognitive training found no effect (Kurtz and Richardson, 2012). In a meta-analysis of cognitive remediation therapy which evaluated overall symptoms, only a small effect was detected (Wykes et al., 2011). In the UK, NICE have recommended arts therapies as a treatment which has shown consistent efficacy in reduction of negative symptoms (NCCfMH, 2010), however this has since been challenged by the non-significant result of the MATISSE trial (Crawford et al., 2012b). In a broader meta-analysis looking at the effectiveness of a number of different treatment for negative symptoms, some treatments were found to result in statistically significant improvements, but none were considered to result in clinically meaningful improvements (Fusar-Poli et al., 2015). Overall, this current lack of treatment efficacy has led to negative symptoms being recognised as an unmet therapeutic need, and an important target for new interventions (Kirkpatrick et al., 2006).

1.8. The NIMH-MATRICs consensus statement on negative symptoms of schizophrenia

Given the devastating impact of negative symptoms, combined with the limited progress in treatment development, in 2005 a consensus development conference was held on behalf of the National Institute of Mental Health (NIMH). The aim of this meeting was to further develop

the measures and methodologies adopted in negative symptom clinical trials (Kirkpatrick et al., 2006). The meeting followed the success of the MATRICs conference on cognitive symptoms of schizophrenia (Green et al., 2004b), which helped form the basis for standardising the cognitive assessment battery.

The consensus statement concluded that negative and cognitive symptoms are separate domains, with negative symptoms representing an unmet therapeutic need in a large proportion of cases. There was an agreement that blunted affect, alogia, asociality, anhedonia, and avolition should all be considered part of the negative symptom construct. In addition, they proposed that this construct may comprise of at least two distinct factors; expressive deficits, which include alogia and blunted affect, and experiential deficits, which include asociality, anhedonia and avolition (Blanchard and Cohen, 2006, Horan et al., 2011). Despite recognising that patients who experience primary and secondary negative symptoms can be differentiated with relatively good reliability (Kirkpatrick et al., 2001), it was suggested that making a distinction between these types of symptoms was not essential, so long test subjects presented with persistent negative symptoms with sources of secondary negative symptoms controlled for through study design. However, no specific details of what constitutes an appropriate strategy to limit the impact of positive, depressive or medication side effects were presented, an issue which will be further addressed in chapter 4.

In research trials which evaluate the effectiveness of medications taken specifically for negative symptoms, it was agreed that the ideal design would be to conduct a double-blind, placebo-controlled comparison of parallel groups, including clinically stable patients maintained on second-generation antipsychotics. In the case of broad spectrum antipsychotics there was a consensus that it was not possible to establish superior efficacy for negative symptoms due to the “pseudospecificity problem”, which is the inability to disentangle improvements in negative symptoms from improvements in sources of secondary negative symptoms (see section 1.3.1.). There was also a consensus that whilst proof of concept studies may be relatively brief (4-12 weeks), full-scale trials should be much longer (6-months) in order to evaluate the persistent efficacy of treatments. The final point of agreement was that whilst the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) was preferable to single symptom-item scales such as the Positive and Negative Symptom Scale (Kay et al., 1987), the information obtained from single-item scales should still be considered important and valid.

In addition to the points of agreement, the workshop also outlined recommendations for future research. Of these, the key recommendation was the need to develop of new instruments designed to measure negative symptoms which address the limitation of existing scales. This recommendation resulted in the development of the Collaboration to Advance Negative Symptom Assessment for Schizophrenia (CANSAS) (Blanchard et al., 2011), which in turn led to the develop of two new scales; the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011), and the more comprehensive Clinical Assessment Interview for Negative Symptoms (CAINS) (Forbes et al., 2010, Horan et al., 2011, Kring et al., 2013). Whilst the CAINS has since been found to have excellent psychometric properties (Kring et al., 2013), the report highlights the need to evaluate the sensitivity of the scale, which is explored in chapter 5 of this investigation.

Other areas for research identified included the need for more research into the prevalence and longitudinal course of negative symptoms (which will be examined in chapter 3 of this investigation), and determining what improvement in negative symptoms constitutes a clinically meaningful effect size improvement. Whilst it has been suggested that a reduction of 10 to 15 points on the PANSS corresponds to a Clinical Global Impressions (CGI) change of "minimally improved" (Leucht et al., 2006), this figure is dependent upon the baseline severity of symptoms, and more importantly only corresponds to the PANSS total score, as opposed to the PANSS negative subscale alone. In recent work regarding the SANS, a reduction of symptoms by 13-21% was found to correspond to "minimally improved" on the CGI, 42-50% reduction to "much improved" and 67-90% to "much improved" (Levine and Leucht, 2013).

1.8.1. The ISCTM and NEWMEDS update on clinical trials in negative symptoms

Following the original NIMH-MATRIC meeting for negative symptoms, two further workshops were held, one held by the International Society for Central Nervous System Clinical Trials and Methodology, (ISCTM) (Marder et al., 2011), and other held by the Novel methods leading to New MEdications in Depression and Schizophrenia collaboration (NEWMEDS) (Marder et al., 2013). These updates were deemed necessary for a number of reasons. Firstly, concerns were raised that the original 2006 consensus statement (Kirkpatrick et al., 2006) did not include sufficient representation from the pharmaceutical industry, which is important given their involvement in producing and evaluating new pharmacological treatments for negative symptoms. Secondly, there were concerns at the time that the Food and Drug Administration (FDA) were considering amending their guidelines, requiring clinical trials of treatments for

negative symptoms to include a co-primary outcome measure evaluating functional outcomes. Thirdly, it was felt that further consensus regarding trial design would be helpful, particularly given the developments in negative symptoms and lessons learnt from recent clinical trials. The meeting included individuals from academia, pharmacological industry, and from licensing bodies covering both the USA (FDA) and Europe (EMA; the European Medicines Agency).

During the ISCTN meeting, one the main conclusions that was drawn was the recognition that given severe negative symptoms include functional impairment, improvements in negative symptoms alone should be deemed sufficient for drug approval. This conclusion therefore supports research which focuses on negative symptoms specifically as an outcome for research.

In the ISCTN consensus statement, it was agreed that clinical trials need to be no less than 2 months, and ideally at least 6 months in duration (not including pre-randomisation). Clinically meaningful change was defined as a *d*=.05, which Cohen described as an effect "visible to the naked eye". Regarding the evaluation of negative symptom severity, the SANS (Andreasen, 1982), PANSS negative subscale (Kay et al., 1987), and the NSA-16 (Axelrod et al., 1993) were all identified as appropriate for use in clinical trials. However, it was noted that the original PANSS negative symptom subscale does not provide sufficient coverage of the negative construct, which lead to the recommendation that alternative factor solutions, such as the one proposed by Marder and colleagues (Marder et al., 1997), would be preferred (see section 1.9.1.3.). The promising psychometric properties of the scales developed as a consequence of the CANSAS (Blanchard et al., 2011) were noted, and were identified as a potentially importance advance in the field. Last point of consensus was that in order to receive approval as a treatment for negative symptoms then a global improvement in negative symptoms must occur. Therefore, whilst there is evidence to suggest that negative symptoms may consist of at least 2 distinct constructs (Blanchard and Cohen, 2006) evaluating negative symptoms as a singular construct is still the preferred method in clinical trials.

During the NEWMEDS meeting there was considerable debate regarding whether negative symptoms should be prominent or predominant at the point of recruitment. Predominance specifies that the negative symptoms of schizophrenia alone should be present to at least a moderate degree of severity, whilst participants who experience prominent negative symptoms may also experience other symptoms of schizophrenia, with particular reference to positive symptoms. Whilst there was an agreement that participants should present with negative symptoms above a minimum degree of severity and a maximum level of EPS and

depression, no consensus was reached on whether a maximum positive symptom threshold should also be implemented. This is an important issue in the design of clinical trials, and is further explored in chapter 4 of this investigation.

1.9. Assessing negative symptoms

Since positive and negative symptoms of schizophrenia have been identified as distinct constructs, a number of scales have been developed to measure the negative symptom domain. In the MATRICs consensus statement, the manner in which negative symptoms are assessed was recognised as a significant barrier in the development of new treatments (Kirkpatrick et al., 2006).

In this section the scales which are currently used to evaluate the negative symptom construct will be summarised. Alternative assessment methods of negative symptoms which utilise self-report, video, or laboratory assessments of negative symptoms are not included, however details of these are available elsewhere (Horan et al., 2006, Kupper et al., 2010). Older assessment scales which are no longer adopted in negative symptom research, such as the Krawiecka-Manchester Scale (Krawiecka et al., 1977), the Negative Symptom Scale produced by Lewine (Lewine et al., 1983), or the Negative Symptom Scale produced by Pogue-Geile and Harrow (Pogue-Geile and Harrow, 1985) are also not evaluated. Finally, only tools which evaluate the whole negative symptom construct will be summarised, meaning single symptom scales such as the Chapman physical and social anhedonia scales (Chapman et al., 1976), the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006), and the emotional blunting scale (Abrams and Taylor, 1978), have also not been considered.

In an evaluation of any assessment tool it is important to consider which symptoms are being evaluated. This is particularly important in regards to negative symptoms, given the construct has undergone a number of substantial revisions over time (see section 1.1.5.). In addition, it is important to consider how these scales evaluate the different domains. For example, Blanchard and colleagues (Blanchard et al., 2011) suggest that for symptoms such as asociality, anhedonia and avolition it is important to evaluate the experiential components of these symptoms, rather than just relying on the behavioural aspects. This is because behaviours may be influenced by other factors such as finances, housing arrangements, and available support from family and friends, unlike an internal drive to action which may better represent core pathology. Lastly, dependent upon the nature of the enquiry it may be important to determine

the aetiology of symptoms, i.e. determining whether symptoms represent core pathology, or whether they are a consequence of other factors such as depression.

1.9.1. Structured interviews of negative symptoms

1.9.1.1. CGI-SCH: Clinical Global Impressions Scale (schizophrenia version)

The Clinical Global Impressions scale (Guy, 1976) is a brief, 3-item questionnaire designed to evaluate symptom severity, change in symptoms over time, and therapeutic response. Each item relates to a global assessment of multiple constructs, rating symptoms, behaviour, and the impact of illness on functioning over a set period (typically the past 2 days). The symptom severity item is rated on a 7 item scale, ranging from 1 "not at all ill", to 7 "Amongst the most extremely ill patients". The change items range from 1- "very much improved" to 7- "very much worse".

In a later adaptation, Haro et al. (Haro et al., 2003) modified the scale to assess positive, negative, depressive, and cognitive symptoms of schizophrenia, in addition to providing a global assessment of the illness. The scale assesses the severity of the illness over previous week, and degree of change relative to the previous assessment. The convergent validity of the CGI-SCH with the PANSS was found to be high with the cognitive, negative, positive, and global items (ICC= .78, .80, .86 and .75 respectively), and moderate with the depressive item (ICC=.61) (Haro et al., 2003). In addition, the inter-rater reliability of the scale was high for the cognitive, positive, negative, and global items (ICC range= .73-.82), and moderate for the depressive item (ICC=.64).

Given the scale only measures negative symptoms using a single item it was not identified in the MATRICS or ISCTM consensus report as an appropriate primary outcome for use in clinical trials for negative symptoms (Kirkpatrick et al., 2006, Marder et al., 2011). In addition, the CGI has been criticised for lacking standardised definitions given the scale scoring is framed in the context of other patients (Beneke and Rasmus, 1992). One significant advantage of the CGI is that it provides a result that translates into an easily interpretable clinical assessment (Nierenberg and DeCecco, 2000). Consequently, the scale has been used as a way to provide anchor points for measuring how changes in other measures such as the BPRS (Overall and Gorham, 1962) and the PANSS (Kay et al., 1987) translate into clinical response (Leucht and Engel, 2006, Leucht et al., 2005, Levine et al., 2008, Mortimer, 2007).

1.9.1.2 BPRS: Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale (BPRS) was developed by Overall and Gorham (Overall and Gorham, 1962) as an assessment tool to evaluate symptom change. The original model comprises of 16 items, measuring somatic concern, anxiety, emotional withdrawal, conceptual disorganisation, feelings of guilt, tension, mannerisms and posturing, grandiosity, depression, hostility, suspiciousness, hallucinations, motor retardation, uncooperativeness, unusual thought content, and blunted affect. Each item is rated on a scale of 1 (absent) to 7 (extremely severe). Severity is defined both by the frequency of symptoms experienced, and their impact on functioning over the past week. Five items are rated based on observations made during the interview and information from clinicians and caregivers, whilst 11 are based primarily on the verbal report of the interviewee. In an assessment of the item-level rater reliability, moderate to high correlations have been detected (r= .56 - .86) (Overall and Rhoades, 1982).

Since the original model the scale has been expanded to include 18 items, adding disorientation and excitement (Overall and Klett, 1972). The scale was then later expanded to 24 items, adding motor hyperactivity, elevated mood, distractibility, self-neglect, bizarre behaviour, and suicidality (Lukoff et al., 1986). Subsequent evaluations of the expanded version of the scale found the interview is a sensitive measure with good inter-rater reliability (Ventura et al., 1993)

Whilst the original scale was designed to provide a single summary score, since its inception a series of factor analytic studies have been completed with schizophrenia patients which suggest the scale comprises of multiple symptom subdomains (Burger et al., 1997, Dingemans et al., 1995, Long and Brekke, 1999, Malla et al., 1993, Mueser et al., 1997, Overall and Beller, 1984, Ruggeri et al., 2005, Van der Does et al., 1993, Velligan et al., 2005, Ventura et al., 2000). A summary of the different factor loadings of the 24-item version of the scale are presented in table 2. These studies appear to suggest a 4 or 5 factor solution, covering negative/anergia symptoms, positive/psychosis symptoms, anxiety/depressive/affective symptoms, and hostility/activation symptoms. For the purposes of this investigation four factor solution proposed by Velligan (Velligan et al., 2005) was adopted for two reasons. Firstly, this study was completed on a significantly larger sample size than the others (1440 participants), which is important given all but the Ruggeri study included less than 200 participants, which has been deemed inadequate for factor-analytic studies (Comrey and Lee, 2013). Secondly, in the

Velligan study both exploratory and confirmatory factor analysis were conducted, meaning the findings are more robust.

Table 2: Different configurations of the 24-Item BPRS-E from different factor analysis studies[a]

BPRS Items	Study					
	(Velligan et al., 2005)	(Dingemans et al., 1995)	(Van der Does et al., 1995)	(Burger et al., 1997)	(Ventura et al., 2000)	(Ruggeri et al., 2005)
Somatic Concern			5	5		5
Anxiety	5	5	5	5	5	5
Emotional Withdrawal	1	1	1	1	1	1
Conceptual disorganisation	2	4	4	2		2
Guilt	5	5	5	5	5	5
Tension	4	4	4	4		5
Mannerisms and Posturing			4	4		4
Grandiosity		2		2	4	2
Depression	5	5	5	5	5	5
Hostility			4	3	4	4
Suspiciousness		2	2	3	2	2
Hallucinations	2	2	2	2	2	2
Motor retardation	1	1	1	1	1	1
Uncooperativeness		2		3		4
Unusual thought content	2	2	2	2	2	2
Blunted Affect	1	1	1	1	1	1
Disorientation				1	2	1
Excitement	4	4	4	4	4	4
Motor hyperactivity	4	4	4	4	4	4
Elevated mood			4		4	4
Distractibility		4	4		4	4
Self-neglect		1	1	1	1	4
Bizarre behaviour	2	2	4	2	2	4
Suicidality	5	5	5	5	5	5

Factor loadings: 1= Negative / Anergia symptoms, 2= Positive symptoms/ thinking disorder 3= Hostility / suspiciousness 4=Excitement/activation symptoms 5= Depression/anxiety / affective symptoms

[a]Highest factor loadings presented, with those lower than <.4 omitted.

Grey highlighting indicates the negative symptom construct adopted in chapter 7.

Despite being extensively used in clinical and research settings, the BPRS has a number of limitations with regards to negative symptom assessment. One significant issue is that the scale does not appear to tap into a number of domains which are considered part of the

negative symptom construct, such motivational and anhedonic deficits, as outlined in section 1.2.3. In addition, whilst the item "emotional withdrawal" is included, it appears to relate specifically to how emotionally engaged the participant is during the interview, and so does not represent the broader concept of asociality. As a result it has been suggested that the BPRS insufficiently evaluates the experiential features of negative symptoms (Blanchard et al., 2011). This was evident during the development of the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) which found a moderate correlation between the BPRS and expressive symptoms (r=.52), but only a low correlation with experiential features of negative symptoms (r=.28). A second issue is that in a comparison to the Negative symptom Assessment scale (NSA) (Axelrod et al., 1993), and the Scale to Assess Negative Symptoms (SANS) (Andreasen, 1983) the BPRS was found to be a much less sensitive instrument in detecting symptom change (d=.32, in comparison to d=.70 and d=.78 for the SANS and NSA respectively) (Eckert et al., 1996). This is a significant issue given the lack of instrument sensitivity has been identified as one of the major barriers to treatment development in negative symptoms (Kirkpatrick et al., 2006).

1.9.1.3 PANSS: Positive and Negative Symptom Scale

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is a structured clinical interview designed to measure the symptoms of schizophrenia, and along with the CGI and the BPRS is one of the most extensively used assessment tools in the field of schizophrenia research (Mortimer, 2007). The PANSS is based on items from the BPRS (Overall and Gorham, 1962) and the Psychopathology Ratings Scale (Singh and Kay, 1975). In a similar fashion to the BPRS (Overall and Gorham, 1962), symptom severity is defined both by the frequency of symptoms experienced, and their impact on functioning over the past week The scale is composed of 30 items; 7 positive symptom items, 7 negative, and 16 general symptoms which include, amongst other things, affective symptoms and cognitive deficits. Each item is rated from 1 to 7, giving a range of 7-49 for the positive and negative subscales, and 16-112 for the general subscale. Obermeier and colleagues (Obermeier et al., 2010) recommend transforming the data to be re-scaled at ratio level (i.e. 1 subtracted from each item so they are scaled from 0-6), which was completed in chapter 6 in sections where percentage changes were considered. However, this was not adopted in other sections given this has not consistently been adopted in the literature, meaning it would be harder to interpret any findings from this investigation in the context of other studies.

An early evaluation of the scale suggested it is possible to achieve high levels of inter-rater reliability (ICC>.8) (Kay et al., 1988, Peralta and Cuesta, 1994), which has been since been replicated in a series of major trials. The scale has also been found to have high convergent validity to the SANS and the SAPS (Andreasen, 1983, Andreasen, 1984).

Since the publication of the PANSS, a series of factor analytic studies have suggested that the positive, negative and general symptoms subscale structure is not sufficiently stable. Instead, the majority of studies appear to support a 5 factor solution comprising of negative, positive, disorganised/cognitive, excited, and depression/anxiety symptoms (see table 3 for a summary).

These five domains have been found to be consistent over age, symptom severity, chronicity, and in patients both in the chronic and first-episode of the disorder (Emsley et al., 2003). However, as indicated in table 3 there has been some disagreement with regards to the different items which correspond to each factor. Given the negative symptom construct is the principle focus or this investigation, the priority was to adopt the most consistent factor solution for this domain. In the 9 studies evaluated (Emsley et al., 2003, Kay and Sevy, 1990, Lancon et al., 2000, Lancon et al., 1999, Lindenmayer et al., 1994, Lykouras et al., 2000, Marder et al., 1997, Mass et al., 2000, White et al., 1997) there was a consensus that five of the original negative items; affective blunting, emotional withdrawal, apathetic social withdrawal, poor rapport, and impaired conversation flow all related to the negative symptom construct. Of the remaining two, deficits in abstract thinking appeared to correspond to cognitive deficits, whilst stereotypical thinking appeared somewhat unstable and was found to relate to positive, cognitive, manic-excitement factors, or else did not load onto any factor at all. Instead, the general psychopathology items active social avoidance and motor retardation were found to consistently load on to the negative factor. Other items, such as preoccupation, disturbance of volition, mannerisms and posturing and poor attention were not found to load consistently onto negative symptoms and so were not considered. Following the results of these factor analytic studies, the 7-item negative subscale comprising of affective blunting, emotional withdrawal, apathetic social withdrawal, poor rapport, impaired conversation flow, motor retardation and active social avoidance was adopted throughout this investigation. This model, whilst proposed by a number of studies (Lancon et al., 2000, Lindenmayer et al., 1994, Marder et al., 1997), has been most commonly referred to as the Marder configuration, the term adopted in this thesis.

Table 3: Different configurations of the PANSS present from factor analytic studies according to highest factor loadings[a]

PANSS Items (configured in standard factor loadings)	Study								
	Marder et al., 1997	White et al., 1997	Linden-mayer et al., 1994	Emsley et al., 2003	Kay & Sevy, 1990	Lancon et al., 1999	Lancon et al., 2000	Mass et al., 2000	Lykouras et al., 2000
Negative subscale:									
N1: Blunted affect	1	1	1	1	1	1	1	1	1
N2: Emotional withdrawal	1	1	1	1	1	1	1	1	1
N3: Poor rapport	1	1	1	1	1	1	1	1	1
N4: Passive social withdrawal	1	1	1	1	1	1	1	1	1
N5: Difficulty in abstract thinking	3	3	3	3	3	3	3	3	3
N6: Lack of spontaneity	1	1	1	1	1	1	1	1	1
N7: Stereotypical thinking	2	3	4	3	-	4	-	-	3
Positive subscale:									
P1: Delusions	2	2	2	2	2	2	2	2	2
P2: Conceptual disorganisation	3	-	3	3	3	3	3	3	3
P3: Hallucinations	2	2	2	2	2	2	2	2	2
P4: Excitation	4	4	4	4	4	4	4	4	4
P5: Grandiosity	2	2	2	2	2	2	2	4	2
P6: Suspiciousness	2	-	2	2	-	2	2	-	2
P7: Hostility	4	4	4	4	4	4	4	4	4
General Psychopathology subscale:									
G1: Somatic concern	2	5	5	5	5	2	-	-	4
G2: Anxiety	5	5	5	5	5	5	5	5	5
G3: Guilt Feelings	5	5	5	5	5	5	5	5	5
G4: Tension	5	5	4	5	4	4	4	4	4
G5: Mannerisms and posturing	2	1	3	3	1	2	-	4	1/3
G6: Depression	5	5	5	5	5	5	5	5	5
G7: Motor retardation	1	1	1	1	1	1	1	-	1
G8: Uncooperativeness	4	4	4	4	4	4	-	4	4
G9: Unusual thought content	2	2	2	2	2	2	2	2	2
G10: Disorientation	3	-	3	3	3	3	3	-	3
G11: Poor attention	3	3	3	3	1	3	3	3	3
G12: Lack of judgement	2	-	2	2	2	2	2	-	2/5
G13: Disturbance of volition	3	3	3	1	1	1	-	-	1
G14: Impulsivity	4	4	4	4	4	4	4	4	4
G15: Preoccupation	3	3	5	3	5	1	-	-	1
G16: Active social avoidance	1	-	1	1	1	1	1	1	1

Factor loadings: 1= Negative symptoms, 2=Positive symptoms 3: Disorganised/cognitive symptoms 4=Excited symptoms 5= Anxiety/ depressive symptoms

[a]Table adapted from Emsley et al., 2003. Grey highlighting represents the negative symptom construct adopted in this investigation

Despite the widespread use of the scale, the PANSS has been recognised to have a number of limitations in measuring the negative symptom construct (Blanchard et al., 2011). Firstly, it has been suggested that the PANSS relies primarily on behavioural referents such as the range and frequency of activities, interviewer observations, and reports from family members or carers, and insufficiently taps into what the interviewees themselves experience. The problem of basing results exclusively on behavioural referents is the fact that other factors such as finances, depressive and positive symptoms, lack of social skill (Bellack et al., 1994), and social rejection (Corrigan, 2004) may contribute to a lack of social activity, independent of the will to engage in such activities. Secondly, by focusing on behavioural referents, the scale may under-represent deficits in interviewee experiences which has been found constitute a distinct construct in negative symptoms (Blanchard and Cohen, 2006).

1.9.1.4 SANS: Scale for the Assessment of Negative Symptoms

Unlike the previous tools outlined, the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) is designed exclusively to measure the negative symptoms of schizophrenia. The scale comprises of 30 items covering five domains, with each symptom measured on a 6-point scale ranging from 0 (none) to 5 (severe). The five domains evaluate affective flattening, anhedonia-asociality, alogia, avolition-apathy, and attention rated over the previous month. The affective flattening subscale comprises of 9 items, measuring reductions in facial, vocal, and gestural expressiveness; a decrease in spontaneous movements; poor eye contact; inappropriate affect; affective non-responsivity; and a subjective rating of affective flattening. The alogia subscale consists of 6 items, and rates the poverty of the quantity and content of speech; increased latency of response; the presence of blocking; and a subjective rating of alogia. Avolition-apathy includes 4 items, assessing motivation to address grooming and hygiene; vocational pursuits; physical anergia; and a subjective assessment of avolition-apathy. The anhedonia-asociality subscale measures deficits relating to interest and pursuit in recreational activities; sexual interest and activity; ability to feel intimacy; relationships with friends; and a measure of subjective awareness of anhedonia-asociality. The final subscale, attentional impairments, measures inattentiveness during work and assessment; in addition to a subjective measure of attentiveness deficits.

In the original study the Interrater reliability of single items (ICC=.701-.926), subscale scores (ICC=.860-.925) and the overall summary score (ICC=.838) were all found to be high (Andreasen, 1982). In addition, the internal consistency of each of the subscales were all high (α=.799 - .844), other than the anhedonia-asociality subscale score (α=.632). In an examination

of the correlation of individual items, the subjective assessments were all found to correlate relatively poorly to the subscale scores, leading to Andreasen to suggest that these should be omitted in calculating the summary ratings.

One major limitation of the SANS is the fact that some of the symptoms measured are now not considered to represent part of the negative symptom construct. For example, the SANS subscale "attention" is now considered to evaluate cognitive, rather than negative symptoms (Blanchard et al., 2011, Harvey et al., 2006, Milev et al., 2005). Consequently, a number of studies using the SANS have removed this subscale (Rabany et al., 2011), supported by evidence which suggests that omitting attention improves the internal consistency of the scale overall (Peralta et al., 1992b). In addition, a number of individual items have also been found to be problematic such as poor eye contact, which does not load on to any factor (Rabany et al., 2011), blocking, which is an expression of thought disorder and so therefore a positive symptom (Rule, 2005), and poverty of content of speech, which is understood to represent symptoms of cognitive impairment (Liddle, 1987). Another significant issue with the SANS is the fact that individual subscales can relate to multiple, conceptually distinct domains (Blanchard et al., 2011). The anhedonia-asociality subscale can reflect frequency of social contacts, interest, experience of pleasure and hostility, meaning it is unclear what psychological processes are reflected in the ratings given. Lastly, whilst the scale was designed to focus on behavioural referents due to evidence at the time which suggested this is a more reliable approach to measuring negative symptoms (Andreasen, 1979), this could also be considered somewhat problematic. Conceptually, symptoms such as avolition and asociality are defined by internal states, such as ones desire for relationships and contact, whilst the behavioural measures of these constructs, (i.e. the amount of friend contacts they have had) are representations of these internal states. However, these behaviours can potentially be influenced by a number of extrinsic factors such as social skill (Bellack et al., 1990), opportunities for social contacts, and the level of support they are given to encourage social encounters which do not represent core negative symptoms (Blanchard et al., 2011).

1.9.1.5. NSA: Negative Symptoms Assessment scale

In its original format the Negative Symptom Assessment scale (NSA) (Alphs et al., 1988) is a 26-item tool evaluating 5 distinct domains, including impaired communication, disturbed affect/emotion, reduced social involvement, reduced motivation, and impaired gross cognition. Following a subsequent factor analytic study of the scale a number of minor

adjustments were made, including dropping the item “slowed movements”, and splitting the impaired communication domain into two distinct clusters, covering impaired communication and retardation (Axelrod et al., 1993). The inter-rater reliability and test-retest reliability of the scale was found to be excellent (Alphs et al., 1988), whilst the internal consistency was also found to be high (α=0.94) (Axelrod et al., 1993). In addition, after only a 30 minute training session novice raters were able to complete assessments consistent with expert ratings (Axelrod and Alphs, 1993).

In response to concerns regarding the length of the scale, a shorter 16-item version of the scale was devised (Axelrod et al., 1993). In this scale the gross cognition domain was dropped, whilst 4 other items were removed due to redundancy. In the alternative 16-item version impaired communication was assessed over 4 items, measuring quantity, content, and latency of speech. Three items assessed affect/emotion, measuring the range of emotions experienced, reduced emotional display, and reduced modulation. Social involvement was measured by 3 items assessing social drive, rapport, and sexual interest. Four items are included in the motivation domain, covering a reduced sense of purpose, daily activity, hobbies and interests, and poor grooming and hygiene. Finally, retardation was measured by 2 items, evaluating reduced expressive gestures and slow movements.

In this amended version of the scale the internal consistency was found to be high (α=.85). In addition, the scale was found to have good convergent validity with the PANSS negative subscale, and good discriminant validity from scales assessing depression, positive symptoms and quality of life (Alphs et al., 2011). In a further shortening of the scale, a 4-item version of the NSA was devised, designed for routine clinical use (Alphs et al., 2011). This scale was found have good convergent validity with the NSA-16, the PANSS negative subscale, and the Strauss-Carpenter Level of Functioning scale (Strauss and Carpenter, 1977), in addition good discriminant validity from scales assessing depression, positive symptoms and quality of life scales.

As with the PANSS and the BPRS, the NSA has been criticised for not representing what is currently understood to constitute the negative symptom construct, in addition to other conceptual issues (Blanchard et al., 2011). For example, the item “reduced emotional range” can theoretically lead to conflating anhedonic response with a lack of experiences, both positive and negative. In addition, this item can also result in the counter-intuitive position where people report experiencing more negative experiences at follow-up, relative to baseline, which would result in a lower symptom severity score. In addition, the scale also

explicitly instructs raters to focus on behaviours, meaning the experiential features of negative symptoms are under-represented.

1.9.1.6. CAINS: Clinical Assessment Interview for Negative Symptoms of schizophrenia

In the 2005 NIMH-MATRICS consensus meeting on negative symptoms of schizophrenia, issues regarding current negative symptom assessment scales were identified as a significant barrier to the development of new treatments (Kirkpatrick et al., 2006). In recognition of this problem, the Collaboration to Advance Negative Symptom Assessment Scales (CANSAS) (Blanchard et al., 2011) was established, which in turn developed two assessment scales; the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011) and the Clinical Assessment Interview for Negative Symptoms of Schizophrenia (CAINS) (Forbes et al., 2010, Horan et al., 2011, Kring et al., 2013).

The CANSAS followed a process modelled on the original MATRICS collaboration that developed the MCCB for cognitive symptoms (Nuechterlein et al., 2008), which was similar to the method outlined by Clark and Watson (Clark and Watson, 1995). Clark and Watson emphasised the importance of developing a detailed conception of the construct, and its theoretical context, as the first step in the scale development process. In order to achieve this, the CANSAS group conducted a series of literature reviews and biweekly conference calls between members in order to develop the theoretical concept of the negative symptom construct that the scale would be designed to measure. As identified in the MATRICS consensus statement, the negative symptom construct was defined to include alogia, blunted affect, anhedonia, avolition and asociality (Kirkpatrick et al., 2006), with the possibility that the construct comprises of two distinct subdomains of expressive and experiential deficits. How these symptoms were evaluated was guided by related current neurobiological models, such as the recognition that different hedonic experiences have distinct neural circuits (Berridge and Robinson, 1998, Knutson et al., 2001), with negative symptoms related specifically to anticipatory pleasure (Gard et al., 2007). In a departure from earlier scales, the decision was taken that the interview would aim to evaluate interviewees' descriptions of their internal states, in addition to behaviours and environmental factors. While it was originally considered that assessing behavioural rather than internal states may be a more reliable approach to measuring negative symptoms (Andreasen, 1979), later work has suggested that the subjective experiences of schizophrenia patients can be both reliable and valid (Jaeger et al., 1990, Liddle and Barnes, 1988). One significant advantage of assessing internal states is that they are

considered to be less influenced by external factors such as finances and input from family and carers, meaning this may represent a more accurate measure of core psychopathology (Blanchard et al., 2011).

In the next stage, a pool of initial items for a clinical rating scale were generated, and were evaluated by group members, other (unspecified) clinical trial researchers, presented at national conferences, and posted to a public website where other academics and researchers from industry could provide further feedback. As recommend by Clark and Watson, in the initial stages the aim was to be over-inclusive in terms of the number of items, with particular attention paid to the wording of the questions presented (Clark and Watson, 1995). Following this feedback, a beta version of the scale was produced and validation of the scale was performed (Forbes et al., 2010).

In the initial feasibility study of the CAINS scale by Forbes and colleagues (Forbes et al., 2010), a 23-item beta-version of the interview was evaluated. Items were rated on a 7-point scale (scored 0-6) with higher scores reflecting greater psychopathology. The scale was designed to cover the 5 symptoms of schizophrenia as specified in the MATRICs consensus statement review (Kirkpatrick et al., 2006), including avolition (4 items), asociality (3 items), anhedonia (9 items), alogia (2 items) and blunted affect (5 items). The internal consistency, discriminant validity, and convergent validity of the overall scale appeared good. However, relatively poor interrater agreement with the avolition (ICC=.53) and alogia (ICC=.48) items, issues with the anchoring of the anhedonia items, and low internal consistency in the asociality (α=.32) and avolition (α=.47) items called for a significant amendments to the scale. In a revised version, outlined by Horan and colleagues (Horan et al., 2011), 16 of 23 items were retained within a 2-factor solution, with each item rated on a scale of 0-4. The first factor covered experiential items, relating to anhedonia, amotivation and asociality, and the second factor expressive symptoms, including items relating to alogia and blunted affect. In this second iteration the items retained were found to have a better distribution, high interrater agreement, and good convergent and discriminant validity (Horan et al., 2011). An assessment of the categories using item response theory suggested that most of the anchor points for each item were able to provide useful distinctions (particularly with the expressive items), but did identify that revisions would be necessary to better demarcate symptom thresholds at lower levels.

The final development and validation stage was outlined by Kring and colleagues (Kring et al., 2013). In this iteration, a 13 item scale comprising to two factors, measuring emotional experience and expression was proposed. The experiential subscale comprises of nine items,

assessing the frequency, motivation and anticipated pleasure in activities and relationships around work and school, friends, and the family. The emotional expression subscale consists of four items, measuring the vocal and gestural features of expression. The subscales can be combined to provide one summary score of negative symptoms, thus adhering to the recommendations outlined in the ISCTM consensus statement (Marder et al., 2011). However, the authors recommend reporting the scores separately given the evidence suggests they appear to be represent distinct constructs (Horan et al., 2011).

In the final version, the interrater reliability for the experiential and expressive subscales were high (ICC=.93 and ICC=.77 respectively). The test-retest reliability of the two subscales also demonstrated adequate reliability (ICC=.69), comparable to those found with the negative symptom subscale of the PANSS. In an assessment of the convergent validity of the scale, both CAINS subscales were positively correlated with the BPRS anergia subscale and the SANS, and negatively associated with the desire for close relationships and social engagement. In an assessment of the scales discriminant validity, both CAINS subscales were found not to be associated with depression, medication side effects, or cognitive impairment. A moderate association was detected between the experiential subscale and positive and agitation symptoms, however this association was significantly weaker than that detected between positive and agitation symptoms and both the SANS and BPRS anergia subscale.

Despite the extensive validation process which went into the production of the CAINS, it is important to note the steps in scale construction which were not adopted. For example, while the opinions of a number of clinical and industry experts in the field were sought, this was not formalised using a process such as the Delphi technique. The Delphi technique, originally developed by the RAND corporation (Dalkey and Helmer, 1963) is a structured, iterative process by which to aggregate the opinions of experts in any particular field. Some of the main advantages of this process are that it allows a diverse panel of participants to be recruited, it is conducted anonymously which can reduce any possible "halo effect" of prominent participants, and that controlled, staged feedback process can reduce any possible effect of noise which may distort the data by focusing on individual interests (Hsu and Sandford, 2007). As a result, adopting this method may have allowed for a consensus to be reached by incorporating a broader range of opinions than may otherwise have been the case.

Conceptually, the CAINS appears to follow a much closer representation of what we currently understand negative symptoms to be, assessing anhedonia, asociality, avolition, alogia and blunted affect (Blanchard et al., 2011). However, at present it is not clear if the scale is more

sensitive in determining change relative to existing scales such as the SANS, or the PANSS. The lack of sensitivity of existing scales has been recognised as significant issue which impedes the evaluation new therapeutic interventions designed to treat these symptoms (Kirkpatrick et al., 2006). In recognition of this current gap in the literature, the relationship between the CAINS and the PANSS negative subscale will be explored in greater depth in chapter 5.

1.9.1.7. BNSS: Brief Negative Symptom Scale

The Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011) is the second scale produced as part of the CANSAS collaboration (Blanchard et al., 2011). Relative to the CAINS, the BNSS is a relatively brief instrument designed for routine clinical use, in addition to clinical trials. The scale itself consists of 13 items, covering the five domains of alogia, anhedonia, avolition, blunted affect and asociality recognised to cover negative symptoms. One of the main advantages of this particular scale is that given its brevity, the scale can be completed in approximately 15 minutes (Strauss et al., 2012). As with the CAINS, an examination of the factor structure of the scale yielded two distinct clusters reflecting expressive and experiential symptoms (Strauss et al., 2012).

In an initial evaluation of the psychometric properties of the scale , the inter-rater reliability of the 5 subscales in addition to the global score were found to be high (global score ICC=.96, individual subscales ICC=.89 - .95). An assessment of the internal consistency of the scale was very high (α=.93), and all items were moderately to highly correlated to the global BNSS score (r=.53 - .85), suggesting the scales measures a singular latent construct. The test-retest reliability over a period of 2 weeks was also found to be relatively high, both for the total score (r=.81), and the subscales (r=.76 – r=.90). In an assessment of the concurrent and discriminant validity of the scale, the BNSS was found to be highly correlated with the PANSS negative subscale and the SANS (r=.80 and r=.84 respectively), whilst not being correlated with the PANSS depression item (r=.14), or cognitive deficits. In a final validation of the scale (Strauss et al., 2012) internal consistency, temporal stability, and appropriate convergent and divergent validity were high.

1.9.2. Pooling negative symptom assessments

In this investigation negative symptoms will be measured by a number of different scales. Given the constructs evaluated in each scale are slightly different, combining scores evaluating individual negative symptoms is not straight forward. One way to pool different items measured by the SANS, PANSS and BPRS is the method proposed by Lyne (Lyne et al., 2012) (see table 4), which was adopted as part of the investigation completed in chapter 3.

Table 4: How different items over different scales relate to each other*

SANS	PANSS	BPRS
Affective flattening	Blunted Affect	Blunted Affect
Alogia	Lack of Spontaneity/flow of conversation	-
Avolition/Apathy	Passive social withdrawal	Self-Neglect
Anhedonia-Asociality	-	-

*Method of combining items proposed by Lyne et al., 2012

Chapter 2. Rationale and research questions

2.1. Rationale for investigation

The negative symptoms of schizophrenia have been found to be largely resistant to current pharmacological and psychosocial treatments (Fusar-Poli et al., 2015). This is a significant issue, given these symptoms are associated with substantial impairments in functioning (Hunter and Barry, 2012). In an attempt to address a lack of progress in treatment development there have been considerable efforts to improve our understanding of the negative symptom construct, their assessment, and the manner in which clinical trials in this area are conducted (Kirkpatrick et al., 2006, Marder et al., 2013, Marder et al., 2011). The aim of this thesis will be to address a series of questions which either may inform the design of clinical trials, or else builds upon recent advances in negative symptom assessment to revisit areas of interest.

Regarding the longitudinal course of negative symptoms, the evidence suggests that whilst secondary negative symptoms improve relatively quickly once the underlying causes are addressed, primary negative symptoms are highly stable. A number of observational studies and randomised controlled trials have reported differing trajectories in negative symptom course, with the heterogeneity likely to be a consequence of factors such as symptom antecedents, clinical variables, socio-demographic differences, and variations in the methodologies employed. The first aim of this investigation will be to uncover broad trends in how these symptoms may change over time in schizophrenia outpatients by pooling studies which utilise different treatment options and exploring the impact of factors considered to influence symptom course. Such an investigation could potentially be informative to future trial design, in addition to clinically relevant.

Whilst conducting a meta-analysis may be useful in uncovering broader trends of negative symptoms over time, methodological limitations mean it it is difficult to determine what degree of change is attributable to transient secondary symptoms. In clinical trials there have been a number of different methods proposed to limit the variability of negative symptoms attributable to secondary sources (Buchanan, 2007, Kirkpatrick et al., 2006, Marder et al., 2013, Marder et al., 2011). However, at present there does not appear to be a consensus on how these criteria should be implemented, particularly with regards to limiting the impact of positive symptoms. There is evidence to suggest that adopting different criteria can result in

large differences in the potential sample pool (Dunayevich et al., 2014, Rabinowitz et al., 2013), whilst it is unclear whether adopting predominant criteria reduces the impact of positive symptoms on negative symptoms (Dunayevich et al., 2014, Stauffer et al., 2012). In this investigation a series of study inclusion criteria will be compared to determine their impact on the association between negative symptoms, and positive and depressive symptoms. Such an investigation may prove helpful in standardising the inclusion criteria used in negative symptom trials.

In the MATRICs consensus statment (Kirkpatrick et al., 2006) the limitations of existing negative symptom assessment tools were identified as a significant barrier in the evaluation of new treatments. The report from this meeting recommended the development of new assessment tools which are both in line with our current conception of the negative symptom construct, and are more sensitive to detect symptom change compared to existing scales. This led to the development of the CAINS (Horan et al., 2011) which has been found to have excellent psychometric properties (Kring et al., 2013). However, at present it is not clear how the sensitivity of the CAINS compares with existing negative symptom scales. In this investigation the sensitivity of the CAINS will be compared to the PANSS negative subscale, both in terms of how the scales differentiate between participants with high and low symptoms, and how they measure the change in symptoms over time. In addition, the incremental validity of the CAINS will be compared to the PANSS negative subscale to determine which scale is a stronger predictor of indicators of social impoverishment. This investigation of the CAINS could be considered the important next step in validating the scale for use in clinical trials evaluating treatments for negative symptoms.

Recent developments in our understanding of negative symptoms suggest that expressive and experiential deficits represent two distinct constructs (Blanchard and Cohen, 2006). However, at present the relationship between these separate subdomains and functional outcomes have not been fully explored, possibly due to limitations in earlier scales which have only recently been addressed by the development of the CAINS (Blanchard et al., 2011, Kring et al., 2013). One such area that may benefit from examining negative symptoms in this manner is reviewing the relationship between negative symptoms and quality of life (QOL).

Whilst a strong inverse relationship between negative symptoms and OQOL has been consistently been reported, only weak associations have been detected between negative symptoms and SQOL (Fitzgerald et al., 2001). It has been proposed that a weak relationship between negative symptoms and SQOL may be attributable to the chronicity of the disorder or

peer group comparison (Priebe, 2007). However, another possibility is that the relationship may have been previously under-reported by earlier assessment tools insufficiently evaluating the experiential features of negative symptoms. In this investigation the relationship between SQOL, negative symptoms, and experiential and expressive deficits will be evaluated, both cross-sectionally and over time. These relationships will be compared to those reported by PANSS negative subscale, which measures negative symptoms as a singular construct.

In addition to SQOL, other subjective reports from patients such as initial appraisal of inpatient treatment are important given they are associated with outcomes long after the patient has been discharged (Priebe et al., 2009). Therefore, it is important to understand the impact of symptoms on initial appraisal of treatment in the acute phase, regardless of whether they can be considered primary or secondary in origin. In this final section of the study the aim will be to look at the impact of negative symptoms, in addition to other symptoms, at the point of admission to examine their impact on subjective initial appraisal of inpatient treatment.

2.2. Study aims and research questions

In order to address the above questions, five different investigations were completed. A summary of each study is presented below.

2.2.1. Examination of the longitudinal course of negative symptoms in schizophrenia outpatients

To evaluate the course of negative symptoms over time a systematic search will be conducted to identify all studies which evaluated negative symptoms over at least two time points in schizophrenic outpatient samples. The identified studies will then be pooled together by way of meta-analysis to examine trends in negative symptom change over time. Next, a series of meta-regressions will be conducted in order to examine the impact of different eligibility criteria, study duration, and assessment scales used. In addition to the evaluation of negative symptoms as a single construct, individual symptoms were also examined. Finally, planned sub-group analyses will be conducted looking at negative symptom change between different assessment scales, in addition to studies which specify minimum negative and maximum positive and depressive symptoms as part of their eligibility criteria. Given the investigation will be exploratory in nature no specific hypothesis will be tested in the main part of the

analysis. In the subgroup analyses it is predicted that the SANS will be a more sensitive instrument to detect negative symptom change relative to the PANSS, and that a smaller change over time will be detected in studies which used criteria which controlled for sources or secondary negative symptoms, in comparison to those that did not.

The principle aim of this chapter is to examine whether negative symptoms change over time, and if so, how. In order to answer this 4 different questions will be addressed:

1a) What is the course of negative symptoms in schizophrenia outpatients?

1b) Is the change of negative symptoms over time lower in samples that control for sources of secondary negative symptoms?

1c) Does the SANS report a greater change in negative symptoms, relative to the PANSS and the BPRS?

1d) Is there any variation in the longitudinal course of individual negative symptoms?

2.2.2. Association between positive and depressive symptoms with negative symptoms after adopting different symptomatic inclusion criteria: A further consideration of the pseudospecificity problem

In the second part of this investigation the impact of adopting different inclusion criteria in clinical trials for negative symptom treatments will be explored. Inclusion criteria identified in the systematic review, and those considered by Dunayevich and colleagues (Dunayevich et al., 2014), will be used to generate different subsamples to assess their impact on the potential sample pool size, and changes in negative symptoms over time. In the second part of the analysis a series of longitudinal regressions will be conducted to evaluate the association between negative symptoms, and depression and positive symptoms in the different subsamples generated. Following earlier findings (Dunayevich et al., 2014, Rabinowitz et al., 2013) it is hypothesised that increasingly restrictive eligibility criteria would result in a substantial reduction in the number of eligible participants. The second part of the analysis is exploratory in nature, and so specific hypothesis will be tested.

In this chapter of the thesis, the impact of adopting different symptom inclusion criteria on the association between negative, and positive and depressive symptoms will be evaluated. In order to answer this question, 3 different areas will be addressed:

2a) What is the change in negative symptoms over time in stable schizophrenia outpatients after excluding participants with prominent positive and depressive symptoms?

2b) What is the impact of adopting different inclusion and exclusion criteria on the proportion of eligible participants?

2c) What is the impact of adopting different symptom inclusion and exclusion criteria on the association between negative symptoms, and positive and depressive symptoms?

2.2.3. Comparing the CAINS and the PANSS; how they relate to indicators of social impoverishment

In this part of the investigation, the first aim will be to assess the convergent validity of the CAINS subscales and the PANSS negative subscales, building upon the previous findings which have evaluated the relationship of this scale with the BPRS (Kring et al., 2013). The second aim will be to assess whether there are any systematic differences in how the CAINS and the PANSS capture negative symptoms. This includes a comparison of how the two scales differentiate high and low negative symptoms using Tukey-mean difference plots, and a comparison of how the scales measure symptom change over time. The third aim will be to examine the incremental validity of the CAINS by comparing its predictive ability of objective and subjective measures of social impoverishment with the PANSS negative subscale using dominance analysis. Negative symptoms relate specifically to deficits in motivation to take part in recreational activities and impairments in the quality and quantity of social networks, so the scale which better predicts these outcomes is likely to be a better indicator of the negative symptom construct. This investigation will test the hypothesis that the CAINS is a more sensitive instrument in detecting negative symptom change, and that the experiential subscale is a significantly better predictor of indicators of social impoverishment.

In an exploration of the relationship between the CAINS and the PANSS negative subscale, 4 subordinate questions will be addressed:

3a) What is the association between the CAINS and the PANSS negative subscale?

3b) Does the CAINS provide a greater differentiation between participants that report high and low symptoms, relative to the PANSS negative subscale?

3c) Is the CAINS more sensitive in detecting symptom change over time, relative to the PANSS negative subscale?

3d) Is the CAINS a better predictor of social outcomes, relative to the PANSS negative subscale?

2.2.4. The relationship between negative symptoms and quality of life.

The aim of this investigation will be to re-evaluate the link between negative symptoms of schizophrenia and subjective quality of life, using both the PANSS and the experiential and expressive subscales of the CAINS. A series of univariate regression analyses will be conducted to examine the relationship between SQOL and expressive and experiential deficits, in addition negative symptoms measured by the PANSS, and depressive symptoms measured by the Calgary depression scale. This analysis will be conducted both cross-sectionally, and in changes over time, with any predictors approaching significance included in a multivariate model. The aim of this investigation will be to test the hypothesis that the association between negative symptoms and subjective quality of life will relate specifically to experiential deficits, and not expressive deficits. In addition, it is hypothesised that this relationship will remain after controlling for depressive symptoms.

In order to explore the association between expressive and experiential features of negative symptoms and subjective quality of life, 2 subordinate questions will be addressed:

4a) What is the cross-sectional association between experiential and expressive deficits and subjective quality of life, and how does this compare to an assessment of negative symptoms as a single construct using the PANSS negative subscale?

4b) What is the association in changes over time between experiential and expressive deficits and subjective quality of life, and how does this compare to an assessment of negative symptoms as a single construct using the PANSS subscale?

2.2.5. The Impact of negative symptoms on appraisal of treatment in acute services.

In the final part of this investigation the relationship between subjective initial appraisal of acute inpatient treatment and negative, manic, positive, and affective symptoms will be explored. Using a pooled sample from three separate studies, the association between these symptoms and the appraisal of treatment will be evaluated in a multivariate regression analysis, controlling for various socio-demographic and clinical variables. All symptoms which approach significance will then be analysed in a single multivariate model to determine their individual impact on treatment appraisal. In the final part of the analysis, the impact of individual symptoms will be compared between those who are admitted voluntarily and involuntarily.

In order to evaluate the association between symptoms and the initial appraisal of inpatient treatment, 2 subordinate research questions will be addressed:

5a) What is the association between negative symptoms and initial appraisal of inpatient treatment, and how does this compare to other symptoms of schizophrenia?

5b) Is the association between symptoms and initial appraisal of treatment different in those that were voluntarily and involuntarily admitted?

Chapter 3: The longitudinal course of negative symptoms

3.1. Introduction

Historically, schizophrenia symptoms relating to a deficit in typical human experience were believed to increase over time as patients experience a progressive deterioration in functioning (Kraepelin, 1971). Such theories were underpinned by the idea that these symptoms were attributable to morphological changes in the brain such as lesions, ventricular enlargement, or cortical atrophy (Andreasen et al., 1982, Crow, 1980, Crow, 1985, Kraepelin, 1971). In observational studies which evaluated the progressive course of these symptoms however, the evidence suggested that negative symptoms are highly stable, with a slight tendency to improve over time in some cases (Dollfus and Petit, 1995b, Eaton et al., 1995, Fenton and McGlashan, 1991, Pogue-Geile and Harrow, 1985). Following the distinction between primary and secondary negative symptoms (Carpenter et al., 1985) it was suggested that secondary symptoms improve relatively quickly once the causes are addressed, whilst primary negative symptoms are thought to be highly persistent (Möller, 2007). Initially the evidence suggested that these primary negative symptoms may increase over time (Fenton and McGlashan, 1994, Kirkpatrick et al., 1996b), however this has since been challenged by a longer term follow-up study (Strauss et al., 2010).

Broadly defined, primary negative symptoms are those that relate to core psychopathology, rather than as a consequence of depressive, psychotic or environmental factors. However, distinguishing between primary and secondary negative symptoms can be a complex undertaking in a research context, given the difficulties in obtaining sufficient historical information on the participant and the level of clinical expertise required by the assessors. In light of this, Buchanan (Buchanan, 2007) suggested the alternative broader distinction of "persistent negative symptoms", which include negative symptoms which remain persistent after treatments for secondary negative symptoms have failed. In the NIMH-MATRICS consensus statement for negative symptoms, it was proposed that distinguishing between primary and secondary negative symptoms was not essential for the purposes of testing therapeutics so long as studies select participants with persistent symptoms and control for secondary sources of negative symptoms (Kirkpatrick et al., 2006). This position has since been supported by the ISCTM consensus statement (Marder et al., 2011), and adopted by the EMA (EMA., 2012). However, to date there appears to be no consensus on how these

recommendations should be implemented (Rabinowitz et al., 2013), nor it is clear how these criteria impact how these symptoms change over time. Given the current focus on developing new interventions for negative symptoms, understanding their longitudinal course may be important for future study design, as well as being clinically informative.

In addition to identifying appropriate participants for clinical trials evaluating treatments for negative symptoms, issues around symptom assessment were also recognised as a significant issue in the MATRICS consensus statement (Kirkpatrick et al., 2006). As highlighted in section 1.9., many of the scales designed to measure negative symptoms such as the PANSS (Kay et al., 1987), SANS (Andreasen, 1983), and NSA-16 (Axelrod et al., 1993) have a number of conceptual and methodological problems, and may not be sufficiently sensitive to detect clinical meaningful change (Kirkpatrick et al., 2006). The MATRICS report suggests that a multi-item scale (i.e. the SANS) may be preferable to tools which measure individual symptoms on a single item, such as the PANSS and the BPRS (Kirkpatrick et al., 2006). A comparison of the change in negative symptoms between trials which adopted different assessment tools would allow for a comparison between the sensitivity of these scales.

The objective of this study was to examine how negative symptoms change over time, whilst exploring the impact of various study level factors. By pooling a wide variety of studies by way of meta-analysis, the aim was uncover broader trends in how these symptoms may change, as opposed to attempting to identify an estimate of effect size for a particular type of treatment, as has been done previously (ie. (Jauhar et al., 2014, Leucht et al., 2009a, Wykes et al., 2011). Many of the earlier observational studies which examined this question included inpatients, which is problematic given this population would typically receive far higher doses of antipsychotic medication, experience higher positive symptoms such as paranoid delusions (Kasckow et al., 2001), and may potentially be held in an underestimating social environment (Oshima et al., 2003), all of which may induce temporary secondary negative symptom. In addition, a number of the earlier studies included other illnesses such as schizoaffective disorder, which follows a different longitudinal course and can have poorer diagnostic stability, potentially influencing the reported change over time (Malhi et al., 2008).

Following a systematic search, we conducted a meta-analysis of the within-group mean changes in negative symptoms. Following the reasons outlined in section 1.1.3., only samples comprising exclusively of schizophrenia patients were considered. Due to the expected heterogeneity between different interventions, separate effect size estimates were calculated for each treatment type. In the next stage, a series of planned meta-regressions were

conducted to explore any impact of factors which may lead to secondary negative symptoms (Carpenter et al., 1985), and possible sources of methodological bias. Following evidence which suggests that alogia and blunted affect may be more stable than other negative symptoms (Dollfus and Petit, 1995b, Johnstone et al., 1987, Kelley et al., 1999), the changes in individual symptoms were also evaluated.

In the final part of the analysis, pre-planned sub group analyses were conducted to examine the impact of adopting inclusion criteria which specify a minimum level of negative symptoms, a maximum level of positive symptoms, and some form of restriction on either depressive symptoms or those who qualify for a diagnosis of depression. In doing so, the aim was to evaluate whether adopting such criteria reduces the change in negative symptoms course over time. Adopting such criteria may result in less change, given the impact of secondary negative symptoms should in theory be minimised. However, at present it is not clear whether this would be the case. In addition, it is possible that criteria specifying a minimum level of negative symptoms may result in a greater reduction through the removal of floor effects and a greater degree of regression to the mean.

3.2. Research questions

In order to answer the principle question "Do negative symptoms change over time and if so, how?" 4 subordinate questions were addressed:

1) What is the course of negative symptoms in stable schizophrenia patients over a standard study period (i.e. 10 weeks-36 months)?
2) Is the change of negative symptoms over time lower in samples which attempt to control for sources of secondary negative symptoms?
3) Does the SANS report a greater change in negative symptoms, relative to the PANSS and the BPRS?
4) Is there any variation in the longitudinal course of individual negative symptoms?

3.3. Methods

3.3.1. Search strategy

The systematic review was conducted following PRISMA statement guidelines (Liberati et al., 2009). An electronic search using the MEDLINE, PsycINFO, EMBASE and CENTRAL databases

was conducted dating back to 1962, which was when the Brief Psychiatric Rating Scale (BPRS) was first published (Overall and Gorham, 1962). The search was conducted on 26th April 2014 and contained three parameters. The first related to diagnosis, the second to negative symptoms, and the third an indicator that the study took place over at least two time points. The terms used for the MEDLINE electronic search are presented in table 5. Minor variations were adopted in the PsychINFO, EMBASE and CENTRAL electronic searches, depending upon the available search options. The protocol for the search procedure is presented in Appendix III.

Table 5: Search terms used for the MEDLINE search

1. Disorder	2. Symptoms	3. Treatment /Duration
*Schizophren$	Negative symptoms	Change$
Deficit syndrome	Reduced affect	Effect$
	Flattened affect	Therap*
	Blunted affect	Intervention /Intervention studies
	Emotional experience	Efficacy
	Emotional expression	Impact
	Alogia	Treatment / *therapeutics
	Anhedonia	Medication
	Avolition	*Longitudinal
	Asociality	*Follow up /*Follow up studies
	Motor retardation	course
	Amotivation	Stability
	Apathy	Time
		Progress$
		Persist$
		Year$ */treatment outcome

* denotes an exploded term
$ denotes an open term
/ denotes a meshed term

A hand-search of the American Journal of Psychiatry, Acta Scandinavica Psychiatrica, British Journal of Psychiatry, Schizophrenia Bulletin, JAMA-Psychiatry, the Lancet, and Schizophrenia Research was conducted, either from 1962 or the date of first issue. Reference lists from all selected papers were hand-searched. Screening was conducted in three stages. At the first stage a title screen was conducted with the aim of removing studies that were clearly not relevant (for example, case studies, non-human studies, and those which include non-psychiatric samples), at the second stage an abstract screen was conducted, and at the third a full paper screen was conducted. Twenty percent of the abstract screen was independently replicated by a colleague in order to test the reliability of the original screening. At the full paper screening stage, two colleagues duplicated 50% of the screening each. All discrepancies

were resolved without the need for the lead supervisor to adjudicate as planned. During the data extraction phase all assessments of negative symptoms, study inclusion/exclusion criteria, demographic details, industry sponsorship, and study methodology details were extracted into a piloted extraction sheet (see Appendix IV). When necessary, corresponding authors were contacted for further information. In the case of missing standard deviations, a mean from the existing sample was imputed when possible.

3.3.2. Eligibility criteria

During the screening process studies were excluded if they were clearly not relevant, did not have repeated assessments of negative symptoms at set time points, included children (<18 years) or older adults (>65 years), contained no usable data on an exclusively schizophrenic sample, were under ten weeks in length, or did not include a follow-up assessment within 3 years. Studies which included inpatients were considered, so long as the study included one time-point where the sample was exclusively outpatients and was then followed up from a standardised time-point from this assessment. Symptoms were required to be measured on a validated scale. Qualitative studies, case reports, letters to the editor, conference abstracts, and book chapters were excluded. In order to aid translation, all articles were required to be published in a language which used Latin-based characters. Due to the analytic strategy adopted and the risk of small samples leading to biased estimates (Morris, 2000), studies with fewer than 50 participants were excluded.

3.3.4. Analysis plan

In the pooled analysis, the measure of effect size for each study was calculated using the standardised mean change (SMC; (Becker, 1988, Morris, 2000). The estimation of the variance was calculated using the large-sample approximation method recommended by Becker (Becker, 1988) (see figure 1), which has been found to provide reasonably accurate estimates provided the sample sizes are adequately sized (Morris, 2000). The estimate of the correlation between the baseline and end of study scores was set at 0.633, based upon datasets held at our research group (Priebe et al., 2007). In order to test the impact of using this estimate on the findings five other figures, ranging from P=.600 and P=.700, were also evaluated as a part of a sensitivity analysis.

Figure 1: Method used to determine the estimation of the variance.

$$\sigma^2_{A3} = \frac{2(1-\rho)}{n} + \frac{\delta^2}{2n}.$$

(Formula taken from Morris, 2000)

In deciding the appropriate effects model to adopt, the decision was complicated by the likelihood that multiple arms of the same study would be separately eligible for inclusion. One method of addressing this which was recognised in the Cochrane Handbook (Higgins and Green), is to conduct a two-level, fixed-effect meta-analysis across arms within studies, followed by a random-effects meta-analysis across studies, as a way to account for the mix in fixed and random effects that are likely to be present. However, this model adds considerable complexity to the analysis, whilst the handbook itself acknowledges that "*in practice the difference between different analyses is likely to be trivial*" (section 16.5.5). This being the case, the method was not used, and the DerSimonion and Laird random effects model was adopted (DerSimonian and Laird, 1986). All analysis was completed using STATA version 11 (StataCorp, 2009).

In cases where multiple scales were used to measure negative symptoms, the primary outcome measure was selected. When negative symptoms were measured over more than two time points, only the baseline and the study endpoint data were selected.

In the first stage of the analysis samples were grouped according to whether the intervention involved testing second generation antipsychotics (SGA), first generation antipsychotics (FGA), adjunctive medications, non-drug interventions, or placebo/treatment as usual arms. In the next stage a series of planned univariate meta-regressions were conducted, with those found to approach significance ($p<.10$) entered into a multivariate model. First, the impact of length of treatment was examined in order to assess whether there was any trend over time. Next, whether there was any difference between studies which incorporated a minimum negative and maximum positive and depressive symptom threshold was tested, compared to those that did not, in order to assess whether the degree of change in negative symptoms varied dependent upon how studies dealt with factors which can cause secondary negative symptoms. Finally, the impact of assessor blinding, a minimum negative symptom inclusion criterion, and whether the study received industry sponsorship was examined.

In any examination of the change in a continuous variable over time which only includes two time points (which is a requirement for meta-analysis) the issue of regression to the mean is an important one that must be considered (Chiolero et al., 2013). This being the case, the mean negative symptoms at baseline were added to the final multivariate model to determine the degree of additional variance which may be explained by a greater reduction in negative symptoms being caused by a higher initial level of symptoms.

3.4. Results

3.4.1. Summary of articles selected

A flow diagram depicting the search strategy for studies is outlined in figure 2. Of the 9480 articles screened, 49 eligible articles were found and 41 were included in the final analysis (see table 6). From these, a total of 89 separate samples were obtained. Of the 41 studies, five came from the USA; four each from Canada, Germany and the UK; three each from India, Spain and Turkey; two each from China, France and Italy; and one each from Brazil, Finland, Israel, Nepal, Poland and Serbia. Four studies were conducted in multiple countries, with sites in Northern America, Europe and Asia. Based on 51 samples, the median of study mean illness duration was 12.4 years (range 0.6 - 27.5 years). Twenty three studies measured negative symptoms using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), 14 used the Scale to Assess Negative Symptoms (SANS) (Andreasen, 1983), and four used the BPRS (Overall and Gorham, 1962). Studies which used alternative scales were screened, but none met eligibility criteria. After pooling all 89 samples, a final total of 5,944 participants were included in the meta-analysis.

Figure 2: Flow diagram outlining study selection procedure.

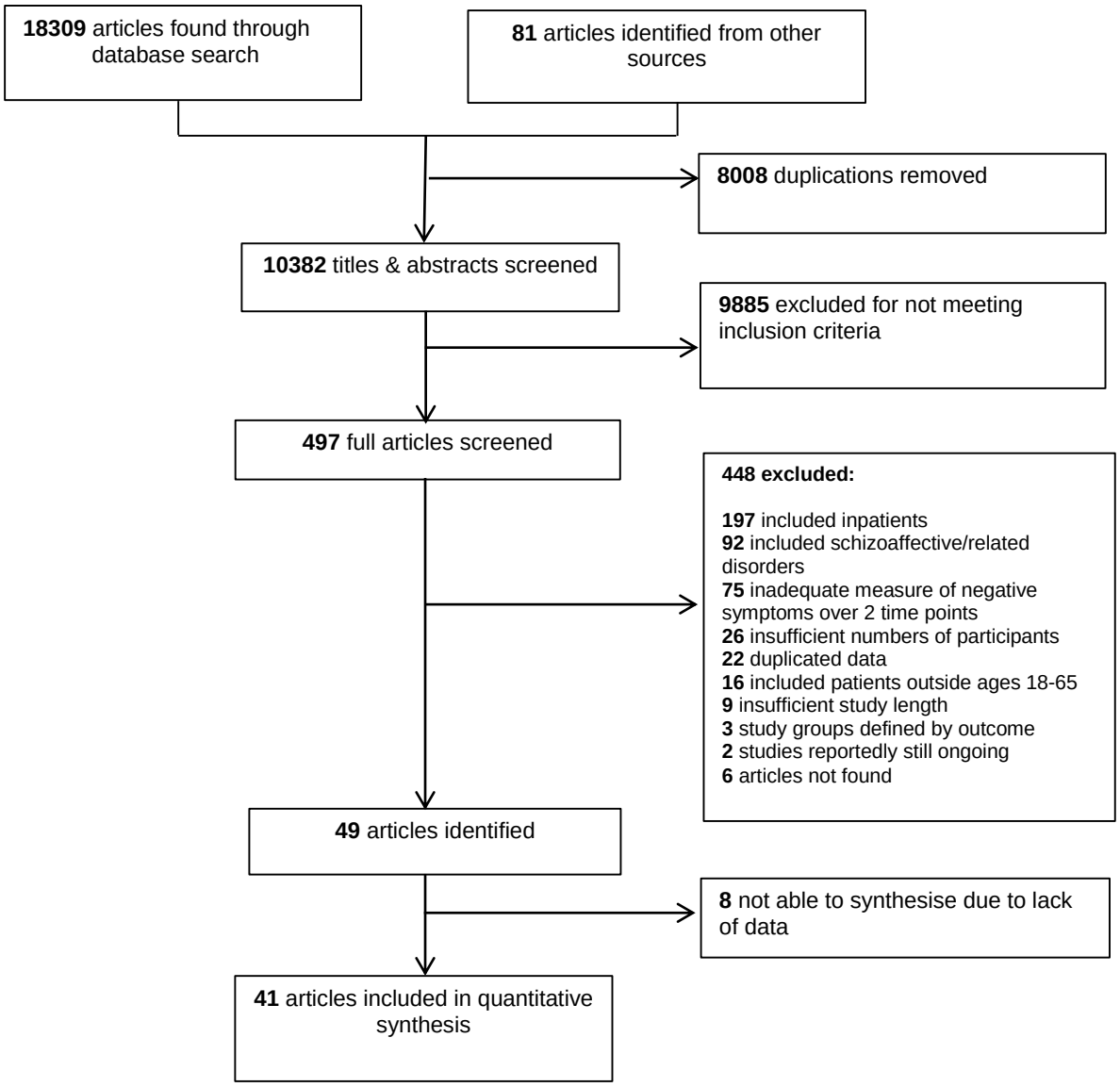


Table 6: Summary of eligible studies

Authors	Year	Country	Study duration (weeks)	Outcome measure[a]	Individual symptoms reported	Intervention type[b]	n
(Addington and Addington, 2000)	2000	Canada	130	PANSS	No	TAU	65
(Aguglia et al., 2002)	2007	Italy	52	SANS	Yes	Non-drug intervention: Psychoeducation	69
						TAU	66
(Alptekin et al., 2005)	2005	Turkey	52	BPRS	No	TAU	382
(Alvarez et al., 2006)	2006	Spain	48	SANS	Yes	SGA: Olanzapine	120
						SGA: Risperidone	115
(Cirici and Obiols, 2008a)	2008	Spain	46	PANSS	Yes	Non-drug intervention: Skills training group	35
						TAU	22
(Bales et al., 2009)	2009	Nepal	18	PANSS	No	TAU	30
						TAU + Betel nuts	30
(Behere et al., 2011)	2011	India	16	PANSS	No	Non-drug intervention: Yoga group	34
						Non-drug intervention: Exercise Group	31
						TAU	26
(Bhowmick et al., 2010)	2010	India	12	SANS	No	SGA: Amisulpride	40
						SGA: Olanzapine	40
(Bio and Gattaz, 2011)	2011	Brazil	26	PANSS	No	TAU	57
(Bobes et al., 2009)	2009	Spain	34	BPRS	No	SGA: Risperidone	362
(Bodkin et al., 2005)	2005	USA	12	SANS	Yes	Adjunctive: Selegiline	33
						Placebo	34
(Crawford et al., 2012a)	2012	UK	52	PANSS	No	TAU	137
						Non-drug intervention: Activity group	140
						Non-drug intervention: Art therapy group	140
(Fleischhacker et al., 2003)	2003	Multi	52	PANSS	No	SGA: Risperidone	120
						SGA: Risperidone	228
						SGA: Risperidone	267
(Gaebel et al., 2007)	2007	Germany	52	PANSS	No	SGA: Risperidone	77
						FGA: Haloperidol	74
(Gorna et al., 2008)	2008	Poland	52	PANSS	No	TAU	88
(Hirsch et al., 2002)	2002	Germany	28	PANSS	No	SGA: Ziprasidone	110
						FGA: Haloperidol	117
(Kane et al., 2011)	2011	USA	26	PANSS	No	TAU: Remained on same drug	194
						Placebo: Switched to Placebo	192
(Kane et al., 2012)	2012	USA	24	PANSS	No	Adjunctive: Armodafinil	70
						Adjunctive: Armodafinil	69
						Adjunctive: Armodafinil	71
						Placebo	70

(Kaphzan et al., 2014)	2014	Israel	12	PANSS	No	Placebo	22
						Adjunctive: Entacapone	23
(Klingberg et al., 2011)	2011	Germany	52	PANSS	Yes	Non-drug intervention: CBT	99
						Non-drug intervention: CRT	99
(Lasser et al., 2013)	2013	USA	10	SANS	No	Adjunctive: lisdexamfetamine dimesylate	92
(Lecrubier et al., 2006)	2006	France	26	SANS	No	Placebo	34
						SGA: Olanzapine	70
						SGA: Olanzapine	70
						SGA: Amisulpride	70
(Liu et al., 2014)	2014	China	16	PANSS	No	Placebo	40
						Adjunctive: Minocycline	39
(Loebel et al., 2007)	2007	India	64	PANSS	No	SGA: Ziprasidone	32
						SGA: Ziprasidone	30
(Loo et al., 1997)	1997	France	26	SANS	Yes	Placebo	72
						SGA: Amisulpride	69
(Meltzer et al., 2010)	2010	USA	52	BPRS	No	SGA: Clozapine	40
						FGA: Various first generation drugs	45
(Olie et al., 2006)	2006	Multi	12	PANSS	No	SGA: Ziprasidone	59
						SGA: Amisulpride	63
(Pach et al., 1998)	1998	Germany	52	SANS	Yes	FGA: Flupenthixol Decanoate	63
(Peet and Horrobin, 2002)	2002	UK	12	PANSS	No	Placebo	31
						Adjunctive: Eicosapentaenoic acid	32
						Adjunctive: Eicosapentaenoic acid	32
						Adjunctive: Eicosapentaenoic acid	27
(Purdon et al., 2000)	2000	Canada	54	PANSS	No	SGA: Olanzapine	21
						FGA: Haloperidol	23
						SGA: Risperidone	21
(Ravanic et al., 2009)	2009	Serbia	52	PANSS	No	FGA: Haloperidol	70
						FGA: Haloperidol	35
						FGA: Chlorpromazine	65
						FGA: Chlorpromazine	40
						SGA: Clozapine	65
						SGA: Clozapine	50
(Richardson et al., 2007)	2007	UK	38	SANS	No	TAU	46
						Non-drug intervention: Art therapy group	43
(Semiz et al., 2007)	2007	Turkey	12	SANS	No	SGA: Clozapine	97
(Schoemaker et al., 2014)	2014	Multi	12	SANS	Yes	Adjunctive: Org25935 low dose	71
						Adjunctive: Org25935 high dose	73
						Placebo	70
(Sumiyoshi et al., 2007)	2007	USA	26	BPRS	No	Adjunctive: Buspirone	30
						TAU	29
(Taiminen et al., 1997)	1997	Finland	12	PANSS	No	TAU	39
						Adjunctive: Citalopram	36

(Turkington et al., 2008)	2008	UK	78	SANS	No	Non-drug intervention: CBT	46
						Non-drug intervention: Befriending	44
(Ucok et al., 2011)	2011	Turkey	52	SANS	No	TAU	52
						TAU	41
(Voruganti et al., 2007)	2007	Canada	52	PANSS	No	SGA: Olanzapine	42
						SGA: Quetiapine	43
(Xiang et al., 2006)	2006	China	34	PANSS	No	Non-drug intervention: Community re-entry	48
						Non-drug intervention: Counselling	48
(Zoccali et al., 2007)	2007	Italy	24	SANS	Yes	Adjunctive: Lamotrigine	26
						Placebo	25
List of studies not included in the main analysis due to insufficient data							
(Adams et al., 2013)	2013	Multi	24	NSA-16	No	SGA: multiple types	130
						SGA: LY2140023	131
(Chouinard et al., 1975)	1975	Canada	12	BPRS	No	Placebo	24
						FGA: Amitriptyline Hydrochloride	24
						FGA: Perphenazine	24
						FGA: Amitriptyline Perphenazine	24
(Goff et al., 2005)	2005	USA	26	SANS	Yes	Adjunctive: D-cycloserine	26
						Placebo	25
(Hayes et al., 1995)	1995	Australia	44	SANS	No	Non-drug intervention: Skills training group	n/s
						Non-drug intervention: Discussion group	n/s
(Liberman et al., 1998)	1988	USA	156	BPRS	No	Non-drug intervention: Occupational therapy	n/s
						Non-drug intervention: Skills training group	n/s
(Lieberman et al., 2013)	2013	Multi	12	SANS	No	Adjunctive: TC-5619	94
						Placebo	91
(Marder et al., 2003)	2003	USA	104	SANS	Yes	SGA: Risperidone + Skills training	33
						FGA: Haloperidol + Skills training	30
(Pinto et al., 1979)	1979	UK	78	BPRS	No	FGA: Flupenthixol decanoate	34
						FGA: Fluphenazine decanoate	30

3.4.2. Longitudinal course of negative symptoms

As indicated in the forest plot (see figure 3), in all five intervention types a significant reduction in negative symptoms was found between the baseline and follow-up. SGA's were found to result in the greatest reduction (ES 1.09, 95% CI's 0.86 to 1.32, I^2= 95.3%) whilst the smallest change was found in placebo/treatment as usual samples (ES 0.33, 95% CI's 0.16 to 0.50, I^2= 92.1%). Substantial heterogeneity was found, as would be expected given the clinical and methodological differences which exist between the studies. In a sensitivity analysis examining the impact of different estimates of the correlation between the baseline and end of study

scores included in the model, minimal differences in the overall effect size was detected (see table 7).

Figure 3: Forest plot of negative symptom change by treatment type

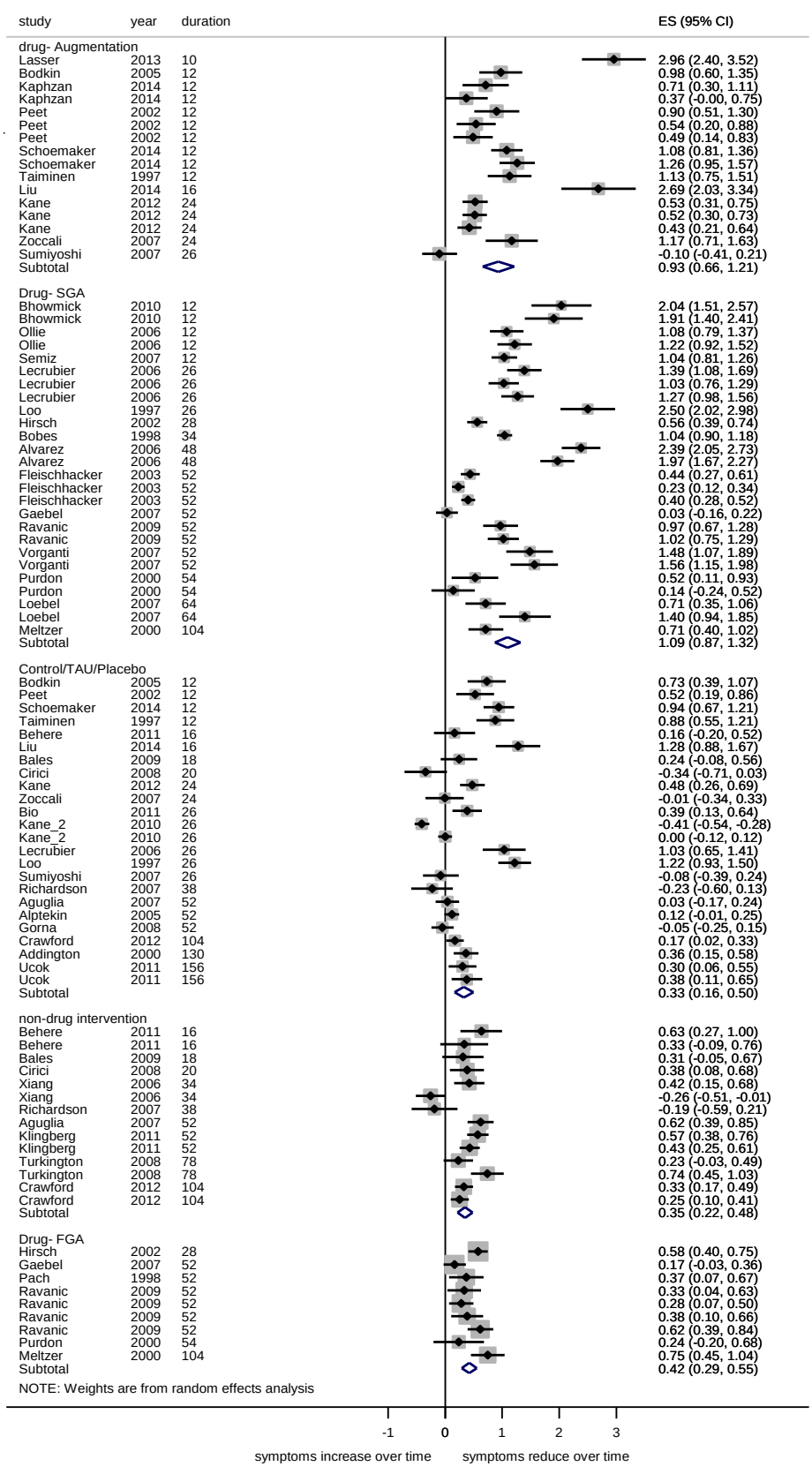


Table 7: Impact of different imputed correlations between T1 and T2 used in the calculation of the standardised mean change score

P	Effect size	95% CI's	I^2
.600	0.572	0.462 - 0.681	93.7%
.625	0.571	0.463 - 0.680	93.9%
.633*	0.571	0.463 - 0.679	94.0%
.650	0.571	0.463 - 0.678	94.1%
.675	0.570	0.464 – 0.677	94.4%
.700	0.569	0.464 - 0.675	94.6%

***figure used in the model**

In order to explore the heterogeneity between studies a series of meta-regressions were conducted. In the univariate analyses the scale used, the intervention type evaluated, the study duration, and a minimum threshold of negative symptoms as an inclusion criterion were all associated with a larger reduction in negative symptom (see table 8). A maximum level of positive symptoms and previous non-response to treatment as exclusion criteria were found to approach significance ($p<.10$), whilst other variables were non-significant. In the multivariate model, only the type of scale used and the type of intervention received remained significant. Overall, the between-model variance accounted for by the covariates was 43.88%. In a sensitivity analysis the sample-level baseline negative symptoms were added to the model which was found to be a significant predictor (B= .010, SE=.004, 95% CI's .002 to .018). However, the additional variance explained was relatively small (3.57%).

Table 8: Meta-regression exploring impact of clinical and socio-demographic study level factors on variability in negative symptom change

Predictor of negative symptom change	Univariate analysis					Multivariate analysis				
	B	SE	95% CI's		P	B	SE	95% CI's		P
Study Duration	-0.01	0.00	-0.01	0.00	.035	0.00	0.00	-0.01	0.00	.421
Scale used (compared to PANSS)					.002					
SANS	0.49	0.14	0.21	0.77		0.43	0.13	0.16	0.70	.002
BPRS	-0.12	0.26	-0.63	0.40		-0.07	0.23	-0.54	0.39	.760
Intervention (compared to SGA)					<.001					
Non-drug intervention	-0.75	0.18	-1.11	-0.38		-0.67	0.19	-1.04	-0.30	.001
TAU/Placebo	-0.76	0.16	-1.07	-0.45		-0.73	0.16	-1.06	-0.41	<.001
Drug- FGA	-0.68	0.18	-1.10	-0.25		-0.73	0.16	-0.93	-0.12	.011
Drug- Augmentation	-0.16	0.18	-0.52	-0.19		-0.21	0.18	-0.57	0.16	.265
Min negative symptoms	0.37	0.13	0.11	0.63	.007	0.10	0.12	-0.15	0.35	.413
Max positive symptoms	0.26	0.14	-0.02	0.54	.071	0.07	0.13	-0.20	0.33	.608
Industry sponsorship	0.15	0.14	-0.14	0.43	.309					
Exclusion: Prev. non-response	0.42	0.18	0.07	0.78	.019	0.05	0.17	-0.29	0.40	.765
Raters blinded to allocation[b]	-0.18	0.15	-0.47	0.12	.234					
Exc: mod levels of depression	0.13	0.17	-0.21	0.46	.452					

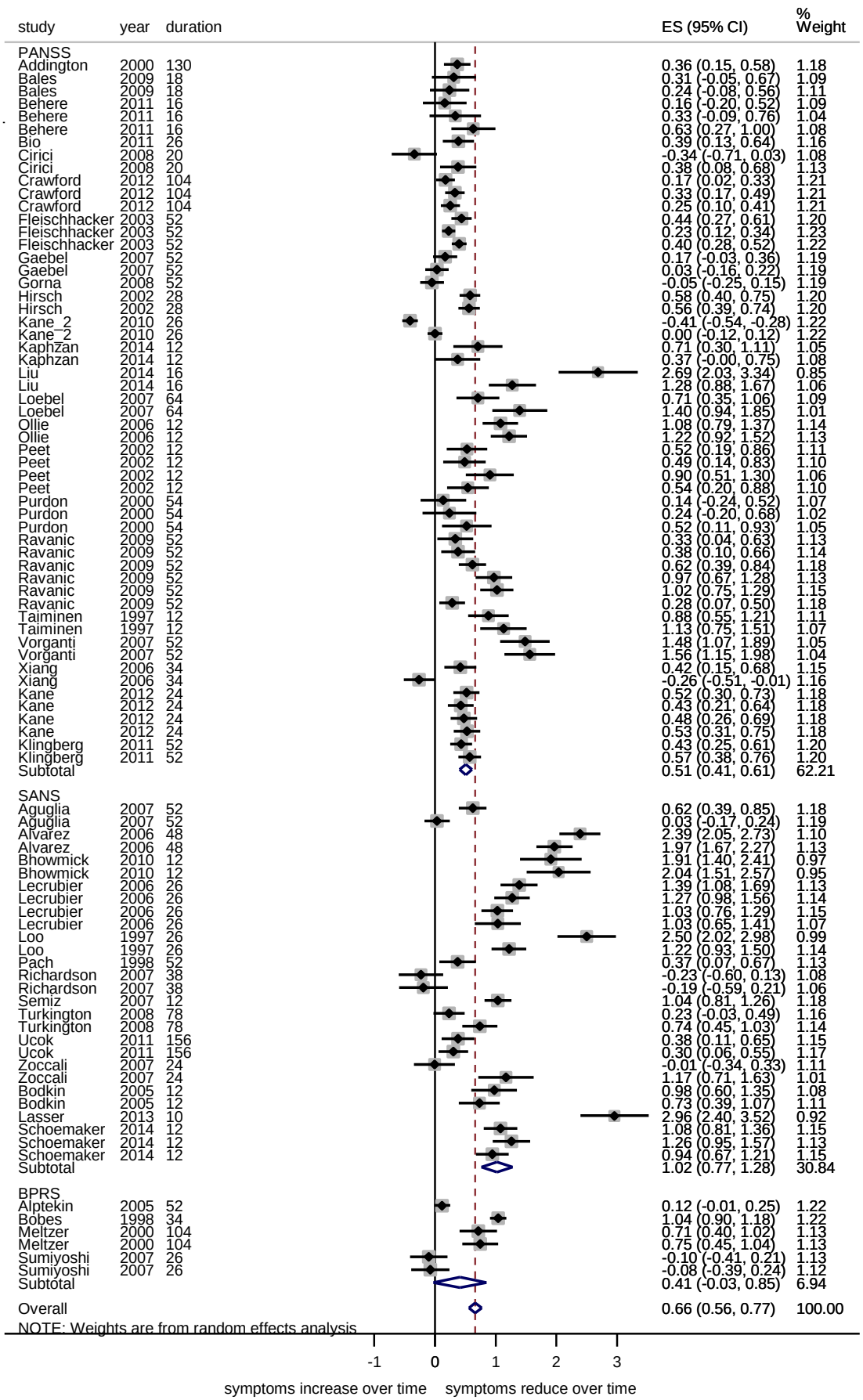
[b] One study not included due to lack of data

Although a significant proportion of the studies evaluated extra-pyramidal symptoms (EPS) as part of their analysis (53.7%), only three studies specified an EPS maximum threshold as an exclusion criterion (Klingberg et al., 2011, Lasser et al., 2013, Schoemaker et al., 2014). Given the lack of data, this was not included in the meta-regression analysis. Of those studies that did report EPS, they were generally considered to be in the low range at study intake, suggesting that the impact of EPS on negative symptoms was likely to be small.

3.4.3. Change in negative symptoms reported by different assessment measures

In order to examine the impact of the different assessment tools used on negative symptom change, studies were grouped by the scale used and the effect sizes were compared. Twenty two Studies (56 samples) used the PANSS negative subscale, 15 studies (29 samples) used the SANS, and four studies (six samples) used the BPRS anergia subscale. A forest plot depicting the different estimates for each of the scales used is presented in figure 4. Studies which used the SANS found a significantly greater reduction in negative symptoms relative to those that used the PANSS or the BPRS (SANS: ES=1.02, 95% CI's 0.77 to 1.28; PANSS: ES= 0.66, 95% CI's 0.56 to 0.77; BPRS: ES=0.41, 95% CI's -0.03 to 0.85).

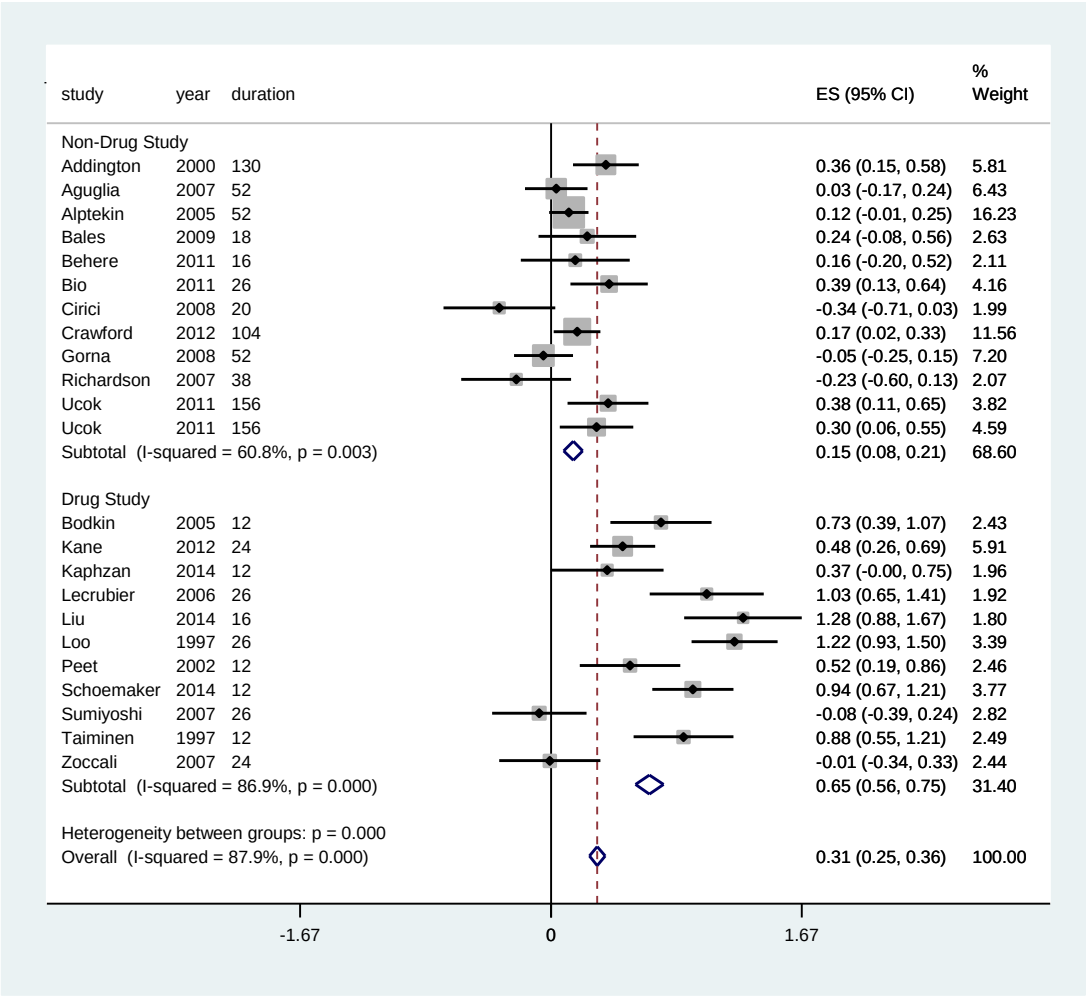
Figure 4: Forest plot comparison negative symptom change between different assessment tools used



3.4.4. Comparing control arms between drug and non-drug trials

The larger effect size improvements in second generation antipsychotics and adjunctive medications, relative to other types of treatment, appear to contradict earlier findings which suggest minimal advantages of these types of treatments (Leucht et al., 2009b, Tuominen et al., 2005). In order to examine whether this reduction over time is a feature of the studies they were part of, as opposed to a specific action of the intervention itself, in a post-hoc analysis the effect size reductions in control arms of studies which were and were not part of an SGA or adjunctive drug study were compared. In total, 12 non- SGA or adjunctive drug study control arms and 11 SGA or adjunctive drug study control arms were compared, with the findings presented in figure 5. Significantly larger reductions in the control arms of studies which were part of an SGA or adjunctive drug study, relative to those control arms which formed part of non-drug studies were detected (ES=0.65, 95% CI 0.56 to 0.75, I^2=86.9%, in comparison to ES=0.15, 95% CI 0.08 to 0.21, I^2=60.8%).

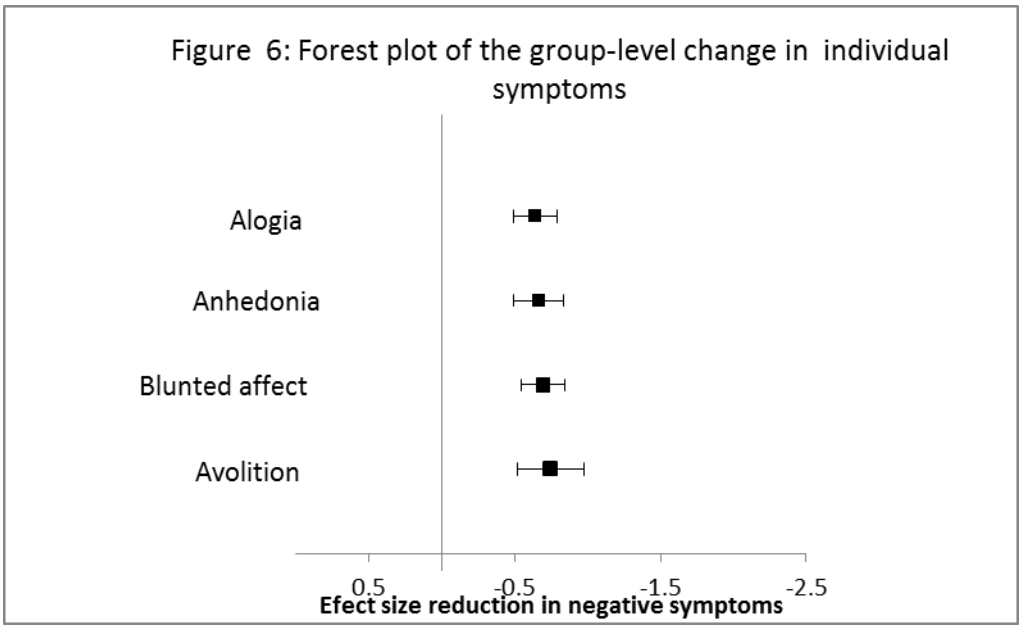
Figure 5: Forest plot comparing the change in second generation antipsychotic drug studies and non-drug study control arms.



3.4.5. Examination of individual negative symptoms

In 18 samples over nine studies the change in individual negative symptoms were also evaluated, with the results presented in figure 6. In seven studies the individual items were rated using the SANS, and in two studies symptoms were rated using the PANSS. Scores from different scales were combined using the method proposed by Lyne and colleagues (Lyne et al., 2012) (see section 1.9.2.). A significant reduction was found in all four of the symptoms measured (blunted affect, alogia, avolition and anhedonia). Of the 4, alogia appeared to reduce the least (ES= 0.64, 95% CI's 0.45 to 0.83, I^2= 90.4%) and avolition the most (ES= 0.77, 95% CI's 0.53 to 1.01, I^2=93.0%), however the difference between the symptoms were minimal.

Figure 6: Forest plot of the group-level change in individual symptoms



3.4.6. Comparing those that do and do not adopt criteria in line with the diagnosis of persistent negative symptoms

Twelve samples over five different studies adopted eligiblity criteria which specified a minimum level of negative symptoms, a maximum positive symptom eligiblity critierion, and some form of restriction on the severity of depressive symptoms. The different studies and the criteria they adopted are presented in table 9. In the comparison of studies which did and did not adopt such criteria, a slightly larger reduction in negative symptoms over time was detected in patients that did (Criteria adopted ES= 0.85, 95% CI's 0.56 - 1.08, I^2= 90.2%; criteria

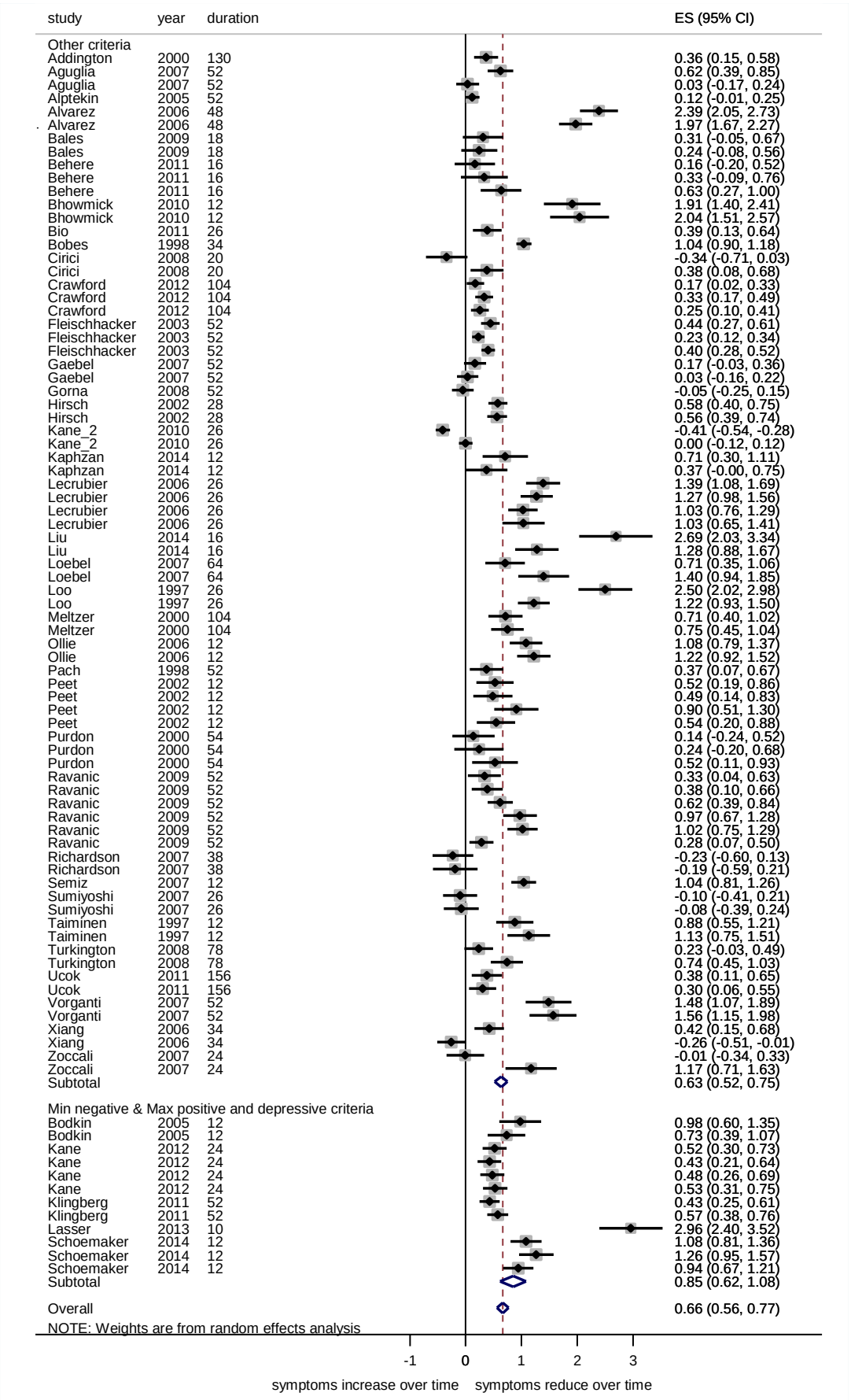
not adopted ES= 0.63, 95% CI's 0.51 – 0.75, I^2= 94.2%). As clear from the forest plot presented in figure 7, the difference between the two groups appeared to be largely attributable to one observational study (Lasser et al., 2013). When this study was omitted, the effect size change was more similar to those that do not adopt the criteria (ES=0.70, CI's 0.54 - 0.85, I^2= 79.1%) Overall, these findings corroborate with the results from the meta-regression (see table 8) which together suggest that adopting such criteria does not appear to reduce the reduction in negative symptoms over time.

Table 9: Summary of different symptom inclusion/exclusion criteria

Study		Year	Scales used	Symptom inclusion and exclusion criterion
1	Bodkin	2005	SANS, BPRS	Inclusion: SANS >12, two subscales >3. Exclusion: ≥5 on the BPRS thinking disturbance subscale, mood disorder
2	Kane	2012	PANSS	Inclusion: ≥15 on the negative subscale. Exclusion: positive items ≥4, >10 Calgary
3	Lasser	2013	SANS	Inclusion: >54 on SANS 18, <2 on <1 SANS global score. Exclusion: >7 Calgary
4	Schoemaker	2014	PANSS	Inclusion: ≥4 on at least 3 items, ≥21 overall on the negative subscale. Exclusion: No more than ≤19 on the PANSS positive, <9 Calgary
5	Klingberg	2011	PANSS	Inclusion: At least 1 PANSS negative item ≥4. Exclusion: no positive or depressive item ≥6

PANSS: Positive and Negative Syndrome Scale; SANS: Scale to Assess Negative Symptoms of Schizophrenia; CALGARY: Calgary depression scale for psychosis

Figure 7: Comparison of trial arms which did and did not specify a minimum negative and maximum negative and depressive symptom criterion.



3.4.7. Examination of publication bias

Publication bias was examined by intervention group using Duval and Tweedie's 'trim and fill' method via the STATA *metatrim* command (Duval and Tweedie, 2000). Possible bias was detected in the non-drug intervention group and the adjunctive medication group, suggesting a small over-estimation of the effect size. Two imputed studies in the non-drug intervention group and one in the adjunctive medication group reduced the effect sizes, but both remained significant (Non drug group: ES= 0.27, 95% CI's 0.12 – 0.41; adjunctive medication group: ES= 0.58, 95% CI's 0.38 – 0.79). However, given the fixed effect differences between samples from the same study resulted in within-group clustering, it is important to recognise that this reported bias is difficult to interpret, and may be an artefact of the study design.

3.4.8. Eligible studies not pooled into the main analysis

In addition to those pooled, eight studies were found to be eligible but could not be included in the main analysis (see table 6). In line with the main results, 11 samples found some form of reduction in negative symptoms from baseline to end of study, five saw no change, and in two the change was not specified.

3.5. Discussion

3.5.1. Main findings

The meta-analysis provided a clear result; negative symptoms of schizophrenia tend to improve significantly in an outpatient setting. A reduction in negative symptoms was found across all intervention types, with the effect sizes ranging from small to large depending upon the intervention type. In addition, a significant reduction was found in all four of the separate negative symptoms examined, representing both experiential and expressive features of the disorder. Whilst substantial heterogeneity was present in the sample, a series of planned meta-regressions indicated that there was no difference in the reduction between studies which did and did not exclude participants with at least moderate levels of positive or depressive symptoms. In addition, study-level methodological differences such as whether assessors were blinded, the symptom eligibility criteria, and whether the study received industry sponsorship also did not appear to influence the result. The largest changes in

negative symptoms were found in trial arms where participants were randomised to receive SGA's or adjunctive medications. However, in these studies a significantly larger reduction was also found in the control arms of studies, suggesting there may be an unspecified feature of the trial itself which may drive at least part of this change. In studies which used the SANS (Andreasen, 1983) as opposed to the PANSS (Kay et al., 1987) or the BPRS (Overall and Gorham, 1962) a significantly larger change in negative symptoms was found, highlighting the impact of adopting different methods of negative symptom assessment.

3.5.2. Strengths and limitations.

One of the main strengths of the study is that, despite the broad range of study interventions considered, the findings are consistent. Of the 89 study arms included, only one found a clear significant increase in symptoms. In this case, the sample was part of a continuation study where patients who had previously responded well to their SGA medication were then switched to a placebo (Kane et al., 2011). When testing for the effect of regression to the mean, adding baseline negative symptoms to the multivariate model appeared to add relatively little additional explanatory power of the variance (3.87%), suggesting the findings are relatively robust to this effect. A further strength of this study is that despite the broad study inclusion criteria, removing samples which included inpatients at baseline, and other psychotic diagnoses, meant the participant inclusion criteria were relatively stringent in comparison to other observational studies that have looked at how negative symptoms change over time (Dollfus and Petit, 1995b, Eaton et al., 1995, Fenton and McGlashan, 1991, Pogue-Geile and Harrow, 1985).

One limitation of the study is that due to the variance estimation method adopted, a number of otherwise eligible studies were excluded due to them containing an insufficient number of participants (Morris, 2000). However, given there is evidence to suggest that smaller studies can often present larger effect sizes (i.e. (Zhang et al., 2013), our findings may have led to a more conservative estimate, with the reduction in negative symptoms possibly being even more substantial than reported here. Another limitation is that, despite the fairly large number of studies included in the analysis (41), the final sample of 5,944 patients was smaller than what was originally anticipated. This was due to the fact that a number of the larger studies in the field either contained inpatients (Lieberman et al., 2005), used a single item to measure negative symptoms rather than a validated scale (Dossenbach et al., 2004), or included patients with other psychotic disorders.

Another limitation is that due to the study design it is difficult to determine whether the changes detected are attributable to an improvement in primary negative symptoms, persistent negative symptoms, or secondary symptoms which one would expect to improve relatively quickly over time once the causes are addressed. No difference in the change in negative symptoms over time was detected between those that did and did not include some form eligibility criteria required to determine persistent negative symptoms (i.e. including a minimum level of negative symptoms, and a maximum level of positive and depressive symptoms in the eligibility criteria; (Buchanan, 2007). Consistent with the results by Stauffer et al. (Stauffer et al., 2012), these findings suggest that the change in negative symptoms are the same in samples that have attempted to minimise the presence of secondary negative symptoms, relative to those that have not. However, examining the change in symptoms between studies with very different criteria adopted is not a recognised method to determine persistent negative symptoms, and cannot provide any insight related to primary negative symptoms (Carpenter and Kirkpatrick, 2015). Consequently, further work is required to disentangle the both how primary negative symptoms change over time, and what the impact of different predominant inclusion criteria may be.

Another important consideration is that it is difficult to determine the nature of the change detected. In the meta-regression the duration of the study was not found to be a predictor of greater negative symptom reduction which suggests that these symptoms do not gradually improve over time. This finding is supported by longitudinal studies over very long periods which have found that negative symptoms follow a fluctuating course and do not typically lead towards recovery (Jääskeläinen et al., 2013, Strauss et al., 2010). One possible reason for the detected improvement may be the impact of the participating in multiple assessments. In subsequent assessments the interviewee may be more relaxed if a rapport has been previously established with the interviewer, and they are likely to have a much better idea of the nature of the questions they would be asked. This could potentially lead to participants being more expressive in the interview, resulting in a less severe symptom rating.

It is important to note that given the limitations of the within-group design, the results should not be interpreted as an assessment of treatment effectiveness. As highlighted earlier, a series of meta-analyses have been conducted to evaluate various treatments for schizophrenia (Jauhar et al., 2014, Kurtz and Mueser, 2008, Leucht et al., 2009a, Wykes et al., 2011) using between-group designs which offer a more appropriate assessment for treatment effectiveness. Overall, these reviews have detected relatively limited benefits for negative symptoms, contrasting with the large within-group effect sizes noted here. At least part of this

difference could be attributable to the fact that effect sizes in control arms of studies evaluating drug treatments appear to be significantly larger in comparison to non-drug studies, suggesting there is something inherent to the methodologies employed which makes drug studies more likely to detect symptoms improvements.

Finally, due to the lack of available data, “no-medication” as a therapeutic option could not be evaluated, meaning it is not clear whether this reduction over time would also occur in non-medicated patients. Given there is evidence to suggest that patients who do not immediately relapse upon termination of their antipsychotic regimen may experience improved global functioning over time (Harrow and Jobe, 2007), it is conceivable that improvements in this participant group may be possible also.

3.5.4. Summary

Based on the available data of almost 6,000 outpatients, negative symptoms of schizophrenia do not tend to be stable or deteriorate, but are instead likely to improve over time. This finding offers a further critique of the historical understandings of schizophrenia originally proposed by Kraepelin and Bleuler, and instead provides further support to the recovery model which suggests the functioning of patients with a diagnosis of schizophrenia can improve over time (Warner, 2009). Overall, these findings suggest that negative symptoms may not be as resistant to change as what has previously been assumed, and perhaps offer new hope to those who may experience such symptoms.

Chapter 4. Association between negative symptoms and positive and depressive symptoms after adopting different study inclusion criteria

4.1. Introduction

In the previous chapter it was found that negative symptoms of schizophrenia appear to significantly reduce in stable outpatients, including in samples which exclude patients with high depressive and positive symptoms. Whilst conducting a meta-analysis may be helpful in understanding broad trends regarding how symptoms may change over time, inherent to the study design exists a number of limitations. Most significantly, using heterogenous study-level criteria is not a recognised method to control for secondary sources of symptoms (Carpenter and Kirkpatrick, 2015), and as such it is unclear to what extent any change in negative symptoms detected may be secondary, rather than primary in origin.

Differentiating between symptoms that are a direct manifestation of the disorder itself, as opposed to being a consequence of positive symptoms, depressive symptoms or medication side effects is seen as an important issue in the testing of new therapeutics for negative symptoms (Kirkpatrick et al., 2006, Marder et al., 2013, Marder et al., 2011). Whilst primary negative symptoms of schizophrenia are typically seen as highly enduring, those resulting from secondary sources are thought to improve relatively quickly if the causes of these symptoms can be addressed (Möller, 2007). Consequently, it is the chronic, persistent negative symptoms, as opposed to transient secondary symptoms, which are regarded as an unmet therapeutic need (Kirkpatrick et al., 2006). To determine the effectiveness of treatments for negative symptoms, it is important to filter out those that would experience improvements due to changes in secondary sources of these symptoms.

Of the different methods proposed to minimise the impact of transient secondary negative symptoms, the criteria of persistent negative symptoms (Buchanan, 2007) is advocated by the NIMH-MATRICS consensus statement (Kirkpatrick et al., 2006). Persistent negative symptoms are defined by the presence of at least a moderate severity of negative symptoms; low positive symptoms, depressive symptoms, and EPS; and evidence of clinical stability. The main differences between these criteria and the deficit syndrome is that less historical information is required (evidence of clinical stability is only recommended for six months, as opposed required for one year), and the distinction between primary and secondary negative symptoms

is dropped with maximum limits to depressive, positive and EPS proposed as an alternative. By using these criteria it means that persistent negative symptoms can be attributable to secondary, as well as primary causes. However, the stability componant ensures that symptoms are not transitory in nature, whilst the maximum EPS, positive and depressive symptoms should theoretically limit the impact of possible causes of secondary negative symptoms.

While there appears to be a consensus that participants should be excluded from negative treatment clinical trials if they are either in the acute phase of the disorder, or present with notable EPS or depressive symptoms, there is still some debate regarding whether those that present with positive symptoms should also be omitted (Marder et al., 2013). Studies which specify maximum positive and minimum negative symptom levels are considered to adopt predominent eligiblity criteria, whilst studies which only specify a minimum level of negative symptoms are defined are considered to adopt prominent eligiblity criteria. Adopting predominent eligiblity criteria can be considered problematic given the association between positive and negative symptoms is relatively low (Horan et al., 2011), they have different neurobiological origins (Berman et al., 1997), follow different trajectories (Ventura et al., 2004), and impact functional outcomes independently (Rabinowitz et al., 2012). In addition, there are concerns that participants that present with negative, but not positive symptoms may only consistitute a relatively small sample of patients, distinct from the broader population that such treatments would be designed for. However, by not specifying a maximum level of positive symptoms any issues related to the pseudospecificity problem may remain.

Aside from whether it is more appropriate to adopt prominent or predominant symptom criteria in negative symptom trials, the issue is further complicated by the fact that there appears to be no clear consensus on how these criteria should be operationalised. For example, in the systematic review completed in chapter 3, three of the 41 selected studies included contraints on the minimum level of negative symptoms, and eight implimented both a minimum negative and maximum positive symptom inclusion criterion (Alvarez et al., 2006, Bodkin et al., 2005, Cirici and Obiols, 2008b, Kane et al., 2012, Kaphzan et al., 2014, Klingberg et al., 2011, Lasser et al., 2013, Lecrubier et al., 2006, Loo et al., 1997, Olie et al., 2006, Schoemaker et al., 2014). The criteria were specified using the PANSS (Kay et al., 1987), SANS (Andreasen, 1983), SAPS (Andreasen, 1984), or a mixture of these scales. In all 11 cases different inclusion and exclusion criteria were adopted. In a recent study by Dunayevich which explored the impact of different inclusion criteria (Dunayevich et al., 2014), a further five

different methods which used the PANSS to determine dominance or predominance were identified (Kinon et al., 2006, Moller et al., 2004, Rabinowitz et al., 2013, Riedel et al., 2005, Stauffer et al., 2012). In all, the 16 studies identified used 16 different ways to determine either the prominance or predominence of negative symptoms. Furthermore, it is important to note that this is not an exhaustive list, with a literature search suggesting that other major trials may have adopted different critiera again (Buchanan et al., 2007, Priebe et al., 2013b).

Adopting such a broard range of dominant and predominant inclusion criteria in negative symptom trials could be considered problematic. Rabinowitz (Rabinowitz et al., 2013) found that different symptom inclusion and exclusion criteria were found to result in very large differences in the amount of potentially eligible participants, ranging from 8.1%-62.% of the pooled sample according to different prominent symptom criteria, and 10.2%-50.2% criteria for predominant criteria. These findings have been replicated using the CATIE trial data (Lieberman et al., 2005), which found inclusion rates between 6%-37% (Dunayevich et al., 2014). These findings suggest that restrictive symptom inclusion criteria can result in a substantially smaller potential pool from which potential participants can be recruited from. As Dunayevich and Rabinowitz highlight (Dunayevich et al., 2014, Rabinowitz et al., 2013), this is likely to result in additional challenges in trial recruitment, and prehaps more concerningly, may result in the study samples being less generalisable to the clinical population who such treatments may be appropriate for. Dunayevich and colleagues (Dunayevich et al., 2014) found that correlations between the changes in negative and positive symptoms were largely consistent regardless of the severity of exclusion criteria used, which suggests that more restrictive criteria may not reduce the association as much as originally presumed. However, Rabinowitz (Rabinowitz et al., 2013) found larger treatment effects for negative symptoms in samples that included participants with both prominent negative and positive symptoms, relative to samples with predominant negative symptoms. These findings merit further consideration as such work may pave the way to appropriately standardising how such criteria are adopted in clinical trials.

The aim of this study was to compare how different eligibility criteria impact the association between negative symptoms, and positive and depressive symptoms, whilst considering their effect on the potential sample pool. This work builds upon the work by Dunayevich (Dunayevich et al., 2014), but with a number of important differences. Firstly, given depressive symptoms have been found to both mimic and cause negative symptoms (see section 1.9.1.2. for a review), it is important to determine whether different eligibility criteria currently used influence the relationship between depressive and negative symptoms. Secondly, in the Dunayevich study the presence of blunted affect, avolition and impairments in conversation

flow were required in addition to the symptom levels specified by the different study criteria. While this may follow the EMA recommendations for negative symptom trials (EMA., 2012), implementing such criteria homogenises the subsamples and makes it difficult to evaluate the impact of the criteria which are being evaluated. Third, in the Dunayevich study the standard PANSS negative subscale was used, despite concerns that the latter formulation includes items which measure cognitive symptoms (Blanchard et al., 2011). In order to address this concern, in the present study the alternative negative subscale configuration proposed by Marder was adopted (Marder et al., 1997). Finally, Dunayevich adopted the last observation carried forward method of as a way of dealing with missing data, which may under-report the degree of change over time given the methods assumes responses remain constant (Hamer and Simpson, 2009). In this study, multi-level modelling was adopted.

4.2. Research Questions

1) What is the change in negative symptoms over time in stable outpatients, after excluding participants with prominent positive and depressive symptoms?

2) What is the impact of adopting different inclusion and exclusion criteria on the proportion of eligible participants?

3) What is the impact of adopting different symptom inclusion and exclusion criteria on the association between negative symptoms, and positive and depressive symptoms?

4.3. Methods

4.3.1. Sample

The data used in this analysis was taken from the DIALOG Study, which is a cluster randomised controlled trial designed to evaluate the effectiveness of a computer-mediated intervention to structure patient-clinician dialogue (Priebe et al., 2007). The study took place in 6 European countries; Granada, Spain; Groningen, The Netherlands; London, United Kingdom; Lund, Sweden; Mannheim, Germany; and Zurich, Switzerland. All participants were community psychiatric outpatients, in receipt of at least 3 months of continuous care from the same service. All participants were aged 18-65, required to be capable of providing informed consent, had a sufficient understanding of the first language from the host country, and were

routinely meeting their keyworker every 2 months with the plan of continuing this for the next 12 months. Participants with either a severe organic psychiatric illness or primary substance abuse disorder were excluded. A more detailed description of the intervention is outlined elsewhere (Priebe et al., 2007). Various outcome measures, including symptoms were measured at baseline and at follow-up 12 months later. In DIALOG study the sample included patients diagnosed with schizophrenia-related disorders such as schizoaffective and schizophreniform disorders, however for the purposes of this study they were excluded from this investigation.

4.3.2. Scales

Socio-demographic details were obtained using the MANSA (Priebe et al., 1999). Symptoms of schizophrenia were measured using the PANSS (Kay et al., 1987), a full summary of which is presented in section 1.9.

Whilst the majority of the original studies which used the PANSS to define their symptom inclusion and exclusion criteria used the standard negative subscale formulation, in one case a modified version was adopted (Klingberg et al., 2011). One significant limitation of the standard PANSS negative subscale is that it includes items which are now recognised to relate to cognitive deficits, rather than what we currently understand negative symptoms to constitute (Blanchard et al., 2011). Consequently, the PANSS Marder reconfiguration of the negative symptom subscale was adopted (Marder et al., 1997). This alternative structure replaces the abstract thinking and stereotypical thinking items with motor retardation and active social avoidance. In cases where more than 1 item was missing from each subscale, the summary score from removed from the analysis.

4.3.3. Prominent and predominant symptom inclusion criteria under evaluation:

The minimum negative symptom and maximum positive symptom inclusion and exclusion criteria evaluated in this study were either identified in the final sample of the systematic review completed in chapter 3, or were used in the analysis completed by Dunayevich (Dunayevich et al., 2014). Prominent symptom criteria refer to utilising a minimum threshold of negative symptoms, whilst predominant symptom criteria refer to utilising both a minimum negative symptoms criterion, and a maximum level of positive symptoms. Within these criteria, minimum negative symptoms can either be specified by the negative subscale score

being above a minimum level threshold, or a particular number of individual negative symptoms being above certain level of severity. The positive symptom exclusion criteria can either be determined by implementing a maximum threshold for positive symptoms, or else by specifying that a measure of negative symptoms be above a measure of positive symptoms by a set amount.

In this study, a different interpretation of what constitutes prominent and predominant criteria was adopted, compared to that used in the Dunayevich investigation. In the Dunayevich study, symptom criteria were only defined as "predominant" if maximum PANSS positive subscale thresholds were specified below the minimum negative symptoms. In criteria where the maximum level of positive symptoms were specified on a single item level, such as Möllers (i.e. that no more than two PANSS positive items could be above 4) there would be defined as a "prominent" negative symptom criteria. However, while such criteria can result in positive symptoms being higher than negative symptoms in theory, in reality this was rare. For example, in the subsample of participants eligible according to the criteria defined by Moller, no participants were found to have higher positive than negative symptoms. Given it was found that such criteria typically resulted in negative symptoms being predominant, in this study they were defined as such.

In total, 16 different methods to determine prominent or predominant negative symptoms were uncovered, the details of which are presented in table 10. All those that used either the SANS, SAPS or the BPRS in the inclusion/exclusion criteria were excluded from this analysis, leaving a total of 11 different methods (3 prominent and 8 predominant).

Whilst no measure of EPS was recorded, data regarding the type and dose of medication prescribed was available. Using this data as a proxy-measure, the prescribed antipsychotic medication dose was transformed into the Defined Daily Dose measure in accordance with the WHO Anatomical Therapeutic Chemical Classification ATC/DDD index (WHO, 2013), which has been found to be a reliable tool for standardising antipsychotic dosages (Nose et al., 2008).

Table 10: Summary of different symptom exclusion criterion adopted in negative symptom trials

Study			Year	Scales used	Symptom inclusion criterion
Criteria for prominent negative symptoms					
1	*	Kinon	2006	PANSS	At least three items of the PANSS negative subscale ≥4, or at least two ≥5
2		Alvarez	2006	SANS	Baseline SANS >10
3	*	Cirici	2008	PANSS	At least three items of the PANSS negative subscale ≥4
4	*	Kaphzan	2014	PANSS	≥19 PANSS negative subscale score.
Criteria for predominant negative symptoms					
5		Bodkin	2005	SANS, BPRS	SANS >12, two subscales >3, ≥5 on the BPRS thinking disturbance subscale
6	*	Kane	2012	PANSS	≥15 on the negative subscale, no positive items ≥4
7		Lasser	2013	SANS	>54 on SANS 18, <2 on <1 SANS global score,
8		Lecrubier	2006	SANS & PANSS	negative symptoms: ≥10 on SANS summary, >4 on any PANSS positive symptom item
9		Loo	1997	SANS & SAPS	Inclusion: score of ≥60 on SANS and ≤50 on the SAPS
10	*	Ollie	2006	PANSS	PANSS negative subscale ≥6 points over positive subscale
11	*	Schoemaker	2014	PANSS	≥4 on at least 3 items, ≥21 overall on the negative subscale. No more than ≤19 on the PANSS positive
12	*	Rabinowitz	2013	PANSS	PANSS negative subscale > positive subscale
13	*	Moller	2004	PANSS	PANSS negative items “Blunted Affect” and “Conversation Flow” ≥4, with at least one other ≥4, and no more than two positive items ≥4
14	*	Riedal	2005	PANSS	PANSS negative subscale ≥21 and ≥1 over the positive subscale score
15	*	Stauffer	2012	PANSS	At least 3 PANSS negative subscale items ≥4, or at least two items ≥5, and a positive subscale score ≤19
16	*	Klingberg	2011	PANSS	1 PANSS negative item ≥4, no positive item ≥6

* Included in the analysis

4.3.4. Analysis plan

The subsamples were produced by implementing the different prominent and predominant criteria specified in table 10, and removing all participants that presented with at least moderately severe depressive symptoms (>4 on the PANSS). In the first part of the analysis, the change in negative symptoms over time was examined in each of the subsamples using a Students repeated-measures t-test. In the second part of the analysis, the association between negative, and positive and depressive symptoms were evaluated by using the *xtreg* command in STATA. In the third part of the analysis longitudinal modelling was used to explore the association between negative symptoms, and positive and depressive symptoms. PANSS Marder negative symptoms scores were included as a dependent variable, nested within participants included as a random effect. In the null model only time point was included as a covariate. Positive and depressive symptoms where then added to the model, and the change in the variance explained was calculated.

Previous studies in this area suggest that symptom eligibility criteria can result in a substantial reduction in the eligible sample pool (Rabinowitz et al., 2013; Dunayevich et al., 2014). With regards to the minimum number of participants necessary to provide meaningful estimates in a regression model, a number of different thresholds have been proposed. Whilst a number of more complex models have been devised (Kelley and Maxwell, 2003), a minimum of 50 participants was suggested a basic rule of thumb, with more participants needed when additional independent variables are added to the model (Green, 1991, Harris, 2014). Based on estimates produced by Miles and Shevlin (Miles and Shevlin, 2001), Field (Field, 2009) suggested that 40 participants would be a sufficient number when a large effect size is predicted and 3 predictors are included in the model (which is the maximum number added in this investigation). Following these guidelines, samples with fewer than 40 participants were omitted from the final summary.

4.4. Results

4.4.1. Summary of sample

In total, 354 participants from the sample were eligible for this investigation, of which data were available for 351. The socio-demographic details are presented in table 11. On average, participants were 42.1 years old, predominantly male (67.8%), and reported a long history of

schizophrenia (mean=16.0 years). Participants had experienced a median of 3 psychiatric hospitalisations, and reported a mean defined daily dose of antipsychotic medication of 1.36 (SD=0.95). Recruitment was split fairly equally between the 6 European countries, with the fewest recruited in Zurich (n=41, 11.7%), and the most in London (n=73, 20.8%).

Table 11: Demographic details of sample

Variables	Baseline n=351	
Study centre (N, %)		
Granada	68	19.4%
Groningen	57	16.2%
London	73	20.8%
Lund	50	14.3%
Mannheim	62	17.7%
Zurich	41	11.7%
Socio-demographic details		
Age years (mean, SD)	42.1	11.5
Female gender (n, %)	106	32.2%
Illness Duration years (n, SD)	16.0	10.2
Prev. number of admissions (median, IQR)	3	1-6
Defined Daily Dose at baseline*	1.36	0.95

*Equivalents calculated using WHO database estimates.

Of the 351 participants that were included in the study, 310 participants were assessed 12 months later, resulting in a study retention rate of 88.3%. Any differences in the baseline socio-demographic details, symptom scores and retention rates between countries are presented in table 12. A significant difference in study retention between research sites was detected (χ (5)= 16.3, P=.006). Groningen reported the highest study retention rate (98.2%), whilst Granada reported the lowest (77.9%). Significantly more females than males dropped out as a proportion of the sample (χ (1)=4.14, P=.042). No other significant differences in dropout were detected in either the baseline symptom scores, or the socio-demographic information.

Table 12 comparison centre, baseline sociodemographic, and symptom levels between those that did and did not attend the 12-month follow-up

	Non-dropouts			Dropouts			P*
	N	Mean	SD / %	n	mean	SD / %	
Study site (n, %)							.006
Granada	53		77.9%	15		22.1%	
Groningen	56		98.2%	1		1.8%	
London	63		86.3%	10		13.7%	
Lund	48		96.0%	2		4.0%	
Mannheim	53		85.5%	9		14.5%	
Zurich	37		90.2%	4		9.8%	
Socio-demographic information							
Age years (mean, SD)	309	42.1	11.4	41	42	12.2	.929
Female gender (n, %)	310	88	28.4%	41	18	43.9%	.042
Illness Duration years (n, SD)	307	16.1	10.0	41	15.6	12.0	.750
Prev. number of admissions (median, IQR)	303	3.0	1-6	38	2	1-5	.254
DDD at baseline (mean, SD)*	282	1.37	0.95	37	1.31	0.94	.713
Symptom scores (mean, SD)							
Negative symptom subscale	309	17.1	7.0	41	16	5.5	.326
Marder negative symptom subscale	309	17.0	7.4	41	16.4	5.7	.622
Positive symptom subscale	310	15.3	6.0	41	15.2	5.6	.899
General Psychopathology subscale	310	32.8	10.2	41	31	8.5	.272
Depression item	310	2.6	1.4	41	2.6	1.4	.976

*DDD=Defined daily dose, Determined through using the students-T, Mann Whitney U test or Chi square, depending upon whether the data was recorded as a mean, median or count value

4.4.2. Baseline and change in symptoms over time

Mean symptom levels are presented in table 13. Negative symptoms at baseline were in the low to moderate-to-moderate range (mean=16.9, SD=7.2), and were slightly lower 12 months later (mean difference -1.6, t(309)= 3.93, P<.001). When compared to the results in chapter 3, this reduction was found to be slightly smaller than that detected in the control study arms (ES change in current study= 0.22, 95% CI 0.13 to 0.32; chapter 3 control arm change= 0.33, 95% CI 0.16 to 0.50). Depressive (mean=2.6, SD=1.4) and positive (mean=15.3, SD=5.9) symptoms were also in the low-to-moderate range, which in both cases were significant lower at follow up (positive symptoms: mean difference -0.9, t(308)=2.31, P=.022; depressive symptoms: mean difference -0.9, t(309)=2.63, P=.009).

Table 13: symptom levels at baseline and 12 months follow-up whole sample

	T1			T2			t	P
	N	Mean	SD	N	Mean	SD		
Marder negative symptom subscale	350	16.9	7.2	308	15.3	6.4	5.19	<.001
Positive symptom subscale	351	15.3	5.9	306	14.6	6.2	2.24	0.025
General Psychopathology subscale	347	32.6	10.4	307	30.7	9.8	4.01	<.001
Depression item	351	2.6	1.4	310	2.4	1.3	2.58	0.010

Prior to implementing the positive and negative symptom criteria, all participants presenting with moderately severe depressive symptoms at baseline as measured by a score of at least 5 on the PANSS depression item were omitted. In this subsample the change in negative symptoms over time was marginally lower (mean difference -1.39, SE=0.33), with the majority of the sample remaining eligible (91.7%; n=321).

Having removed all cases presenting with at least moderately severe depressive symptoms at baseline, the different prominent and predominant negative symptom eligibility criteria were then applied. The mean level of negative symptoms and their change over time in the different subsamples are presented in table 14. As would be expected given participants with low symptoms were omitted, in the 3 prominent symptom criteria subsamples negative symptoms were much higher compared to the whole sample at the baseline stage. In addition, a significantly larger reduction in the level of negative symptoms over time was detected in all three samples, ranging from a mean difference of -4.29 in the Kaphzan subsample, to -4.94 in the Cirici subsample. Of the three different prominent symptom criteria, the method adopted by Kaphzan was found to be the least restrictive, with 30.3% (n=104) of the whole sample being eligible at baseline. The most restrictive was the criteria adopted by Cirici, where 23.4% (n=82) were found to be eligible.

In the 8 predominant symptom criteria subsamples, the mean level of negative symptoms at baseline increased as increasingly restrictive inclusion were adopted, as did the reduction in the proportion of eligible participants. In the broadest criteria (adopted by Rabinowitz et al., 2013), 50.0% (n=175) of the whole sample was eligible, whilst in the most restrictive criteria (Moller et al., 2004) only 6.3% (n=23) were eligible. At baseline, the mean negative symptoms in the Rabinowitz subsample was 19.88 (SD=6.64), substantially lower than the Moller subsample (mean=26.86, SD=5.01). The largest mean reduction in symptoms was present in criteria which specified a high minimum negative symptoms subscale score (Riedal et al., 2005; Schoemaker et al., 2014). The lowest reduction occurred in criteria which either specified a

minimum threshold on single items (Moller et al., 2004; Klingberg et al., 2011) or criteria which merely specify predominance, rather than requiring any a minimum degree of negative symptom severity (Rabinowitz et al., 2013).

Table 14: Change in Marder negative symptoms by the exclusion criteria

	N at T1	Negative symptoms T1		Negative symptoms T2		Change scores T2-T1		
		mean	SD	Mean	SD	mean	SE	P*
All eligible data	350	16.99	7.38	15.35	6.37	-1.64	0.32	<.001
Removing ≥5 depression	321	16.35	7.10	14.96	6.27	-1.39	0.33	<.001
Prominent symptoms criterion								
Kaphzan et al, 2014 criteria	106	24.48	4.72	19.19	6.25	-5.29	0.51	<.001
Kinnon et al., 2006 criteria	84	25.43	4.79	20.12	6.23	-5.31	0.55	<.001
Cirici et al, 2008 criteria	82	25.55	4.78	20.16	6.31	-5.38	0.56	<.001
Predominant symptoms criterion								
Rabinowitz et al., 2013 criteria	175	19.88	6.64	16.65	6.41	-3.23	0.44	<.001
Klingberg et al, 2011 criteria	149	20.82	5.86	17.57	6.21	-3.25	0.49	<.001
Ollie et al., 2006 criteria	84	23.61	6.07	18.59	6.55	-5.01	0.59	<.001
Kane et al, 2012 criteria	71	20.48	4.85	17.08	6.01	-3.40	0.62	<.001
Riedal et al., 2005 criteria	70	26.17	4.54	20.02	6.38	-6.15	0.57	<.001
Stauffer et al., 2004 criteria	58	24.92	4.65	19.33	6.41	-5.59	0.66	<.001
Schoemaker et al, 2014 criteria	48	25.95	4.26	20.02	6.55	-5.93	0.73	<.001
Moller et al., 2004 criteria	23	26.86	5.01	23.00	5.83	-3.86	1.03	.001

*Calculated by repeated measures t-test

4.4.3. Association between negative symptoms, and positive and depressive symptoms after adopting different eligibility criteria

The association between negative symptoms, and positive and depressive symptoms over time in the whole sample are presented in table 15. Both positive and depressive symptoms were found to be positively associated with negative symptoms, with the covariates explaining 19.2% of the variance (R^2=.192). After removing participants with at least moderate depressive symptoms, the association between negative symptoms and depressive symptoms was slightly lower but, still remained significant (B=-1.03, 95% CI 0.65 to 1.41). In this subsample, positive and depressive symptoms explained 14.9% of the variance (see table 16). Even with the

inclusion of positive and negative symptoms as covariates, negative symptoms were found to significantly reduce over time (B=-1.16, 95% -1.75 to -0.57).

Table 15: Association between positive and depressive symptoms and negative symptoms over time in the whole sample

n=350	Change over time			Change over time + Covariates		
	B	95% CI		B	95% CI	
Cons	18.53	17.42	19.63	10.67	8.92	12.42
Timepoint	-1.61	-2.22	-1.00	-1.16	-1.75	-0.57
Positive symptoms				0.27	0.19	0.35
Depressive symptoms				1.26	0.92	1.61
Random Part						
Sigma_u	5.55	5.04	6.11	4.83	4.36	5.35
Sigma_e	3.90	3.60	4.22	3.72	3.44	4.03
Derived estimates						
R				.192		
P	0.67			0.627		

Table 16: Association between positive and depressive symptoms and negative symptoms over time after removing participants with moderate depressive symptoms

	Change over time			Change over time + Covariates		
n=321	B	95% CI		B	95% CI	
Cons	17.6	16.48	18.73	10.93	9.15	12.72
Timepoint	-1.35	-1.98	-0.72	-1.10	-1.71	-0.49
Positive symptoms				0.27	0.18	0.35
Depressive symptoms				1.03	0.65	1.41
Random Part						
Sigma_u	5.28	4.77	5.85	4.75	4.27	5.29
Sigma_e	3.87	3.57	4.20	3.73	3.44	4.05
Derived estimates						
R				.149		
P	0.651			0.619		

4.4.4. Prominent negative symptom inclusion criteria:

The association between negative symptoms, and positive and depressive symptoms over time in the subsamples which adopted prominent negative symptoms criteria are presented in tables 17 to 19. In all three cases, a substantial reduction in the association between negative symptoms and the covariates was detected, with only 8.1% (R^2=0.81) of the variance explained in the Kaphzan subsample, and 11.7% (R^2=0.81) in the Cirici subsample. This weaker association appears to be primarily attributable to a much weaker relationship between negative symptoms and depressive symptoms, which was no longer found to be significant in any of the three subsamples.

Table 17: Association between positive and depressive symptoms and negative symptoms over time after adopting the Kaphzan eligibility criteria

	Change over time			Change over time + Covariates		
n=106	B	95% CI		B	95% CI	
Cons	29.33	27.65	31.02	24.24	21.47	27.02
Timepoint	-5.16	-6.13	-4.20	-4.93	-5.86	-3.99
Positive symptoms				0.21	0.10	0.33
Depressive symptoms				0.46	-0.11	1.03
Random Part						
Sigma_u	4.15	3.43	5.01	4.00	3.31	4.84
Sigma_e	3.46	3.01	3.98	3.29	2.86	3.79
Derived estimates						
R				.081		
P	0.590			0.596		

Table 18: Association between positive and depressive symptoms and negative symptoms over time after adopting the Kinnon eligibility criteria

	Change over time			Change over time + Covariates		
n=84	B	95% CI		B	95% CI	
Cons	30.32	28.45	32.19	24.78	21.79	27.77
Timepoint	-5.19	-6.26	-4.13	-4.99	-6.01	-3.98
Positive symptoms				0.23	0.11	0.36
Depressive symptoms				0.54	-0.09	1.17
Derived estimates						
Sigma_u	4.22	3.44	5.20	4.01	3.24	4.97
Sigma_e	3.39	2.9	3.97	3.20	2.72	3.76
Derived estimates						
R				.098		
P	0.608			0.612		

Table 19: Association between positive and depressive symptoms and negative symptoms over time after adopting the Cirici eligibility criteria

	Change over time			Change over time + Covariates		
n=82	B	95% CI		B	95% CI	
Cons	30.60	28.69	32.51	24.77	21.73	27.81
Timepoint	-5.29	-6.37	-4.21	-5.05	-6.08	-4.01
Positive symptoms				0.25	0.12	0.37
Depressive symptoms				0.57	-0.07	1.2
Random Part						
Sigma_u	4.26	3.46	5.25	4.00	3.22	4.96
Sigma_e	3.40	2.90	3.98	3.20	2.72	3.76
Derived estimates						
R				.117		
P	0.611			0.609		

4.4.5. Predominant negative symptom exclusion criteria

The association between negative symptoms, and positive and depressive symptoms over time in the subsamples which adopted predominant negative symptoms criteria are presented in tables 20 to 27. Substantial differences in the association between the covariates and negative symptoms were found, depending upon the method employed.

In subsamples obtained by using criteria which determined predominance as negative symptoms being higher than positive symptoms by a specified amount (Ollie et al., 2006; Rabinowitz et al., 2013), the association between the covariates was found to be much higher than in the other subsamples (Rabinowitz criteria R^2=.339; Ollie criteria R^2=.333). This stronger relationship between the covariates and negative symptoms appears to be driven primarily between a greater association between positive and negative symptoms (Rabinowitz subsample: Positive symptoms B=0.60; 95% CI 0.48 to 0.71; Ollie subsample: positive symptoms B=0.54; 95% CI 0.39 to 0.69).

Table 20: Association between positive and depressive symptoms and negative symptoms over time after adopting the Rabinowitz eligibility criteria

	Change over time			Change over time + Covariates		
n=175	B	95% CI		B	95% CI	
Cons	22.83	21.32	24.34	13.48	11.42	15.54
Timepoint	-3.16	-4.01	-2.31	-3.32	-4.08	-2.56
Positive symptoms				0.60	0.48	0.71
Depressive symptoms				0.76	0.30	1.21
Random Part						
Sigma_u	5.07	4.40	5.83	3.87	3.31	4.52
Sigma_e	3.87	3.46	4.32	3.45	3.09	3.86
Derived estimates						
R				.339		
P	0.632			0.557		

Table 21: Association between positive and depressive symptoms and negative symptoms over time after adopting the Ollie eligibility criteria

	Change over time			Change over time + Covariates		
n=84	B	95% CI		B	95% CI	
Cons	27.96	25.93	29.98	20.25	17.55	22.95
Timepoint	-4.85	-5.98	-3.72	-5.13	-6.13	4.13
Positive symptoms				0.54	0.39	0.69
Depressive symptoms				0.62	0.00	1.23
Random Part						
Sigma_u	5.02	4.13	6.10	3.93	3.18	4.87
Sigma_e	3.49	2.97	4.10	3.08	2.61	3.63
Derived estimates						
R				.333		
P	0.674			0.620		

In subsamples which were determined by separate minimum negative and maximum positive thresholds the findings are presented in tables 22 to 26. Across all five criteria, the association between the covariates and negative symptoms were found to be broadly similar, comparable to those detected in the prominent criteria samples. The smallest association between was in the Schoemaker subsample (R^2=.080), while the largest association was detected in the Riedal subsample (R^2=.153). Consistent with the findings derived from the prominent negative symptom subsamples, including positive and depressive symptoms as covariates did not significantly reduce the change in negative symptoms over time in any of the five predominant subsamples.

Table 22: Association between positive and depressive symptoms and negative symptoms over time after adopting the Klingberg eligibility criteria

	Change over time			Change over time + Covariates		
n=149	B	95% CI		B	95% CI	
Cons	23.67	22.06	25.28	17.24	14.68	19.79
Timepoint	-3.13	-4.07	-2.19	-2.99	-3.87	-2.1
Positive symptoms				0.30	0.17	0.42
Depressive symptoms				0.73	0.18	1.27
Random Part						
Sigma_u	4.4	3.72	5.20	4.23	3.59	5.01
Sigma_e	3.94	3.49	4.44	3.65	3.24	4.13
Derived estimates						
R				.105		
P	0.555			0.574		

Table 23: Association between positive and depressive symptoms and negative symptoms over time after adopting the Kane eligibility criteria

	Change over time			Change over time + Covariates		
n=71	B	95% CI		B	95% CI	
Cons	23.6	21.56	25.63	18.82	15.92	21.73
Timepoint	-3.32	-4.49	-2.14	-3.71	-4.81	-2.62
Positive symptoms				0.32	0.14	0.51
Depressive symptoms				0.68	-0.03	1.39
Random Part						
Sigma_u	4.01	3.18	5.07	3.95	3.16	4.95
Sigma_e	3.41	2.87	4.05	3.11	2.62	3.7
Derived estimates						
R				.088		
P	0.580			0.618		

Table 24: Association between positive and depressive symptoms and negative symptoms over time after adopting the Riedal eligibility criteria

	Change over time			Change over time + Covariates		
n=70	B	95% CI		B	95% CI	
Cons	32.06	30.08	34.03	24.6	21.57	27.63
Timepoint	-6.08	-7.18	-4.99	-5.89	-6.82	-4.95
Positive symptoms				0.38	0.23	0.52
Depressive symptoms				0.51	-0.10	1.13
Random Part						
Sigma_u	4.36	3.51	5.41	4.17	3.39	5.14
Sigma_e	3.19	2.69	3.78	2.71	2.28	3.23
Derived estimates						
R				.153		
P	0.651			0.702		

Table 25: Association between positive and depressive symptoms and negative symptoms over time after adopting the Stauffer eligibility criteria

	Change over time			Change over time + Covariates		
n=58	B	95% CI		B	95% CI	
Cons	30.08	27.86	32.29	23.78	20.51	27.06
Timepoint	-5.47	-6.72	-4.22	-5.51	-6.58	-4.43
Positive symptoms				0.36	0.20	0.53
Depressive symptoms				0.60	-0.17	1.36
Random Part						
Sigma_u	4.30	3.37	5.48	4.35	3.45	5.48
Sigma_e	3.26	2.69	3.94	2.76	2.27	3.37
Derived estimates						
R				.089		
P	0.635			0.712		

Table 26: Association between positive and depressive symptoms and negative symptoms over time after adopting the Schoemaker eligibility criteria

	Change over time			Change over time + Covariates		
n=48	B	95% CI		B	95% CI	
Cons	31.52	29.08	33.95	24.39	20.53	28.26
Timepoint	-5.83	-7.21	-4.44	-5.62	-6.81	-4.42
Positive symptoms				0.42	0.21	0.62
Depressive symptoms				0.50	-0.34	1.35
Random Part						
Sigma_u	4.17	3.18	5.48	4.27	3.31	5.51
Sigma_e	3.3	2.68	4.07	2.79	2.25	3.46
Derived estimates						
R				.080		
P	0.614			.701		

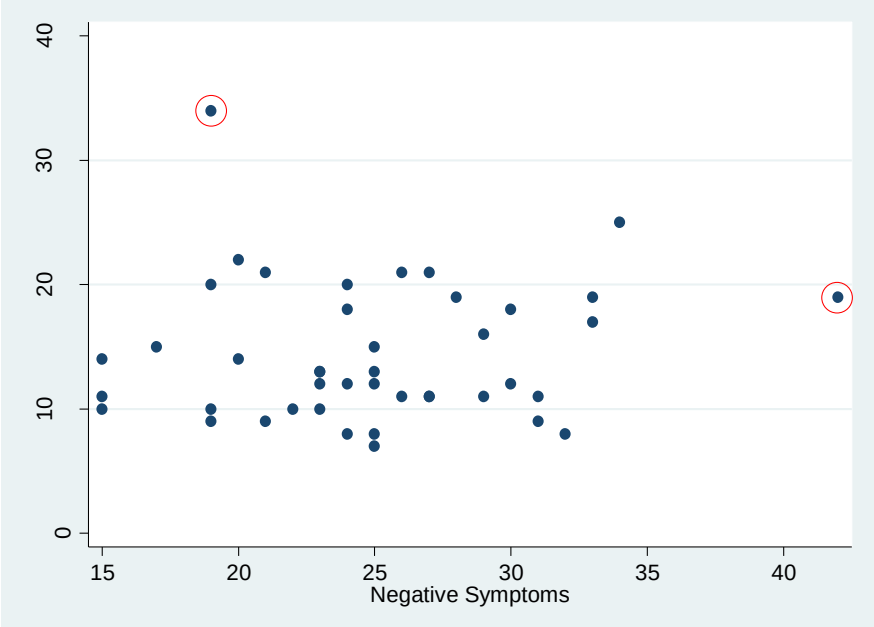
In the final predominant criteria adopted by Moller the association between negative symptoms and the covariates was found to be very small (R^2=0.48, see table 27). However, due to the very small sample size (n=23) this analysis was omitted from the final summary due to concerns that the estimates were not sufficiently stable. In an examination for possible outliers (see figure 8) two estimates in particular (denoted by the red circles) were found to have a disproportionate impact on the association between positive and negative symptoms. When these were removed, the association between negative symptoms and the covariates was found to be substantially larger (R^2=.192, in comparison to R^2=.048), which further supported the decision to omit these findings.

A summary of the associations between the covariates and negative symptoms over the 11 different subsamples are presented in table 28.

Table 27: Association between positive and depressive symptoms and negative symptoms over time after adopting the Moller eligibility criteria

	Change over time			Change over time + Covariates		
n=23	B	95% CI		B	95% CI	
Cons	30.19	26.73	33.65	26.73	21.89	31.58
Timepoint	-3.71	-5.67	-1.76	-4.38	-6.25	-2.52
Positive symptoms				0.21	-0.01	0.42
Depressive symptoms				0.59	-0.59	1.77
Random Part						
Sigma_u	4.11	2.77	6.10	4.17	2.85	6.11
Sigma_e	3.26	2.41	4.40	2.97	2.19	4.02
Derived estimates						
R				.048		
P	0.614			0.664		

Figure 8: Scatterplot of positive and negative symptoms that participants experience in the Moller subsample.[a]



[a]circles denote outliers.

Table 28: Association of depressive and positive symptoms to negative symptoms, after controlling for covariates

Eligibility criteria	N	R^2
All eligible data	350	.192
Removing ≥5 depression	321	.149
Prominent negative criteria		
Kaphzan et al, 2014 criteria	106	.081
Kinnon et al., 2006 criteria	84	.098
Cirici et al, 2008 criteria	82	.117
Predominant negative criteria		
Rabinowitz et al., 2013 criteria	175	.339
Klingberg et al, 2011 criteria	149	.105
Ollie et al., 2006 criteria	84	.333
Kane et al, 2012 criteria	71	.088
Riedal et al., 2005 criteria	70	.153
Stauffer et al., 2004 criteria	58	.089
Schoemaker et al, 2014 criteria	48	.081
Moller et al., criteria	23	—

4.5. Discussion

4.5.1. Main findings

Consistent with the findings presented in chapter 3, significant reductions in negative symptoms over time were detected even after different minimum negative and maximum depressive and positive symptom inclusion criteria were implemented on the overall sample. This reduction in negative symptoms over time was substantially larger in subsamples which resulted in higher mean negative symptoms at baseline.

Excluding participants who present with at least moderately severe depressive symptoms and low negative symptoms resulted in a weaker association between depressive and negative symptoms. However, implementing a maximum positive symptom criterion did not appear to reduce the association between positive and negative symptoms, and in some cases even increased it. Adopting increasingly restrictive eligibility criteria substantially reduced the amount of eligible participants in a standard outpatient sample pool, but appeared to have a minimal effect on the association between these variables. These findings suggest that whilst

adopting such eligibility criteria may be effective in reducing the association between negative and depressive symptoms, it may not be an effective method to reduce the impact of positive symptoms on negative symptoms.

4.5.2. Strengths and limitations

One strength of this study is the relatively high number of different criteria evaluated (11), and the consistency of the findings between them which suggests the findings are relatively robust. Another strength of the study is the fact the sample evaluated had high follow up rates over a period of 12 months (88.3%), minimising a possible selection bias due to attrition. In addition, longitudinal modelling was adopted which allows for a more appropriate way to deal with any missing data, relative to other methods such as LOCF which was adopted by earlier studies (Dunayevich et al., 2014).

Another strength of the study is the fact that the sample was obtained from a non-pharmacological trial evaluating a treatment which was designed to improve quality of life, as opposed to clinical symptoms (Priebe et al., 2007). Consequently, participants were not randomised to receive a drug which may either significantly alter positive symptoms, or else result in side effects that can either mimic or exacerbate negative symptoms. In the Rabinowitz study (Rabinowitz et al., 2013), the sample was obtained from pooling a number of pharmacological studies all designed to treatment the symptoms of schizophrenia. In the CATIE study (Lieberman et al., 2005) which was the sample used by Dunayevich (Dunayevich et al., 2014), 5% of participants discontinued the randomised treatment due to side effects, whilst it is unclear what proportion experienced side effects but still continued with the medication. In both cases, changes in positive symptoms and extrapyramidal symptoms would be expected to be higher than in the sample used in this study which may present additional challenges in disentangling the antecedents of negative symptoms.

One significant limitation of the study is that despite the relatively large initial sample size (n=350), adopting increasingly restrictive inclusion criteria resulted in a substantial loss of participants. Consequently, in the smallest sample obtained by implementing the criteria proposed by Möller (Moller et al., 2004) there were an insufficient number of participants upon which to establish reliable estimates. In addition, the low number of participants in a number of the subsamples meant that comparisons could not be drawn between groups when the R^2 values were similar. Consequently, whilst this study concludes that adopting increasingly

restrictive inclusion criteria do not result in further changes in the association between negative symptoms and positive and depressive symptoms, small differences may become evident if the study was replicated in a far larger sample. However, this may not necessarily be informative in deciding what inclusion criteria to adopt if a small decrease in the association between negative and positive symptoms comes at the cost of a substantial reduction in the pool of potentially eligible participants, which is what this and earlier studies suggest (Dunayevich et al., 2014, Rabinowitz et al., 2013).

Another possible limitation is that in the sample used clinical stability was defined as being an outpatient under the care of the same clinical team for at least three months. In both the EMA guidelines (EMA., 2012) and the persistent negative symptoms criteria (Buchanan, 2007) it is recommended that participants should exhibit clinical stability for six months. As a result, the shorter period of clinical stability required could have potentially impacted the findings. However, in this study participants typically had a very long illness duration (mean 16 years, SD=10.2) and all reported being in the same outpatient service for at least one year. As a result, it is highly unlikely that adopting the recommended 6 month clinical stability criteria would have substantially altered the sample.

In this study, it is important to consider that all participants were considered stable outpatients, with the mean severity of symptoms at baseline low. As a result, it is not clear whether the eligibility criteria evaluated may have a greater impact in inpatients, or in samples which present with higher positive symptoms. However, there is a general consensus that patients in the acute phase of schizophrenia are not appropriate participants for negative symptom clinical trials (Marder et al., 2013). In addition, if the aim is to recruit such participants then it is likely that an even smaller proportion of participants would be eligible, further exacerbating issues regarding recruitment and sample generalisability.

The final limitation of the study is that EPS were not assessed, and so were not included in the analysis. As outlined in section 1.3.1.2., EPS such as bradykinesia and akinesia can mimic negative symptoms such as blunted affect, so it is possible that at least some of the symptoms reported may be a consequence of medication effects, rather than core psychopathology. In this study the defined daily dose of antipsychotic medication in the sample was relatively high (mean DDD=1.37, SD=0.95), which may be problematic given high antipsychotic dose have been found to be associated with higher negative symptoms (Perenyi et al., 1998). If a significant proportion of the negative symptoms reported in this study were associated to EPS, then depending upon whether these were addressed following the baseline assessment this may have either caused a greater or lesser change in negative symptoms than may have

otherwise been the case. In future studies, including EPS either as a covariate in the model, or as part of the exclusion criteria may help to further disentangle how different eligibility criteria may change the association between negative symptoms and causes of secondary symptoms.

4.5.4. Summary

Implementing minimum negative and maximum depressive symptom eligibility criteria were found to reduce the association between these symptoms. These findings suggest adopting such criteria may be a helpful tool in helping to minimise secondary negative symptoms caused by depressive symptomology. However, adopting minimum negative and maximum positive symptom eligibility criteria was not found to reduce the association between these symptoms, and in some cases even increased it. In highly restrictive inclusion criteria the association between these symptoms did not change, but did result in a large proportion of the sample being ineligible. In conjunction with previous findings (Dunayevich et al., 2014), these results suggest that restrictive symptom inclusion criteria may not be an effective method to limit the impact of positive symptoms on negative symptom change.

Chapter 5. Comparing the CAINS and the PANSS as a measure of negative symptoms

5.1. Introduction

In the MATRICs consensus statement on negative symptoms (Kirkpatrick et al., 2006) the limitations of existing assessment tools were identified as a significant barrier in the development of new treatments (see section 1.8. for a full summary). As a consequence, the panel recommended forming a working group with the aim of developing and testing new scales, both in terms of their psychometric properties and their sensitivity to symptom change. Following the MATRICs meeting, the Collaboration to Advance Negative Symptom Assessment in Schizophrenia (CANSAS) was established (Blanchard et al., 2011), which in turn led to the development of two new scales; the Clinical Assessment Interview for Negative Symptoms (CAINS) (Horan et al., 2011), and the Brief Negative Symptom Scale (BNSS) (Strauss et al., 2012). These scales have been designed to reflect our current conception of negative symptoms, which include alogia, blunted affect, asociality, anhedonia and avolition.

Conceptually, the CAINS is viewed as a significant advance on earlier instruments such as the PANSS (Kay et al., 1987) and the SANS (Andreasen, 1983) which are currently the most used scales in negative symptom assessment. Despite their extensive use in schizophrenia research, the PANSS and the SANS are recognised to have a number of limitations (Blanchard et al., 2011),. These include combining cognitive symptoms into negative symptom subscales, capturing multiple, conceptually distinct domains within a singular item, and not making an appropriate distinction between anticipatory and consummatory pleasure, which is important given it appears it is only the former which relates to negative symptoms (Gard et al., 2007). In addition, the PANSS and SANS largely rely on behavioural referents; be they either interviewer observations, or reports from the interviewee, a care giver, or clinicians, as evidence of experiential deficits. This is potentially problematic, given symptoms such as anhedonia and apathy relate primarily to experiential states, where what participants actually do can be affected a number of secondary factors.

As summarised in section 1.9.1.7., the CAINS has been to have good psychometric properties (Kring et al., 2013). The interrater reliability for the CAINS experiential and expressive subscale was high (ICC=.93 and ICC=.77 respectively), whilst the test-retest reliability of the two

subscales was found to be comparable to that found with the negative symptom subscale of the PANSS (Kay et al., 1987). The CAINS subscales significantly correlated with the corresponding items on the SANS (Andreasen, 1983) and the BPRS (Overall and Gorham, 1962), and was divergent from distinct concepts such as depression, IQ, positive symptoms and EPS. In addition, the CAINS was found to moderately correlate with indicators of functioning, relating specifically to what patients actually do, as opposed to what they physically capable of doing (Kring et al., 2013).

With the CAINS scale exhibiting promising conceptual and psychometric characteristics, the next stage of evaluation proposed by the MATRIC consensus statement would be to determine the sensitivity of the scale (Kirkpatrick et al., 2006). This is important, as earlier negative symptom assessment scales have been found to report very different effect sizes (Eckert et al., 1996). Further evidence for this is presented in chapter 3 of this investigation, where it was found that the SANS reported a significantly greater change in negative symptoms over time relative to the PANSS. If the CAINS is found to be a more sensitive instrument than existing assessment scales then this could represent a major step forward in the evaluation of new therapeutics given it would be more capable of detecting any treatment effects, and would also mean that smaller sample sizes would be required to detect meaningful changes.

In a related issue to determining the sensitivity of the scale, assessing whether the measure adds predictive power above what can be predicted by other sources has been considered an important but neglected area in most areas of applied psychology (Hunsley and Meyer, 2003). This concept, known as incremental validity, was originally proposed by Sechrest (Sechrest, 1963) who stated that in order for a new psychological test to be valid then it must result in an improvement in prediction over existing methods which are routinely adopted as part of the assessment process. Yates and Taub (Yates and Taub, 2003) went on to suggest that that the assessment of incremental validity needs to be considered against the associated costs (both time and financial) of using the measure over existing alternatives. Based on experiences from a recent full-scale trial which used both the CAINS and the PANSS as part of its full assessment battery (Priebe et al., 2013a), the CAINS scale at 13 items is slightly quicker to complete than the 30-item PANSS assessment, and requires an equivalent degree of training and experience, meaning the associated costs can be considered similar. Therefore, if the CAINS is found to provide greater predictive power of concepts related to the negative symptom construct, then it could be argued that this scale has greater incremental validity in this context.

As outlined in section 1.6., negative symptoms have been found to be associated with a reduced frequency of recreational activities, lower quality and frequency of social interactions, and reduced work performance (Hunter and Barry, 2012, Lysaker and Davis, 2004, Milev et al., 2005). In this study, the degree to which the CAINS and the PANSS negative subscale could predict such outcomes was compared. These outcomes include the participant's reported social network size, the number of activities they took part in over the previous week, and whether they could identify anyone as being close friend, which were collectively defined as indicators of social impoverishment. The term 'social impoverishment' is more typically used in social psychology, and refers to concepts such as community integration and participation (Gracia et al., 1995).The decision to adopt this particular label, rather than more common alternatives which include terms such as social or functional 'impairment', 'deficit' and/or 'disability' was due to concerns that this might imply that reported behaviours are considered pathological, when may be problematic given the factors associated with these behaviours were not fully explored.

In this part of the investigation three different aims will be addressed. First, the convergent validity between the CAINS and the PANSS negative subscale will be examined, given in the original study (Kring et al., 2013), the convergent validity was examined using the BPRS anergia scale. Whilst the PANSS negative and BPRS anergia symptom subscales have been found to be highly correlated (r=.82) (Bell et al., 1992), a number of negative symptoms are not assessed by the BPRS, such as apathy and asociality, and so it could be argued that the scale provides a poorer coverage of the negative symptom construct. It is notable that whilst the SANS and the PANSS were recognised as appropriate measures for use in clinical trials for negative symptoms in both the NIMH-MATRICs and the ISCTM consensus statements (Kirkpatrick et al., 2006; Marder et al., 2011), the BPRS was not mentioned. The PANSS is recognised as one of the most extensively used scales in the field of schizophrenia research (Mortimer, 2007) and, as identified in the systematic review presented in chapter 3, has been used in a number of large trials designed to evaluate the effectiveness of treatments for negative symptoms. Consequently, understanding the relationship between the PANSS negative subscale and the CAINS may give a better understanding both of the CAINS scale itself, and also place earlier findings which have used the PANSS in better context in light of developments in our understanding of what constitutes negative symptoms.

The second part of this investigation will assess the degree of agreement between the CAINS and the PANSS to examine whether there are any systematic differences in how they capture negative symptoms. This investigation will involve both comparing how the scales differentiate

between participants that present with high and low negative symptoms, and comparing how sensitive the two scales are in detecting changes in negative symptoms over time.

The third aim will be to examine the incremental validity of the CAINS by comparing its predictive ability of objective and subjective measures of social impoverishment with the PANSS negative subscale using Dominance Analysis (Azen and Budescu, 2003, Azen and Traxel, 2009). Negative symptoms relate specifically to deficits in motivation to take part in recreational activities and impairments in the quality and quantity of social networks, so the scale which better predicts these outcomes could be considered a better indicator of the negative symptom construct. Given the PANSS negative subscale in its standard form has been extensively used in negative symptom trials in the past, both this and the alternative Marder configuration was included in the analysis.

5.2. Research questions

1) What is the association between the CAINS and the PANSS negative subscale?
2) Does the CAINS provide a greater differentiation between participants that report high and low symptoms, relative to the PANSS negative subscale?
3) Is the CAINS more sensitive in detecting symptom change over time relative to the PANSS negative subscale?
4) Is the CAINS a better predictor of objective social outcomes relative to the PANSS negative subscale?

5.3. Method

5.3.1. Sample

The data for this study was taken from the NESS study (Priebe et al., 2013a), which was a multi-site randomised controlled trial designed to evaluate the effectiveness and cost effectiveness of body psychotherapy in the treatment of negative symptoms of schizophrenia. The inclusion criteria for the study included having an established diagnosis of schizophrenia according to ICD-10, displaying negative symptoms for a period of at least six months, not changing the type of antipsychotic medication six weeks prior the baseline assessment, and an ability and willingness to take part in a physically active group. In addition, participants were required to present with at least moderate levels of negative symptoms, indicated by a score of at least 18 on the negative subscale of the PANSS. Because this skewed the baseline

distribution of the PANSS negative subscale, in this study only the end of treatment and 6 month follow-up data were analysed. A full summary of the study has been reported elsewhere (Priebe et al., 2013a)

5.3.2. Scales

The psychometric properties of the Clinical Assessment Interview for Negative symptoms (CAINS) (Horan et al., 2011, Kring et al., 2013) have been summarised in detail in section 1.9.1.7. Whilst the authors have proposed reporting the experiential and expressive subscales separately given they appear to represent distinct constructs (Blanchard and Cohen, 2006), the current consensus regarding the evaluation of negative symptoms for clinical trials recommend evaluating this outcome as a singular construct (Kirkpatrick et al., 2006, Marder et al., 2011). Consequently, both the individual subscales and the overall summary score were evaluated.

In this study the CAINS was compared to the PANSS negative subscale (Kay et al., 1987). A full summary regarding the details of this scale have been summarised in section 1.9.1.3. Given it is important to understand the relationship between the CAINS and the PANSS both in the context of earlier studies and in line with current recommendations (Marder et al., 2011), the original PANSS negative subscale and the Marder negative symptom subscale (Marder et al., 1997) were included. In the standard version, the items which formulate the negative symptom construct include affective blunting, emotional withdrawal, apathetic social withdrawal, poor rapport, stereotypical thinking, difficulties in abstract thinking and impaired conversation flow. In the alternative Marder subscale, stereotypical thinking and difficulties in abstract thinking were removed, and replaced with the active social avoidance and motor retardation items.

In order to capture objective and self-report indicators of social impoverishment, individual items from the Manchester Short Assessment Scale (MANSA) (Priebe et al., 1999), an adapted version of the Social Network Scale (SNS) (Dunn et al., 1990), and the Time Use Survey (TUS) (Lader et al., 2006) were used. From the SNS, the question “Who did you see or speak to in the last week?” was asked, with the number of friend contacts added together. From the MANSA, item 4 was used which asked “Do you have anyone you would call a close friend?”. With the TUS, participants were asked whether they had taken part in activities like going out to eat, shopping for anything over than food, going to any place of entertainment, or going out

on any form of outdoor trip, with all activities added together to provide a final summary score.

5.3.3. Analysis plan

5.3.3.1. Associations between the CAINS and the PANSS

In the first part of the analysis the correlations between the CAINS and the PANSS negative subscales were calculated. In the initial development phase of the CAINS (Horan et al., 2011) a significantly stronger correlation was detected between the BPRS anergia subscale and CAINS expressive subscale, relative to the experiential subscale. This fits with the limitations identified in the review of earlier scales (Blanchard et al., 2011) which state that scales such as the PANSS, BPRS and the SANS appear to insufficiently tap into experiential states. Whilst there is a substantial degree of overlap between the BPRS anergia subscale and the PANSS negative subscale, the PANSS includes extra items relating to social withdrawal and alogia, so at present it is unclear whether the relationship would be similar to that identified by Horan and colleagues (Horan et al., 2011).

5.3.3.2. A comparison of how the PANSS and CAINS differentiates between high and low negative symptoms

In the next part of the analysis, the relationship between the CAINS and the PANSS negative subscales were further explored. Tukey mean-difference plots were conducted to examine the degree of agreement between the two scales across the range of symptom severity. This form of plotting the data is extensively used in biomedical statistics in the form of Bland-Altman plots (Bland and Altman, 1986), where objective measures are taken (i.e. blood pressure) against which one can be compared to a recognised “gold standard”. However, in this context where there is no gold standard against which either scale can be compared, the aim instead will be to explore systematic differences between the scales. Given the different scaling of the subscale scores (0-4 in the CAINS, versus 7-49 for the PANSS negative subscale) the scores plotted were a proportion of their possible range. The Bland Altman plots were modelled in STATA using the *batplot* command. Trends in the degree of change between the scales were explored in a regression analysis, using the STATA *regress* command. Both the standard PANSS negative subscale, in addition to the alternative Marder configuration of the negative

symptom construct (Marder et al., 1997) were evaluated, in addition to both the CAINS total, and experiential and expressive subscales.

5.3.3.3. Examination of the difference in negative symptom change scores between the CAINS and PANSS over time

In order to explore the sensitivity of the PANSS and CAINS in detecting negative symptom change, the analysis was extended to look at the relationship between the change scores in the PANSS and CAINS over time. To achieve this, a comparison of the rate of change in one scale relative to the other was examined in a subsample of the dataset which included all participants that reported a clinically meaningful change in negative symptoms, in the same direction, over both the CAINS and PANSS. However, determining what constitutes a clinically meaning change in negative symptoms using these rating scales is a complex issue, particularly so in the case of the CAINS given the scale has not yet been extensively tested.

In the PANSS total score, a 25% reduction in symptoms has been found to correspond to a 1 point reduction in the CGI (Guy, 1976, Leucht et al., 2006), denoting observable clinical improvement. However, it is not clear how this reported figure translates to the negative symptom subscale, while at lower symptom levels the degree of improvement required appears to be substantially less. Regarding negative symptom change specifically, in the NESS trial (Priebe et al., 2013a) a 3-point reduction in the PANSS negative subscale score was deemed clinically significant in the power analysis calculation, which was the figure adopted to denote clinically meaningful change in this analysis. However, given the uncertainty around this as an appropriate figure, in a sensitivity analysis an equivalent 2-point and 4-point change in the PANSS negative symptom subscale was also examined. Given the analysis was conducted as a change in the proportional score of the scale, as opposed to raw-change scores, these figures were transformed into percentage changes in the PANSS negative subscale. The subscale has a range of 42 (7-49), meaning a 3-point change equates to a proportional change of at least ±7.14%, a 2-point change to at least ±4.76%, and a 4-point change to at least ±9.52%.

Given all participants had previously been randomised to receive a treatment of either Pilates or Body Psychotherapy (see Priebe et al., 2013a for a full description of the original study) it is possible that the symptom trajectory may be different depending upon the treatment group they were randomised into. Consequently, trends were examined using a mixed effects models

fitted by maximum likelihood estimation. The mean percentage change scores were added as an independent variable; the difference in that change between the CAINS and the PANSS negative subscales were added as a dependent variable, and therapy group allocation was included as a random effect.

5.3.3.4. Assessment of the incremental validity of the CAINS over the PANSS

In the final part of the study the aim was to assess the incremental validity of the CAINS over the PANSS negative subscale as a predictor of social impoverishment, as defined by the number of friend contacts over the past, and the number of activities they have taken part in over the past week, and whether they have somebody they consider to be a close friend. In the first part of the analysis, these relationships were explored using logistic or Poisson univariate regression, depending upon whether the dependent variable was count or dichotomous in nature. Given there is likely to be substantial a correlation between the PANSS negative subscales and CAINS as they have been designed to measure the same construct (i.e. negative symptoms), multivariate regression analysis was not conducted given concerns regarding collinearity. As an alternative, dominance analysis was conducted, which has been used in the past to compare the predictive strength of two different scales designed to measure the same construct (Miller et al., 2012).

Whilst in a traditional multivariate regression model the aim is to build the strongest predictive model, in dominance analysis the question instead focuses on "given X number of predictors, which is more useful in predicting the criterion Y?" (Pedhazur, 1982). To answer this question, the contribution of one individual variable is compared with the other independent variables in all possible subset models, in addition to the full model where all predictors are included. In doing so, the superiority of a predictor can be specified at three levels; the first (and lowest) level is conditional dominance, which is specified by the variable with the higher mean contribution of the explained variance over all the models (L1). If one variable dominates another at each model size then it is said to generally dominate (L2). Lastly, if one variable provides greater explanatory power over another in every subset model then is recognised to completely dominate (L3). To test the reproducibility of complete dominance 50 bootstrapped samples were produced, which is a number considered adequate to calculate estimates of standard error (Mooney et al., 1993). Following the method proposed by Azen and Budescu (Azen and Budescu, 2003), in all bootstrapped replications the variable was given a score of 1 if it completely dominated the other variable, 0.5 if neither variable completely dominated, and

0 if it was completely dominated by the other variable. The figures reported denote the mean of these findings over all the bootstrapped samples. In this study the dependent variables were either binary or count outcomes, so a logistic or poisson statistic was adopted as appropriate, modelled within the STATA *domin* command (Luchman, 2014). Following the recommendations from Azen and Traxel (Azen and Traxel, 2009), McFadden's pseudo R^2 was adopted to provide an estimate of the measure of fit (McFadden). All analysis was conducted using STATA version 12.0 (STATA Corp, 2012).

5.4. Results

5.4.1. Description of sample

The participant characteristics are presented in table 29. The mean age of participants was 42.2 years, and were predominately male (74%), unemployed (96%), with a long history of schizophrenia (mean= 12.8 years, SD= 8.8). Participants presented with moderate levels of negative symptoms (PANSS negative=21.68, SD=5.04; CAINS total= 2.12, SD= 0.59) and low levels of positive symptoms (PANSS positive =13.21, SD=4.48).

The inter-rater reliability for both the CAINS and the PANSS between raters measured at study end was high (PANSS total ICC= .85; CAINS total ICC= .80). The study retention between the two time points included in this study was found to be very high (252/264; 95.5%).

Table 29: Clinical and socio-demographic information of the sample at baseline

Variable	Total N=265.	
Age (mean, SD)	41.93	10.5
Gender (n, %)		
Male	194	73.5%
Female	70	26.5%
Ethnicity (n, %)		
White	135	51.1%
Black	78	29.5%
Asian	30	11.4%
Other	21	8.0%
Employment (n, %)		
Work/training/education	7	2.6%
Other	258	97.4%
Living situation (n, %)		
Alone	149	56.4%
With others	115	43.6%
No. of Children (median, IQR)	0	0-6
PANSS total score (mean, SD)	64.76	12.82
PANSS negative	21.68	5.04
PANSS positive	13.21	4.48
PANSS Marder negative	20.51	5.42
CAINS total score (mean, SD)	2.12	0.59
Expression Subscale	1.85	0.98
Experience Subscale	2.34	0.64
# Activities completed (median, IQR)	3	1-7
Do you have a close friend (n, %)		
Yes	167	64.5%
No	92	35.5%
# friends contacts (median, IQR)	1	0-2

SD, standard deviation; IQR, interquartile range;

5.4.2. Association between variables

A correlation matrix of the outcome variables assessed is presented in table 30. The correlation between the PANSS negative subscale and the CAINS expression subscale (r=.754) and CAINS total score (r=.742) was high, whilst the correlation with the CAINS experience subscale was moderate (r=.480). The four different methods in which to assess negative symptoms (the PANSS negative subscale standard format, the PANSS negative Marder configuration, the CAINS experiential subscale, and the CAINS expressive subscale) were all

positively associated with each other, and negatively associated with the number of friend contacts participants reported in the past week, whether they had a close friend, and the number of activities taken part in over the past week.

Table 30: correlation matrix of the variables at end of treatment stage

	CAINS Total	CAINS Expression	CAINS Experience	PANSS Negative	PANSS Marder negative	# Activities	# Friend contacts	Close friend (Y/N)
CAINS Total	**	.685	.870	.742	.730	-.159	-.304	-.347
CAINS Expression		**	.237	.754	.777	-.091	-.081	-.208
CAINS Experience			**	.480	.448	-.151	-.350	-.322
PANSS Negative				**	.888	-.139	-.237	-.309
PANSS Marder negative					**	-.114	-.204	-.346
# Activities						**	.113	.046
# Friend contacts							**	.263
close friend (Y/N)								**

5.4.3. Relationship between the PANSS negative and the CAINS total subscales

A mean of the proportional values of the CAINS total score and the PANSS negative subscale score, plotted against the difference between these values is presented in figure 9a. The CAINS was found to report negative symptoms at a proportionally higher level, relative to the PANSS negative subscale, as indicated by the dotted line. In addition, this proportionally larger score of the CAINS over the PANSS increased as the average of the CAINS total and PANSS negative subscale values increased (B=0.26, 95% CI 0.16 to 0.35, P<.001. R^2=.101). This relationship, whilst still significant, was found to be slightly weaker in the comparison of the CAINS total and the PANSS Marder negative subscale (B=0.17, 95% CI 0.07 to 0.27, P=.001. R^2=.047), with greater dispersion in the values evident (see figure 9b).

Figure 9a: Relationship between the CAINS total and the the PANSS Negative subscale.

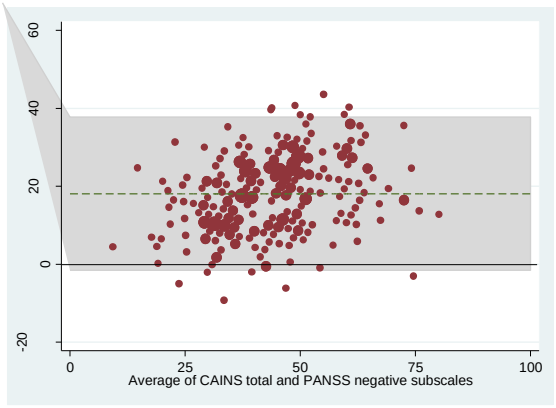
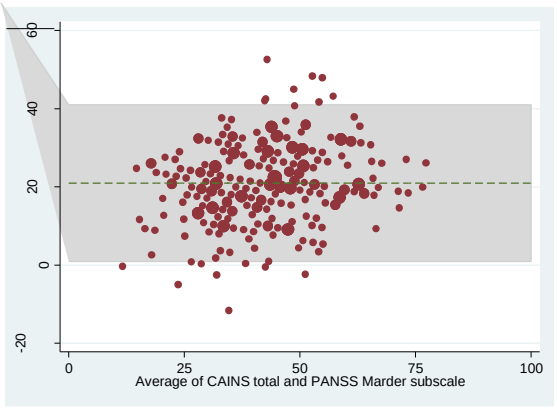


Figure 9b: Relationship between the CAINS total and PANSS Marder Negative subscale.



The x axis denotes the mean score the PANSS negative and CAINS subscale for each participant. The y axis denotes the degree of difference between the CAINS subscale and the PANSS negative subscale. The Solid line denotes where the proportional scale scores are equivalent. Scores below this line indicate that the participant was rated proportionately higher on the PANSS negative subscale in comparison to the CAINS subscale, whilst those higher than the dotted indicate that they scored proportionately higher on the CAINS. The Dotted line denotes the mean difference between the subscales over the sample.

5.4.4. Degree of agreement between the PANSS negative subscale and the CAINS experiential and expressive subscales

In order to assess the level of agreement between each of the CAINS subscales and the PANSS negative subscale, two further Tukey-mean plots were plotted comparing an average of the subscales against the difference between the scores (see figures 10a and 10b). In a similar fashion to the relationship between the CAINS total subscale score and the PANSS negative subscale, the mean difference between the two scales over the whole sample indicate that the CAINS experiential subscale scored participants substantially higher as a proportion of its range, relative to the PANSS negative subscale. In addition, this difference increased as the average of the CAINS total and PANSS negative subscale values increased (B=0.28; 95% CI 0.18 to 0.37, P<.001. R^2=.118).

In figure 10b, which depicts the level of disagreement between the PANSS negative scale and the CAINS expression subscale, large differences between the scales were also evident. However, in contrast with the previous plots, a much clearer systematic difference was evident over the range of severity. When the mean level of negative symptoms between the PANSS negative subscale and the CAINS Expression subscale was low, the CAINS Expression subscale appeared to rate the symptoms as lower. When the mean score from the two scales was high,

the experience subscale proportional score was substantially larger. In the regression analysis a strong positive relationship between the difference in the subscale scores and the mean of the two subscales was evident (B=0.77; 95% CI 0.70 to 0.85, P<.001, R^2=.606). Overall, this suggests that the CAINS expression subscale in particular provides a much greater differentiation between patients that report high and low symptoms, relative to the PANSS negative subscale.

Figure 10a: Relationship between the CAINS experiential subscale and the PANSS negative subscale score

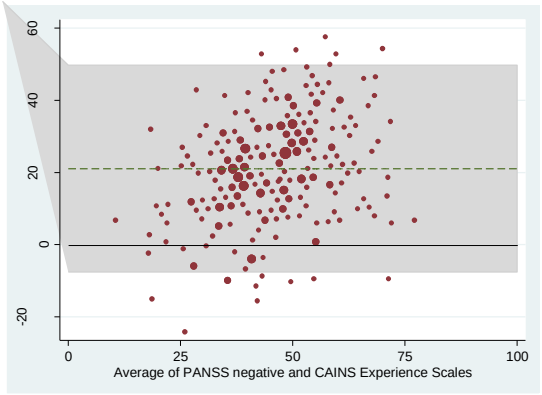
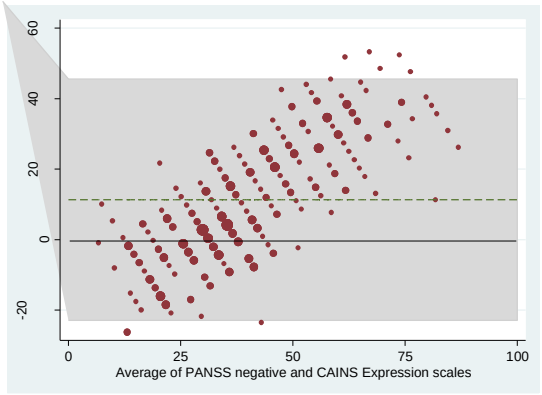


Figure 10b: Relationship between the CAINS expressive subscale and the PANSS negative subscale score



The x axis denotes the mean score the PANSS negative and CAINS subscale for each participant. The y axis denotes the degree of difference between the CAINS subscale and the PANSS negative subscale. The Solid line denotes where the proportional scale scores are equivalent. Scores below this line indicate that the participant was rated proportionately higher on the PANSS negative subscale in comparison to the CAINS subscale, whilst those higher than the dotted indicate that they scored proportionately higher on the CAINS. The Dotted line is the mean difference between the subscales over the sample.

In order to examine whether the differences are attributable to the PANSS negative subscale including items not recognised to be part of the negative symptom construct, the analysis was replicated using the PANSS Marder negative factor configuration (Marder et al., 1997). The relationship between the CAINS expressive and experiential subscales, and the PANSS Marder negative subscale are presented in figures 11a and 11b. In both the expressive and experiential subscales, the relationships detected were found to be highly consistent with the results reported in the PANSS negative symptom subscale analysis. In a comparison of the CAINS experiential subscale and the PANSS Marder negative subscale, the experiential subscale reported participants as having substantially higher negative symptoms as a proportion of its range, relative to the PANSS negative subscale. This difference increased as the average of the CAINS total and PANSS negative subscale values increased (B=0.30, 95% CI 0.16 to 0.45, P<.001. R^2=.061). In the comparison between the CAINS expressive subscale and the PANSS

Marder negative subscale, when the two scales reported negative symptoms in the low range the expressive subscale reported symptoms as lower, and when a mean of the scales reported negative symptoms in the high range the expressive subscale score was again much higher. This relationship was found to explain a large proportion of the variance between the scoring of the two scales (B=0.69, 95% CI 0.61 to 0.77, P<.001, R^2=.544).

Figure 11a: Relationship between the CAINS experiential subscale and the PANSS Marder negative subscale score

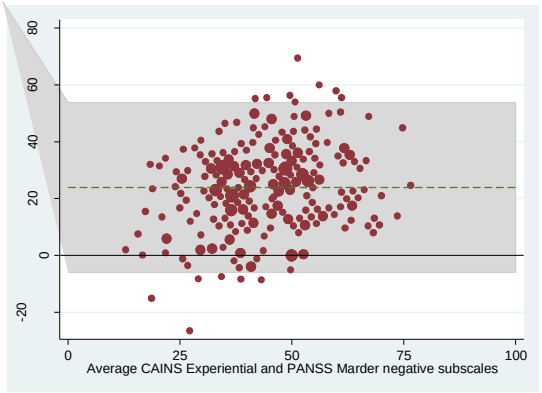
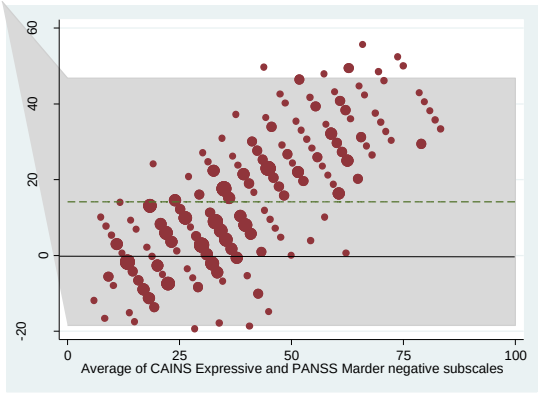


Figure 11b: Relationship between the CAINS expressive subscale and the PANSS Marder negative subscale score



The x axis denotes the mean score the PANSS negative and CAINS subscale for each participant. The y axis denotes the degree of difference between the CAINS subscale and the PANSS negative subscale. The Solid line denotes where the proportional scale scores are equivalent. Scores below this line indicate that the participant was rated proportionately higher on the PANSS negative subscale in comparison to the CAINS subscale, whilst those higher than the dotted indicate that they scored proportionately higher on the CAINS. The Dotted line is the mean difference between the subscales over the sample.

5.4.5. A comparison of the change scores in the PANSS negative and the CAINS total score over time

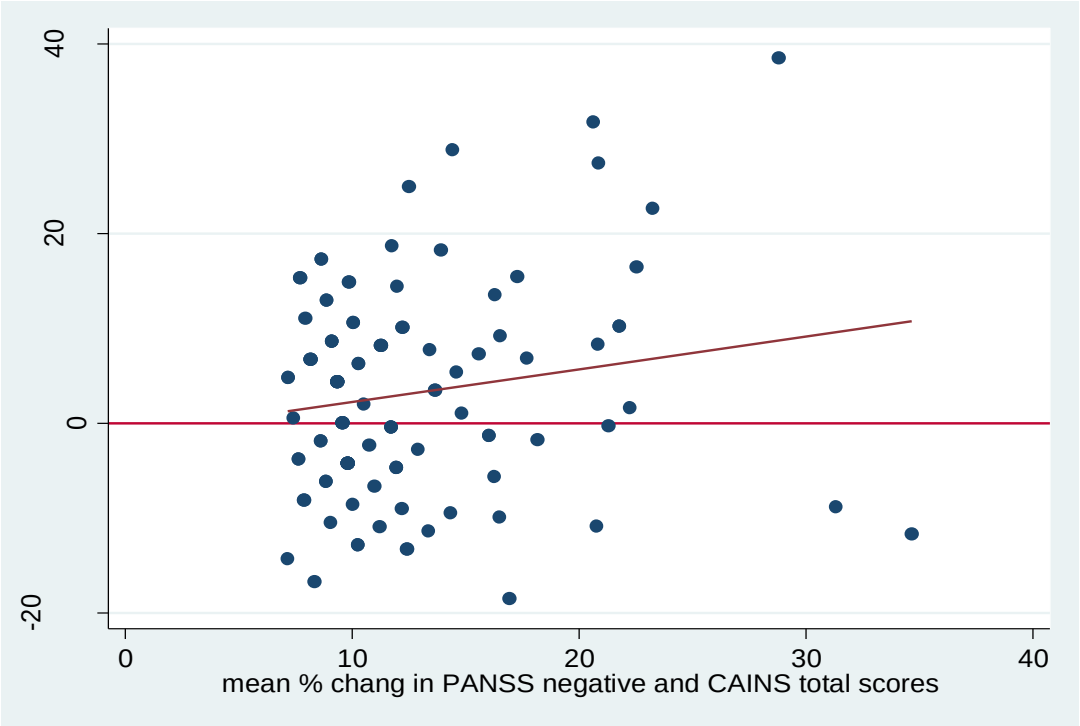
In the next part of the analysis, a comparison of the change over time assessed using the CAINS and the PANSS was compared. Meaningful change of negative symptoms was determined as a mean change of at least ±7.14% in the CAINS and PANSS subscale analysed, which corresponds to a change of 3 points in the PANSS negative subscale. In a sensitivity analysis, subsamples of participants who reported an equivalent mean change of at least 2 points (mean proportional change of ≥±4.76%) and 4 points (mean proportional change of ≥±9.52%) in the PANSS negative subscale over both scales were also examined. In addition to the CAINS total score and the PANSS negative subscale being compared, the analysis was extended to include the subscales of the CAINS, and the PANSS Marder negative symptom configuration.

5.4.5.1. A comparison of the PANSS negative subscale standard configuration and the CAINS total score

Of the 241 participants who had complete data for both the CAINS total and PANSS negative subscale, 109 reported a reported a mean change of at least ±7.14%. Of these, 106 (97.2%) reported the change as occurring in the same direction in both scales and so were therefore eligible for analysis.

A comparison of the degree of change over time in the PANSS negative subscale and the CAINS total score using a mean change of ≥±7.14% as an indicator of clinically meaningful change is presented in figure 12. The scatterplot suggests that as the mean change in symptom scores in the PANSS negative and CAINS total score increased, a greater magnitude of change in the CAINS was reported relative to the PANSS negative subscale. However, in a regression analysis this relationship was not found to be statistically significant (B= 0.34, 95% CI -0.04 to 0.74, P=0.081), instead only suggesting evidence of a possible weak effect.

Figure 12. Relationship between the CAINS total and PANSS subscale change scores using a ±7.14% mean difference over time as an indicator of change



The 'x' axis denotes the mean % change in both the PANSS negative and CAINS total score over 6 months. The 'y' axis denotes the degree in which the % change was larger in the CAINS subscale (>.0), or the PANSS negative subscale (<.0).

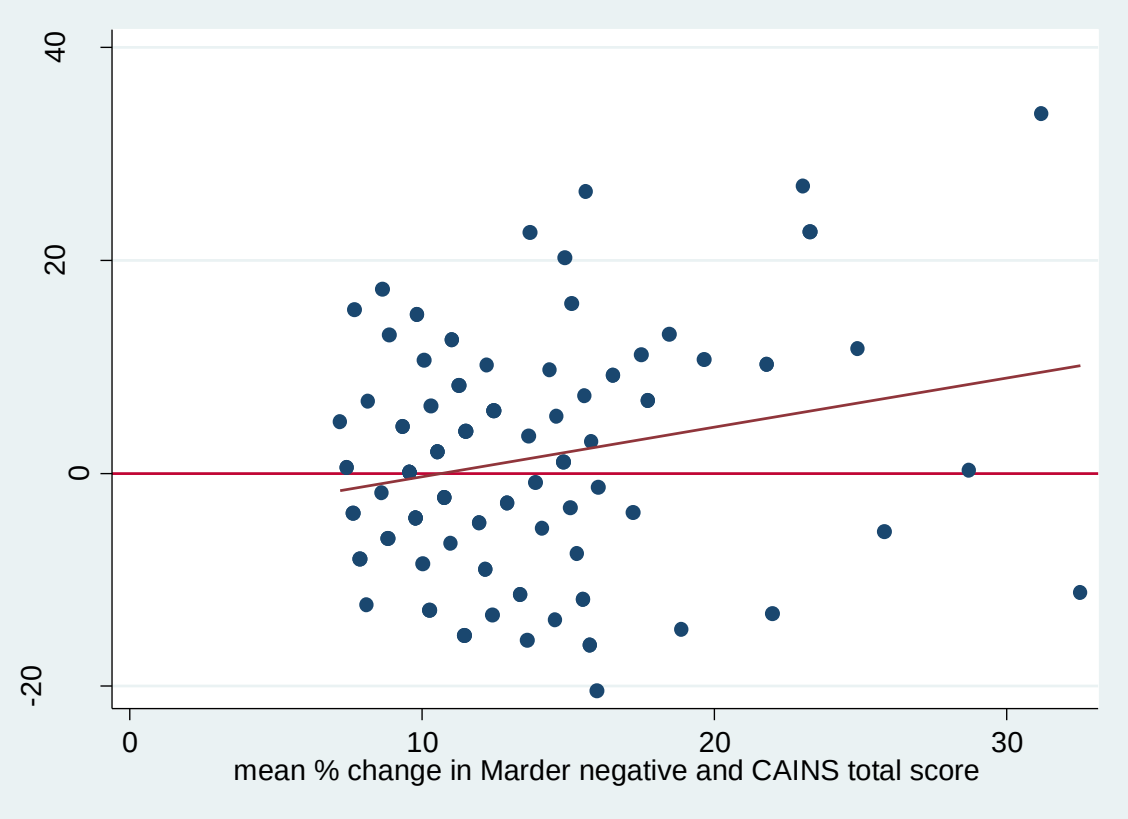
In the sensitivity analysis, a comparison of the change over time in the PANSS negative and CAINS total scores was completed in participants that reported a ≥±4.76% mean change, and a ≥±9.52% mean change in negative symptom scores respectively. In both cases the findings were highly consistent with the original ±7.14% threshold, suggesting that as the magnitude of change measured in the PANSS negative subscale and the CAINS increases, the more the CAINS changes relative to the PANSS. In the sample obtained through adopting a change of at least ±4.76% to determine a clinically significant change, this relationship was found to be significant (B= 0.37, 95% CI 0.06 to 0.68, P=.020). In the sample obtained through adopting a change of at least ±9.52% to determine a clinically significant change, the relationship was not found to be statistically significant (B= 0.47, 95% CI -0.03 to 0.96, P=.063), instead suggesting evidence of a weak effect.

5.4.5.2. A comparison of the PANSS Marder negative subscale standard configuration and the CAINS total score

The analysis completed in section 5.4.5.1. was replicated using the PANSS Marder negative subscale in place of the standard PANSS negative factor configuration. Complete data was available for 241 participants, of which 108 reported a mean change of at least ±7.14% in the CAINS total and PANSS Marder negative subscale scores. Of this subsample, 105 participants (97.2%) reported a change in the same direction in the both the CAINS total and PANSS Marder negative subscale and so were included in the analysis.

The comparison of the degree of change over time in the PANSS Marder negative subscale and the CAINS total score is presented in figure 13. The magnitude of change in the CAINS total score was found to significantly increase as mean change in both the PANSS Marder negative subscale and CAINS total score increased (B=0.46, 95% CI 0.06 to 0.85, P=.020). In the sensitivity analysis, a comparison of the change over time in the PANSS Marder negative subscale and CAINS was completed in participants that reported a mean change of least ±4.76%, and ±9.52%. In both cases the magnitude of change in the CAINS total score over the PANSS Marder negative subscale score was found to significantly increase as the mean change in both increased (≥±4.76% subsample: B= 0.32, 95% CI 0.03 to 0.63, P=.034; ≥±9.52% subsample: B= 0.57, 95% CI 0.11 to 1.03, P=.016)

Figure 13. Relationship between the CAINS total and PANSS Marder negative subscale change scores using a ±7.14% mean difference over time threshold as an indicator of change



The 'x' axis denotes the mean % change in both the PANSS negative and CAINS total score over 6 months. The 'y' axis denotes the degree in which the % change was larger in the CAINS subscale (>.0), or the PANSS negative subscale (<.0).

5.4.6. A comparison of the PANSS negative subscales and the CAINS experiential and expressive subscales over time

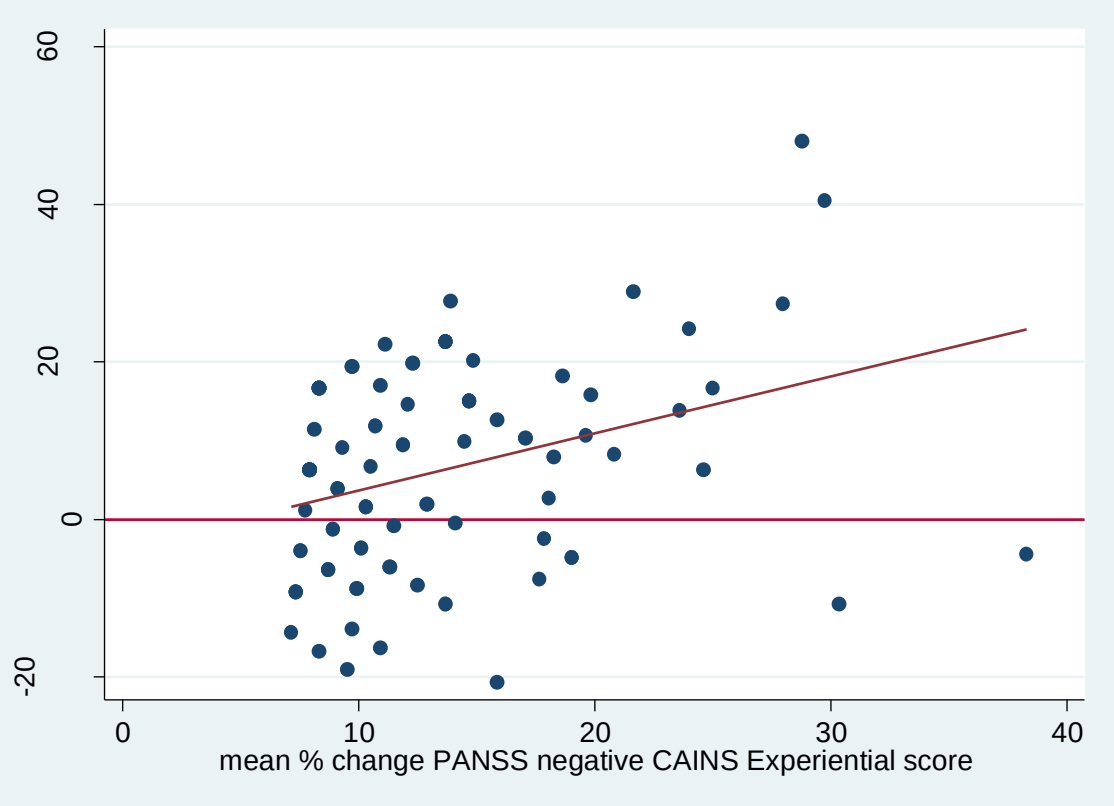
Following the comparison of the PANSS negative and PANSS Marder negative subscales to the CAINS total scores, the relationship between the PANSS negative subscale and the CAINS expressive and experiential subscales were also examined.

5.3.6.1. Comparison of the CAINS Experiential and the PANSS negative subscales

Of the 242 participants who had complete data at both time points for the CAINS experiential and PANSS negative subscale, 103 reported a reported a mean change in symptoms of at least ±7.14%. Of these, 95 (92.2%) were eligible for analysis. A comparison of the degree of change

over time in the CAINS experiential subscale and the PANSS negative subscale is presented in figure 14. The magnitude of change in the CAINS experiential subscale over the PANSS negative subscale was found to significantly increase as the overall mean change score increased (B= .71, 95% CI 0.32 to 1.11, P<.001). This significant increase was also found to be consistent when clinically meaningful change was set at ≥±4.76% and ≥±9.52% respectively (≥±4.76% criteria: B=0 .64, 95% CI 0.32 to 0.95, P<.001; ≥±9.52% criteria B= 0.62, 95% CI 0.08 to 1.16, P=.024).

Figure 14. Relationship between the CAINS experiential and PANSS negative subscale change scores using a ±7.14% mean difference over time as an indicator of change

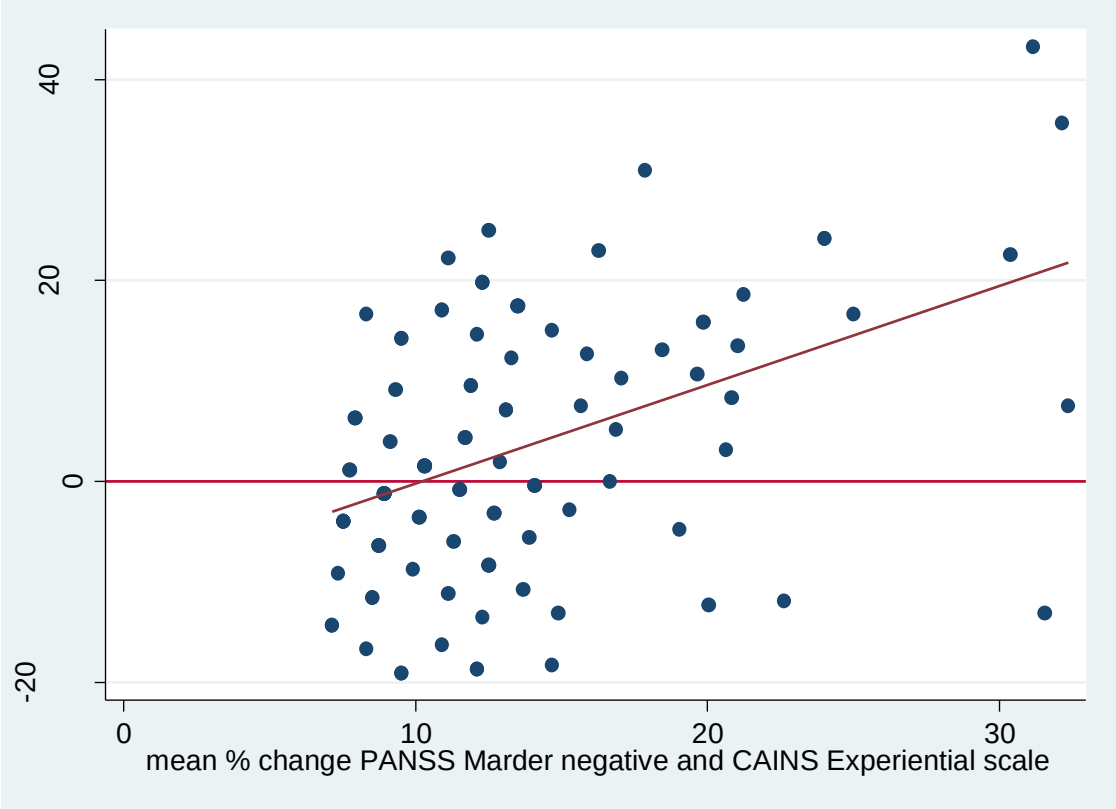


The 'x' axis denotes the mean % change in both the PANSS and CAINS subscales over 6 months. The 'y' axis denotes the degree in which the % change was larger in the CAINS subscale (>.0), or the PANSS negative subscale (<.0).

In a comparison between of the degree of change over time in the CAINS experiential subscale and the PANSS Marder negative subscale, data was available for 242 participants. Of 113 participants that reported a mean change of at least ±7.14% in the two subscales, 101 (89.4%) were eligible for analysis.

A comparison of the degree of change over time in the CAINS experiential subscale and the PANSS Marder negative subscale is presented in figure 18. The magnitude change in the CAINS experiential subscale over the PANSS Marder negative subscale was found to significantly increase as the mean change in both subscales increased (B=0.98, 95% 0.59 to 1.37, P<.001). This was found to be consistent in the sensitivity analysis where clinically meaningful change was set at ≥±4.76% and ≥±9.52% (≥±4.76% criteria: B=0.75, 95% 0.44 to 1.06, P<.001; ≥±9.52% criteria: B=0.91, 95% 0.41 to 1.41, P<.001)

Figure 15. Relationship between the CAINS experiential and PANSS Marder negative subscale change scores using a ±7.14% mean difference over time as an indicator of change



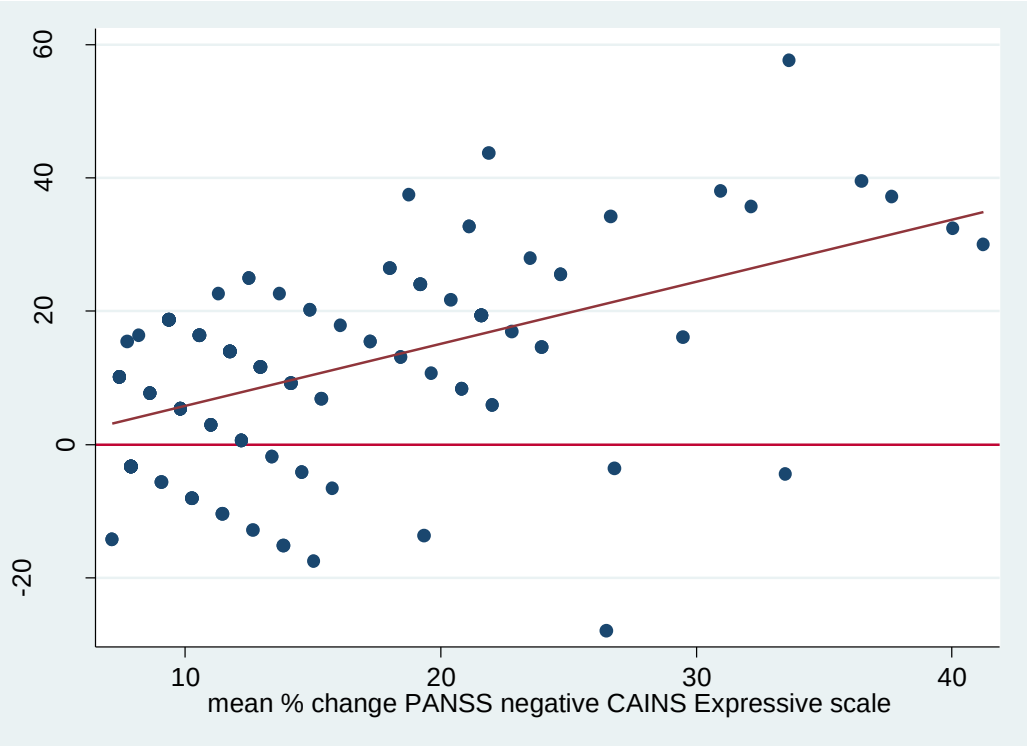
The 'x' axis denotes the mean % change in both the PANSS and CAINS subscales over 6 months. The 'y' axis denotes the degree in which the % change was larger in the CAINS subscale (>.0), or the PANSS negative subscale (<.0).

5.3.6.2. Comparison of the CAINS Expressive and the PANSS negative subscales

Of the 247 participants who had complete data for both the CAINS expressive and PANSS negative subscale, 131 reported a reported a mean change of at least ±7.14%. Of these, 128 (97.7%) were eligible for analysis.

A comparison of the degree of change over time in the CAINS expressive subscale and the PANSS negative subscale is presented in figure 16. The magnitude of change in the CAINS expressive subscale over the PANSS negative subscale was found to significantly increase as the mean change in both scales increased (B= 0.94, 95% CI 0.66 to 1.21, P<.001). This increase was found to be consistent in the sensitivity analysis comparing the magnitude of change in subsamples which defined a clinically meaningful change at ≥±4.76% and ≥±9.52% respectively (≥±4.76% criteria: B=0 .88, 95% CI 0.66 to 1.11, P<.001; ≥±9.52% criteria: B= 1.03, 95% CI 0.68 to 1.37, P<.001).

Figure 16. Relationship between the CAINS expressive and PANSS negative subscale change scores using a ±7.14% mean difference over time as an indicator of change

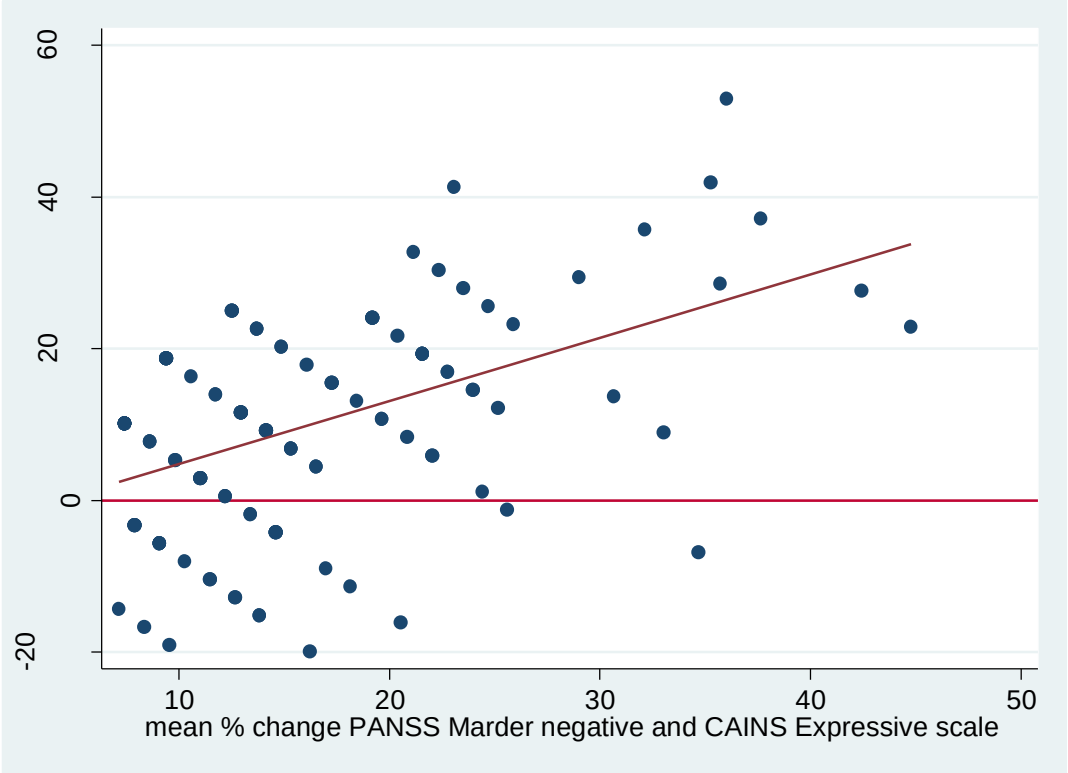


The 'x' axis denotes the mean % change in both the PANSS and CAINS subscales over 6 months. The 'y' axis denotes the degree in which the % change was larger in the CAINS subscale (>.0), or the PANSS negative subscale (<.0).

In a comparison between of the degree of change over time in the CAINS expressive subscale and the PANSS Marder negative subscale, complete data was available for 248 participants. One hundred and thirty one participants reported a mean change of symptoms of at least ±7.14%, of which 129 (98.4%) were eligible.

A comparison of the degree of change over time in the CAINS expressive subscale and the PANSS Marder negative subscale is presented in figure 17. The change in the CAINS expressive subscale over the PANSS Marder negative subscale was found to significantly increase as the mean change in both subscales increased (B=0.83, 95% CI 0.57 to 1.09, P<.001). This was found to be consistent in the sensitivity analysis comparing the magnitude of change in subsamples which defined a clinically meaningful change at >±4.76% and >±9.52% (B=0.91, 95% 0.69 to 1.11, P<.001; B=0.96, 95% 0.64 to 1.29, P<.001).

Figure 17. Relationship between the CAINS expressive and PANSS Marder negative subscale change scores using a ±7.14% mean difference over time as an indicator of change



The 'x' axis denotes the mean % change in both the PANSS and CAINS subscales over 6 months. The 'y' axis denotes the degree in which the % change was larger in the CAINS subscale (>.0), or the PANSS negative subscale (<.0).

5.4.7. An assessment of the incremental validity of the CAINS over the PANSS negative subscales

In the final part of this investigation the incremental validity of the CAINS over the PANSS negative subscale in three indicators of social impoverishment was examined. These include the number of activities participants reported taking part in over the previous week, whether they could identify somebody they considered to be a close friend, and the number of friends they have been in contact with over the past week. Univariate regression analyses examining the associations between these indicators and the CAINS total and experiential and expressive subscales, the PANSS negative standard configuration, and alternative PANSS negative Marder factor loading are presented in table 31. In all 5 forms of negative symptom assessment a significant negative association was detected with all three outcomes. In the outcome "how many activities did you take part in over the past week" the CAINS expressive subscale was found to explain the smallest proportion of the variance (B=-0.18, 95% CI -0.23 to -0.12, P<.001; R^2=.014), and CAINS total score the largest (B=-0.43, 95% CI -0.52 to -0.35, P<.001; R^2=.032). Regarding whether participants report having a close friend, the CAINS expressive subscale again explained the lowest proportion of the variance (B=-0.47, 95% CI -0.74 to -0.20, P<.001; R^2=.036) and the CAINS total scale the highest (B=-1.45, 95% CI -1.96 to -0.93, P<.001; R^2=.108). In the last outcome, assessing the number of activities participants reported taking part in over the past week, the CAINS expressive subscale again explained the smallest degree of variance (B=-0.15, 95% CI -0.27 to -0.04, P<.010; R^2=.007), and the CAINS experiential subscale the highest (B=-0.90, 95% CI -1.07 to -0.74, P<.001; R^2=.118).

Table 31: Univariate analysis of the association between assessments of negative symptoms and indicators of social impoverishment

Predictor variables	Univariate analysis				
	B	95% CI		*P*	R^a
How many activities did you take part in last week?					
CAINS Expression	-0.18	-0.23	-0.12	<.001	.014
CAINS Experience	-0.35	-0.43	-0.28	<.001	.026
CAINS total score	-0.43	-0.52	-0.35	<.001	.032
PANSS Negative	-0.05	-0.06	-0.04	<.001	.027
PANSS Marder negative	-0.04	-0.05	-0.03	<.001	.019
Do you have a close Friend?					
CAINS Expression	-0.47	-0.74	-0.20	.001	.036
CAINS Experience	-1.28	-1.77	-0.80	<.001	.096
CAINS total score	-1.45	-1.96	-0.93	<.001	.108
PANSS Negative	-0.15	-0.20	-0.09	<.001	.083
PANSS Marder negative	-0.15	-0.21	-0.10	<.001	.103
Number of reported friend contacts in past week					
CAINS Expression	-0.15	-0.27	-0.04	.010	.007
CAINS Experience	-0.90	-1.07	-0.74	<.001	.118
CAINS total score	-0.90	-1.09	-0.71	<.001	.091
PANSS Negative	-0.09	-0.11	-0.06	<.001	.062
PANSS Marder negative	-0.07	-0.09	-0.04	<.001	.046

The pseudo R^2 was calculated using logistic or poisson regression depending upon whether the independent variable was count or dichotomous in nature.

5.4.7.1. Incremental validity using the whole CAINS score

The dominance analysis comparing the CAINS total score and the PANSS negative subscale is presented in table 32. Overall, the CAINS total subscale score was found to dominate the PANSS negative subscale in all three cases. Both scales were found to be a weak predictor of the number of activities participants took part in over the past week (R^2_M = .033). Of this association, only a negligible amount of unique variance was explained by the PANSS negative subscale (R^2 =.001), relative to the CAINS total score (R^2 =.009). The CAINS total subscale was found to completely dominate, albeit with a relatively low degree of reproducibility (.627).

Relative to the number of activities undertaken, the CAINS total and PANSS negative subscale was found to be a stronger predictor of whether they report having a close friend (R^2_M = .114). Whilst the majority of this association was shared (R^2 =.081), the CAINS total score explained a

larger degree of unique variance in comparison to the PANSS negative subscale (R^2 =.026, in comparison to R^2 =.007). The CAINS total subscale was found to completely dominate with a moderately degree of reproducibility (.740).

In the number of reported friend contacts, the CAINS total and PANSS negative subscale explained a moderate proportion of the variance (R^2_M = .092). Of this variance, a relatively large proportion was explained uniquely by the CAINS total score (R^2 =.031), whilst only a negligible amount was determined uniquely by the PANSS negative subscale (R^2 =.001). In the bootstrapped estimates the CAINS was found to dominate with a very high degree of consistency (.923).

Table 32: Dominance Analysis comparing the PANSS negative subscale and CAINS total score as predictors of indicators of social impoverishment

	No. additional variables in existing model		Dominance weight	Standardised weight	Rank	Bootstrapped reproducibility of complete dominance	
	0	1				CAINS total	PANSS Negative
How many activities did you take part in last week?							
X_1 CAINS total	.032	.009	.020	.615	1[a]	-	.627
X_2 PANSS Negative	.024	.001	.013	.385	2	.373	-
Overall fit R^2_M = .033							
Do you have a close Friend?							
X_1 CAINS total	.108	.026	.067	.586	1[a]	-	.740
X_2 PANSS Negative	.088	.007	.047	.414	2	.260	-
Overall fit R^2_M = .114							
Number of reported friend contacts in past week							
X_1 CAINS total	.091	.031	.061	.661	1[a]	-	.923
X_2 PANSS Negative	.061	.001	.031	.339	2	.077	-
Overall fit R^2_M = .092							

[a] Variable completely dominated all other predictors in the full model

The dominance analysis of the PANSS Marder negative subscale and the CAINS total score is presented in table 33. In how many activities participants completed in the past week, the CAINS total score was found to explain a substantially larger proportion of unique variance relative to the PANSS Marder negative subscale (R^2 =.015, in comparison to R^2 =<.001), and be completely dominant to a moderately high degree of reproducibility (.808). In the number of

friends contacts reported over the past week, the proportion of unique variance explained by the CAINS total score was even higher (R^2=.047, in comparison to R^2=<.001), and was completely dominant in a large proportion of the bootstrapped samples (.961). In whether participants report having a close friend, the CAINS total and PANSS Marder negative subscale together explained a moderate proportion of the variance (R^2_M = .125), with both scales explaining an equal proportion of the unique variance (R^2= .017). However, the PANSS Marder negative subscale was found to marginally dominate the CAINS total score (standardised weight=.502, to .498), which was found to reproduced in 62.7% of bootstrapped samples

Table 33: Dominance Analysis comparing the PANSS Marder negative subscale and CAINS total score as predictors of indicators of social impoverishment

	No. variables in existing model		Dominance weight	Standardised weight	Rank	Bootstrapped reproducibility of complete dominance	
	0	1				CAINS total	PANSS Marder
How many activities did you take part in last week?							
X_1 CAINS total	.032	.015	.023	.728	1[a]	-	.808
X_2 PANSS Marder	.017	<.001	.009	.272	2	.192	-
Overall fit R^2_M = .032							
Do you have a close Friend?							
X_1 CAINS total	.108	.017	.062	.499	2	-	.627
X_2 PANSS Marder	.108	.017	.063	.502	1[a]	.373	-
Overall fit R^2_M = .125							
Number of reported friend contacts in past week							
X_1 CAINS total	.091	.047	.069	.760	1[a]	-	.961
X_2 PANSS Marder	.043	>.001	.022	.240	2	.039	-
Overall fit R^2_M = .091							

[a] Variable completely dominated all other predictors in the full model

5.4.7.2. Incremental validity using the CAINS experience and expression subscales

The dominance analysis of the separate CAINS subscales and the PANSS negative subscale is presented in table 34. In all three cases, the CAINS experiential subscale was found to dominate the other two subscales, with the CAINS expressive subscale explaining the smallest proportion of the variance.

In a measure of how many activities participants took part in over the past week, the three subscales together were only able to explain a relatively small proportion of the variance (R^2_M = .034). The largest proportion of the variance was explained by the CAINS experiential subscale (standardised weight .492), with both the CAINS expression subscale (R^2 <.001), and the PANSS negative subscale (R^2 =.002) accounting for only a very small proportion of unique variance. In the bootstrapped estimates, the complete dominance of the CAINS experiential subscale completely dominated the CAINS expressive subscale in 76.5% of cases, and the PANSS negative subscale in 56.9% of cases. In whether participants report having a close friend, a moderate proportion of the total variance was explained by the three subscales (R^2_M = .126). The CAINS experiential subscale explained both the largest degree of variance (standardised weight .497), and largest proportion of unique variance (R^2=.035). The CAINS experiential subscale was found to completely dominate the CAINS expressive subscale to a high degree of reproducibility (.980), and the PANSS negative subscale to a moderate degree (.657). In the number of friend contacts participants report having over the past week, the three subscales explained a moderate degree of variance (R^2_M = .134). The CAINS experiential subscale explained the largest degree of variance (standardised weight .630), including unique variance (R^2=.049). The experiential subscale was found to dominate the CAINS expressive subscale to a high degree of reproducibility (.951), and the PANSS negative subscale to a moderate degree of reproducibility (.725).

Table 34: Dominance Analysis comparing the PANSS negative and CAINS subscales as predictors of indicators of social impoverishment

	No. variables in existing model (K)			Dom weight	Std. weight	Rank	Bootstrapped reproducibility of complete dominance		
	0	1	2				CAINS Express.	CAINS Exper.	PANSS Neg.
How many activities did you take part in last week? (n=248)									
X_1 C. Expression	.013	.003	<.001	.005	.154	3	-	.235	.216
X_2 C. Experience	.026	.015	.010	.017	.492	1	.765	-	.569
X_3 PANSS Negative	.024	.010	.002	.012	.353	2	.784	.431	-
Overall fit R^2_M = .034									
Do you have a close Friend? (n=254)									
X_1 C. Expression	.035	.009	<.001	.015	.117	3	-	.020	.108
X_2 C. Experience	.096	.057	.035	.063	.497	1[a]	.980	-	.657
X_3 PANSS Negative	.088	.043	.015	.049	.386	2	.892	0.343	-
Overall fit R^2_M = .126									
Number of reported friend contacts in past week (n=255)									
X_1 C. Expression	.006	.012	.010	.009	.068	3	-	.049	.108
X_2 C. Experience	.117	.088	.049	.085	.630	1[a]	.951	-	.725
X_3 PANSS Negative	.061	.044	.017	.041	.302	2	.892	.275	-
Overall fit R^2_M = .134									

[a] Variable completely dominated all other predictors in the full model

The dominance analysis of the CAINS subscales and the PANSS Marder negative subscale is presented in table 35. The CAINS experiential subscale was found to dominate as a predictor of how many activities the participant took part in, and the number of friend contacts they made over the past week, whilst the PANSS Marder subscale was found to dominate as a predictor of whether the participants report having somebody they consider to be a close friend.

Table 35: Dominance Analysis comparing the PANSS Marder negative and CAINS subscales as predictors of indicators of social impoverishment

Additional contribution of	No. additional variables in existing model (K)			Dom. weigh t	Std. weight	Rank	Bootstrapped reproducibility of complete dominance		
	0	1	2				CAINS Express.	CAINS Exper.	PANSS Neg.
How many activities did you take part in last week? (n=248)									
X_1 C. Expression	.013	.003	.002	.006	.179	3	-	.245	.471
X_2 C. Experience	.026	.016	.015	.019	.591	1[a]	.755	-	.657
X_3 PANSS Marder	.017	.005	<.001	.007	.231	2	.529	.343	-
Overall fit R^2_M = .032									
Do you have a close Friend? (n=254)									
X_1 C. Expression	.035	.013	.005	.018	.120	3	-	.069	.000
X_2 C. Experience	.096	.055	.028	.060	.406	2	.931	-	.324
X_3 PANSS Marder	.108	.065	.037	.070	.475	1[a]	1.000	.676	-
Overall fit R^2_M = .147									
Number of reported friend contacts in past week (n=255)									
X_1 C. Expression	.006	.009	.006	.007	.054	3	-	.010	.115
X_2 C. Experience	.117	.095	.066	.093	.729	1[a]	.990	-	.904
X_3 PANSS Marder	.043	.030	.010	.028	.217	2	.885	.096	-
Overall fit R^2_M = .127									

[a] Variable completely dominated all other predictors in the full model

Regarding how many activities the participants took part in over the past week, the three subscales together explained a relatively small proportion of the variance (R^2_M = .032). In a similar manner to the PANSS negative subscale, the PANSS Marder negative subscale explains only a minimal amount of unique variance (R^2<.001). In the bootstrapped estimates the experiential subscale was found to dominate both the CAINS expressive subscale in 75.5% of cases, and the PANSS Marder negative subscale in 65.7% of cases. In whether participants report having a close friend, contrasting with the PANSS negative subscale the PANSS Marder negative subscale was found to dominate the CAINS expressive subscale with a moderate degree of reproducibility in the bootstrapped analysis (.676). Whilst the CAINS expressive subscale was only found to explain a relatively small proportion of unique variance (R^2=.005), both the CAINS experiential and the PANSS Marder negative subscale explained a relatively large proportion of the unique variance (R^2=.028 and R^2=.037 respectively).

5.5. Discussion

5.5.1. Main findings

Overall, the association between the CAINS total score and the PANSS negative subscales was found to be high. When the CAINS experiential and expressive subscales were considered separately, the PANSS negative subscales were found to be strongly associated to the expressive subscale, but only moderately associated to the experiential subscale. This finding was consistent both with the original configuration of the PANSS negative subscale, and the alternative proposed by Marder (Marder et al., 1997) which is considered to be a closer representation of the negative symptom construct (Marder et al., 2011). These results appear to support earlier findings which suggest the PANSS insufficiently tap into the experiential features of negative symptoms (Blanchard et al., 2011).

In a comparison of the sensitivity of the two scales, the CAINS was found to report a greater distinction between participants that reported high and low symptoms, and a larger degree of symptom change as the mean change in both scales increased . This relationship was found to be particularly robust in the comparison between the CAINS expressive subscale and the PANSS negative subscales. In an assessment of incremental validity, the findings suggest that the CAINS total and the CAINS experience subscale in particular is a superior predictor to both the PANSS negative standard and Marder configuration in a range of indicators relating to social impoverishment. However, this relationship was not found to be consistent throughout, with the PANSS Marder negative subscale found to be a superior predictor of whether participants report having a close friend.

5.5.2. Strengths and limitations:

The trial from which this data was obtained was a rigorous, multisite trial with a high degree of inter-rater agreement on the instruments under investigation. The minimal dropout between the two stages assessed means the result is unlikely to have been influenced by a selection bias due to attrition. Despite the fact the methodologies undertaken here have been extensively used in other disciplines, this study appears to be the first to use either dominance analysis or the Bland-Altman plot method to evaluate the properties of this important new scale in relation to the PANSS negative subscales. In addition, whilst the convergent validity of the CAINS with the BPRS and the SANS has been evaluated (Kring et al., 2013), the scale has

not yet been compared to the PANSS despite the instruments extensive use in schizophrenia research (Mortimer, 2007). In the assessment of symptom change sensitivity, the direction and the effect sizes of the relationships detected were broadly consistent over the three different thresholds evaluated, suggesting the results are robust.

One important limitation of the study is the fact that the sample included only outpatients with at least a moderate level of negative symptoms, assessed ten weeks prior to first time point included in this analysis. As a result, it is unclear whether the difference detected between the CAINS and PANSS negative subscales detected here would be consistent during either a period of acute psychotic exacerbation, or in samples where the mean level of negative symptoms are very low. In addition, this study was completed with participants that were diagnosed with schizophrenia only, and so it is not clear whether these findings would extend to patients with other psychotic disorders. Evaluating these outcomes in different populations would be helpful in determining the generalisability of these findings.

Another issue to consider is the fact that the threshold used to determine meaningful negative symptom change at 7.14% is substantially lower than the 25% change proposed following a comparison of PANSS and the CGI (Leucht et al., 2006). As stated previously, this figure was not adopted given the figure corresponds to the PANSS total score, as opposed to the negative subscale specifically. In addition, this 25% change score figure was not linear, with smaller changes required with participants who reported lower symptoms at baseline. From a practical standpoint, adopting a 25% change threshold would have resulted in the vast majority of the sample not being eligible, meaning such an analysis would not be feasible in this dataset. As an example of this, only five participants experienced a >25% in the PANSS negative subscale. In the sensitivity analysis looking at a higher change score threshold (≥±9.5%) slightly larger coefficients were reported, even if the estimates were less stable due to the smaller sample overall. This suggests that the differences between the CAINS and the PANSS negative subscale may be even larger if more stringent change thresholds were adopted.

In the assessment of incremental validity, one limitation to consider is the fact that social impoverishment, determined in this study by social network size, frequency of activity, and the closeness of friendships, may be significantly influenced by environmental factors such as finances, geography, and the behaviour of friends and family. As a result, it is possible that while these findings appear to support the improved incremental validity of the CAINS, this improvement may be attributable to the fact that it is influenced to a greater extent by environmental factors, rather than a better representation of core negative symptom

psychopathology. This argument is supported by the finding that the incremental validity of the CAINS experiential subscale appears to be more prominent in determining social network size and the frequency of activities conducted, which would be more strongly influenced by environmental factors, relative to how close they feel to friends. However, while this is possible, it could be considered somewhat surprising given the development process of the scale. As outlined in the initial CANSAS review (Blanchard et al., 2011), one of the main limitations of earlier scales is the fact that they appear to rely predominantly on observational and behavioural indicators. In response to this, the CAINS was designed to focus more on the experiential features of negative symptoms, rather than relying on observational referents, with the aim of limiting possible environmental effects. This being the case, further work examining the incremental validity of the CAINS over the PANSS negative subscale in alternative areas, including those less influenced by environmental effects, would be informative.

This study suggests that the CAINS may represent an important advance in negative symptom assessment over the PANSS, both in terms of its sensitivity and incremental validity. This is important, given the PANSS is recognised to be one of the most established assessment tools used in schizophrenia research (Mortimer, 2007). However, in the NIMH-MATRICs consensus statement it has been suggested the SANS may be a more sensitive instrument than the PANSS, given multiple items are used to measure single constructs (Kirkpatrick et al., 2006), a conclusion supported by the findings reported in chapter 3. Therefore, while this study supports the use of the CAINS over the PANSS negative subscale in assessing negative symptoms, at present it is not clear whether this improvement in sensitivity and incremental validity also extends to the SANS. A replication of this study using the SANS in place of the PANSS would be important in determining whether the CAINS is a more sensitive instrument than the best of those previously available.

The final limitation is that given there was no effect of treatment in the original trial from which the data was obtained (Priebe et al., 2013a), it was not possible to assess whether the CAINS was a more sensitive instrument to evaluate treatment effects, relative to the PANSS negative subscale. The finding that the CAINS total and subscale scores appears to better differentiate between participants that report high and low symptoms, both cross-sectionally and in terms of clinically meaningful change over time, supports the argument that the CAINS may be a more sensitive instrument. However, it is not clear whether or how this may translate into larger effects sizes in clinical trials.

5.5.4. Summary

In comparison to earlier negative symptom assessment tools such as the PANSS negative subscale and the SANS, the CAINS assessment tool is recognised to represent a much closer conception of the negative symptom construct as it is currently understood (Blanchard et al., 2011). In addition, a recent evaluation of the scale suggest excellent psychometric properties, with high test-retest reliability, good convergent and divergent validity and, with appropriate training, excellent inter-rater reliability (Kring et al., 2013). The current study supports both the incremental validity and the sensitivity of the scale relative to one of the most extensively used scales in negative symptom assessment (the PANSS), adding further weight to the current body of evidence supporting the CAINS as an alternative measure of negative symptoms. In addition, the findings support the conclusion that reporting expressive and experiential subscales separately may yield further insights, given their heterogeneous association to outcomes relating to social impoverishment (Horan et al., 2011). Given the limitation of existing scales have been identified as a major barrier in the development of new treatments for these symptoms (Kirkpatrick et al., 2006), the CAINS may be considered an important advance in the field of schizophrenia research.

Chapter 6. Association between negative symptoms and subjective quality of life

6.1. Introduction

The findings in chapter 5 suggest that the CAINS (Kring et al., 2013) may be a more sensitive instrument to detect changes in negative symptoms, and that examining experiential and expressive deficits as separate constructs may yield new insights in the field. One such area that may benefit from examining negative symptoms in this manner is reviewing the relationship between negative symptoms and quality of life (QOL). For decades there has been a consensus that improving psychopathological symptoms alone should not be deemed a sufficient outcome in schizophrenia (Priebe, 2007). In addition to symptom remission, objective (OQOL) and subjective (SQOL) quality of life domains such as the ability to manage ones needs, maintain satisfying relationships, and participate in productive and enjoyable activities are seen as central to the concept of recovery (Liberman et al., 2002). In order to achieve these aims, understanding the relationship between quality of life and psychopathological symptoms is important.

Quality of life is typically defined to comprise of two separate constructs, including subjective components such as wellbeing and satisfaction with life, and objective components such as daily life functioning and external resources, both material and social (Katschnig, 2000, Lehman et al., 1982, Priebe, 2007). As highlighted in section 1.6, there is a wealth of evidence to suggest there is a strong association between negative symptoms and various aspects of objective quality of life (Ho et al., 1998, Hunter and Barry, 2012, Milev et al., 2005, Whitty et al., 2008), and either a weak or no association with subjective quality of life (Eack and Newhill, 2007, Fitzgerald et al., 2001, Priebe et al., 2011b)

The absence of a strong relationship between negative symptoms and subjective quality of life may appear somewhat surprising given the their impact on functional outcomes. However, only weak-to-moderate associations between objective and subjective indicators of quality of life have been detected in the past (r=.04–.57; Priebe and Fakhoury, 2007). This finding extends to patients who exhibit good insight their illness, suggesting this is not attributable to merely to a lack of awareness (Doyle et al., 1999). One reason for this weak association may be that subjective quality of life appears to be determined by multiple processes, including the comparison between expectations and aspirations, a comparison with others, and adaptation

over time (Priebe, 2007). Given schizophrenia is highly chronic in nature, with functional impairments usually present long before the first psychotic episode (Cornblatt et al., 2007), patients are likely to have had a long time to adapt to their current situation. Regarding comparison with others, patients with schizophrenia have been found to have small friendship networks, with the majority of members being other mental health service users (Harley et al., 2012), who may well have experienced similar disadvantages and impairments. Consequently, whilst the quality of life in these patients may be objectively low, it may not appear so when considered in the context of earlier experiences, or to those they are typically in contact with. However, it may also be possible that the relationship between subjective quality of life and negative symptoms has previously been under-reported due to the manner in which negative symptoms have previously been assessed.

As noted in a review by Blanchard (Blanchard et al., 2011), many of the current assessment tools used to measure negative symptoms such as the BPRS (Overall and Gorham, 1962), the SANS (Andreasen, 1983), and the PANSS (Kay et al., 1987) insufficiently tap into what the interviewees themselves experience, instead relying primarily on behavioural referents. As a result, there is evidence to suggest that these scales appear to relate much more to the expressive features of negative symptoms, rather than to deficits in experience (Horan et al., 2011), which is supported by the findings presented in chapter 5. This being the case, it is perhaps unsurprising that scales which primarily focus on external, behavioural referents of negative symptoms report a much stronger association with external, objective indicators of QOL, in comparison to an individuals subjective experiences. In order to examine the link between negative symptoms and SQOL properly, it is important to utilise an assessment tool which appropriately captures the experiential features of negative symptoms.

With this in mind, the aim of this study is to re-evaluate the link between negative symptoms of schizophrenia and SQOL using the the two subscales of the CAINS which measure expressive and experiential deficits in schizophrenia separately, in addition to the PANSS negative subscale. We tested the hypothesis that the association between negative symptoms and SQOL relate specifically to experiential deficits, as opposed to expressive deficits, both cross sectionally and over time. In addition, we hypothesised that this relationship would maintain after controlling for depressive symptoms. Controlling for depression is important, given the associations consistently detected between low mood and subjective quality of life (Eack and Newhill, 2007, Priebe et al., 2011b)

6.2. Research questions

1) What is the cross-sectional association between experiential and expressive deficits and subjective quality of life, and how does this compare to an assessment of negative symptoms as a single construct using the PANSS negative subscale?

2) What is the association in changes over time between experiential and expressive deficits and subjective quality of life, and how does this compare to an assessment of negative symptoms as a single construct using the PANSS subscale?

6.3. Method

6.3.1. Sample

The data used in this analysis was taken from the NESS Study (Priebe et al., 2013a), which is a multisite randomised controlled trial designed to evaluate the effectiveness and cost-effectiveness of body psychotherapy as a treatment for schizophrenia. All participants were community outpatients diagnosed with schizophrenia (F20.0-F20.9). The inclusion criteria for the study included displaying negative symptoms for a period of at least six months, not changing the type of antipsychotic medication six weeks prior the baseline assessment, and an ability and willingness to take part in a physically active group. In addition, all participants were required to present with at least moderate levels of negative symptoms at the baseline assessment stage, defined by a score of at least 18 on the PANSS negative subscale (Kay et al., 1987). Further details regarding the procedures, inclusion and exclusion criteria are described elsewhere (Priebe et al., 2013a).

6.3.2. Assessment tools

Assessments were conducted at three timepoints; baseline, end of treatment 10 weeks later, and then at six months follow-up. At each stage the CAINS (Horan et al., 2011), the PANSS (Kay et al., 1987), the Manchester Short Assessment of Quality of Life scale (MANSA) (Priebe et al., 1999), and the Calgary depression scale (Addington et al., 1993) were completed.

The CAINS (Horan et al., 2011) is a scale designed to address the conceptual and methodological limitations of earlier negative symptom assessment tools (Blanchard et al.,

2011). Although the scale can provide a single summary score, the authors recommend reporting the emotional experience and expression subscales seperately given the evidence that they are measure distinct constructs (Kring et al., 2013). The PANSS (Kay et al., 1987) is a 30-item semi-structured interview designed to provide an overall measure of the symptoms of schizophrenia. In this study, the Marder factor solution of the PANSS negative subscale was adopted (Marder et al., 1997). This subscale excludes the abstract thinking and stereotypical items from the negative subscale given they are understood to relate more to cognitive defecits (Bryson et al., 1999), and are replaced by the active social withdrawal and motor retardation items.

Subjective quality of life was measured by the MANSA (Priebe et al., 1999). The questionnaire consists of 16 items; 12 subjective and 4 objective. The 12 subjective items are rated on a 1-7 scale, and cover self-rated satisfaction regarding employment, finances, recreational activities, friendships, safety, housing, health, sex-life, family and overall life satisfaction. The 4 objective items are rated as yes or no, and cover whether they have been a victim of a crime, been accused of crime, have anyone they consider a close friend, or have seen a friend in the past 7 days. In this analysis, a mean total of the 12 subjective items were calculated to create a summary score. In cases where more than 1 item was not completed, the summary score was not included in the analysis.

Given the substantial overlap between low mood and a reduced subjective quality of life, it has been recommended that any investigation of subjective indicators of social outcomes be controlled for mood as a potential confounder (Priebe, 2007). This being the case, depressive symptoms were assessed using the Calgary depression scale (Addington et al., 1993), which a scale designed to measure such symptoms specifically in schizophrenia populations. The questionnaire comprises of 9 items, rated from 0-2, with a higher score indicating more severe depressive symptoms.

6.3.3. Analysis

In the first part of the analysis the association between SQOL and expressive deficits, experiential deficits, depressive symptoms, and a summary of the overall negative symptom construct was examined cross-sectionally using univariate regression analysis. Any predictors approaching significance ($p<.10$) were then included in a multivariate regression model. In order to test the robustness of any associations detected, this part of the analysis was

replicated using both the end of treatment and six month follow up data in a sensitivity analysis.

In the second part of the analysis, longitudinal modelling was used to explore the association between the change in negative symptoms and SQOL over time. Symptom change-scores were calculated by subtracting the follow-up stage assessment scores (T3) from the end of treatment scores (T2), and then the end of treatment scores (T2) from the baseline scores (T1), resulting in two panels of change-score data. The univariate associations between the change scores in SQOL and different measures of negative symptoms were then evaluated by way of multi-level modelling, with each change score (level-1) nested within participants (level-2) included as a random effect. Variables significant in univariate analysis were then analysed in a multivariate model, including the change scores of the Calgary depression scale to control for the association between depression and SQOL. All analysis was conducted using STATA version 11.0 (StataCorp, 2009).

6.4. Results

6.4.1. Description of sample

The participant characteristics are presented in table 36. Participants were mostly male (73.8%) with a relatively long history of illness (mean=13.6 years, SD=9.1). At study intake, participants reported depressive symptoms in the low range (Calgary scale mean=4.70, SD=4.37), and negative symptoms in the moderate range (PANSS Marder negative subscale total score=22.1, SD=4.8). A total of 275 participants completed the baseline assessment and 255 were successfully followed up, resulting in a retention rate of 92.7%. No significant differences were detected between completers and drop-outs at the baseline assessment in either the MANSA, CAINS, or PANSS negative standard or Marder subscale scores. The inter-rater reliability scores between the assessors in both the CAINS and the PANSS was high (PANSS ICC=.850; CAINS total ICC=.802). At all three timepoints the Calgary depression mean score distributions were found to be highly positively skewed, so a square root transformation of the data was performed.

Table 36: socio-demographic details of the sample

Variable	Total N=275.	
Age (mean, SD)	42.2	10.65
Gender (n, %)		
Male	203	73.8%
Female	72	26.2%
Ethnicity (n, %)		
White	142	51.6%
Black	80	29.1%
Asian	30	10.9%
Other	23	8.4%
Employment (n, %)		
Unemployed	263	95.6%
Other	12	4.4%
Living situation (n, %)		
Alone	156	56.7%
With others	119	43.3%
Duration of illness in years (mean, SD)	13.6	9.1
Number hospitalisations (median, IQR)	3	1-5

The mean values of the CAINS subscales, the PANSS Marder negative subscale, the Calgary and the MANSA are presented in table 37. A small significant reduction was detected in the CAINS experience subscale, and the PANSS Marder negative subscale. No signifcant difference was detected in the Calgary scale, the MANSA, or the CAINS expressive subscale.

Table 37: Mean scores and change over time.

Variable	T1		T2		T3		F	P
	Mean	SD	Mean	SD	Mean	SD		
MANSA SQOL	4.44	0.93	4.58	0.89	4.52	0.95	1.51	0.221
PANSS Negative (Marder)	22.07	4.83	20.51	5.43	20.13	5.61	10.07	<.001
CAINS Expression	1.94	0.92	1.85	0.98	1.78	1.04	1.76	0.174
CAINS Experience	2.42	0.62	2.24	0.64	2.29	0.71	4.92	0.008
Calgary Depression scale	4.69	4.36	3.92	4.30	4.11	4.15	2.37	0.094

6.4.2. The association between negative symptoms and subjective quality of life

The associations between negative symptoms and SQOL are reported in table 38. In the cross-sectional analysis at baseline a significant negative association was found between SQOL and the CAINS experiential subscale (B=-0.43, 95% CI=-0.62 to -0.25, R^2=.083). No association was detected between the SQOL and the PANSS Marder negative subscale (B=-.01, 95% CI=-0.04 to 0.01, R^2=.004), or the CAINS expression subscale (B=-0.09, 95% CI=-0.03 to 0.22, R^2=.009). As expected, a strong negative association between depressive symptoms and SQOL was detected (B=-0.10, 95% CI= -0.12 to -0.08, R^2=.220). In the multivariate analysis, a significant negative association was detected between experiential symptoms and SQOL after controlling for depressive symptoms (adj. B= -0.25, 95% CI -0.42 to -0.08).

Table 38: Cross sectional associations between negative symptoms, depression and SQOL at baseline

	Univariate model						Multivariate model				
	B	SE B	95% CI		P	R^2	Adj. B	SE B	95% CI		P
CAINS Experiential	-0.434	0.092	-0.616	-0.252	<.001	.083	-0.254	0.087	-0.425	-0.083	.004
CAINS Expressive	0.093	0.064	-0.033	0.218	.147	.009	-				
PANSS Negative	-0.013	0.012	-0.037	0.012	.306	.004	-				
Calgary Scale	-0.098	0.012	-0.122	-0.075	<.001	.220	-0.090	0.012	-0.114	-0.066	<.001

In the sensitivity analysis, the association between negative symptoms and SQOL are presented in table 39. Overall, the findings were broadly consistent with those reported at the baseline stage. At both the end of treatment and 6 months follow-up, the Calgary depression

scale and the CAINS experiential subscale was found to be negatively associated with SQOL. After controlling for depressive symptoms, an inverse association between SQOL and the CAINS experiential subscale remained significant at 6-months follow-up (adj. B=-0.20, 95% CI=-0.36 to -0.04, P=.014). At the end of treatment stage the relationship between experiential symptoms and SQOL was not found be significant (adj. B=-0.15, 95% CI=-0.32 to 0.01, P=.061), however evidence of a weak effect was detected.

Table 39: Sensitivity analysis exploring the cross sectional associations at end of treatment and 6 months follow up

	Univariate model						Multivariate model				
	B	SE B	95% CI		P	R^2	Adj. B	SE B	95% CI		P
Associations at end of treatment											
CAINS Experiential	-0.314	0.087	-0.486	-0.143	<.001	.053	-0.154	0.082	-0.316	0.007	.061
CAINS Expressive	0.049	0.059	-0.068	0.166	.414	.003	-				
PANSS Negative	-0.018	0.011	-0.040	0.003	.093	.012	-				
Calgary Scale	-0.095	0.012	-0.118	-0.071	<.001	.217	-0.089	0.012	-0.113	-0.065	<.001
Associations at 6 months follow-up											
CAINS Experiential	-0.373	0.086	-0.541	-0.204	<.001	.077	-0.200	0.081	-0.359	-0.042	.014
CAINS Expressive	0.098	0.596	-0.019	0.215	.102	.012	-				
PANSS negative	-0.008	0.011	-0.031	0.014	.452	.002	-				
Calgary Scale	-0.114	0.013	-0.140	-0.087	<.001	.234	-0.103	0.014	-0.131	-0.075	<.001

6.4.3. The association between the changes in negative symptoms and subjective quality of life over time

The association between the change in negative symptoms and SQOL over time are reported in table 40. A negative association was detected between SQOL and experiential symptoms (B=-0.21, 95% CI= -0.34 to -0.09, P=.001), depressive symptoms (B=-04, 95% CI= -0.05 to -0.02, P<.001), and the PANSS Marder negative subscale (B=-02, 95% CI= -0.03 to 0.00, P=.044). No significant association was detected between the changes in expressive symptoms and SQOL. In the multivariate analysis, experiential symptoms, depressive symptoms and the PANSS Marder negative subscale were all included in the model. Significant negative associations between SQOL and depressive symptoms (adj. B=-0.03, 95% CI= -0.05 to -.01, P=014), and

experiential symptoms (adj. B=-0.18, 95% CI= -0.31to -.04, P=.008) were detected, whilst the relationship between the PANSS Marder negative subscale and SQOL was no longer significant (adj. B= 0.00, 95% CI= -0.02 to 0.02, P=.882).

Table 40: Associations between the change in negative symptoms, depression and SQOL over time

	Univariate model						Multivariate model				
	B	SE B	95% CI		P	R^2	Adj. B	SE B	95% CI		P
CAINS Experiential	-0.212	0.063	-0.336	-0.089	.001	.027	-0.175	0.067	-0.306	-0.045	.008
CAINS Expressive	-0.048	0.052	-0.150	-.0533	.352	.002	-				
PANSS negative	-0.016	0.008	-0.321	.000	.044	.009	-0.001	0.009	-0.019	0.016	.882
Calgary Scale	-0.035	0.010	-0.055	-0.015	<.001	.028	-0.026	0.010	-0.046	-0.005	.014

6.5. Discussion

6.5.1. Main findings

These findings suggest that there is a stronger association between SQOL and negative symptoms than has been previously reported (Eack and Newhill, 2007), however this relationship appears to relate specifically to experiential deficits. In the cross-sectional analysis, a significant negative association was detected between subjective quality of life and the experiential deficits in negative symptoms of schizophrenia, which remained significant after controlling for depressive symptoms. In an analysis of the association between negative symptoms and SQOL over time, again only the experiential features of negative symptoms were found to be a significant predictor. These findings suggest that relationship between SQOL and negative symptoms may have previously been under-reported due to a number of assessment tools not adequately assessing experiential deficits, and the way in which negative symptoms have been typically examined as a singular construct.

6.5.2. Strengths and weaknesses

The data came from a large, multi-centre trial with excellent study retention rates (92.7% from baseline to the final follow-up assessment). The inter-rater reliability between the assessors on

both the PANSS and the CAINS was high (PANSS ICC=.85; CAINS ICC=.80). In the sensitivity analysis, the findings were broadly consistent at all three assessment stages. The specificity of the results (i.e. that only the relationship to experiential deficits, and not expressive deficits, was significant) suggest that the effect over time is not a consequence of regression to the mean. Lastly, a significant association was detected between the change scores in expressive symptoms and SQOL, despite only a small reduction in these variables over time, which suggests that the findings are robust.

The main limitation of the study relates to a possible selection bias. The data came from a study evaluating participants which all reported at least moderate levels of negative symptoms at baseline, and were all outpatients at study intake. Consequently, it is not clear whether similar estimates would be present in either acute samples, or in participants with lower negative symptoms at study intake. In addition, the sample is predominantly male, and chronic in nature with an average duration of illness of 13.6 years. This being the case, it is not clear whether the findings are generalisable to females, which may be significant given there is some evidence which suggests that different factors may influence subjective quality different between genders (Röder-Wanner and Priebe, 1998). In addition, evaluating the relationship in samples with a less chronic duration of illness may also be important given SQOL appears to be lower in newly treated patients (Priebe et al., 2000), with evidence to suggest that the impact of symptoms on SQOL appears to be more prominent in the early stages of the illness (Browne et al., 2000).

6.5.4. Conclusion

The link between SQOL and negative symptoms appears to be stronger than what was originally presumed, however this relationship appears to exist almost exclusively with experiential deficits. These findings support the model which suggests that an improvement in symptoms can result in improvements in SQOL, and so have important implications for treatment development. In the future, it may be important to focus on interventions which are effective at ameliorating experiential symptoms if the aim is to improve quality of life as part of a wider programme to support patient recovery. In addition, these findings lend further support for the use of the CAINS over other assessment tools for negative symptoms such as the PANSS, and highlight the importance of assessing the experiential and expressive subdomains of negative symptoms separately.

Chapter 7. The impact of negative symptoms on the subjective initial appraisal of psychiatric inpatient treatment

7.1. Introduction

Following the examination of the link between negative symptoms and subjective quality of life, in this investigation the aim is to extend this to another patient reported outcome, namely the appraisal of treatment. The evidence suggests that patients with schizophrenia who have a more positive initial appraisal of their treatment are likely to benefit more from that treatment eventually. This applies to pharmacological treatment (Awad et al., 1995, Bartkó et al., 1987, Van Putten et al., 1981, Van Putten and May, 1978) and complex interventions (Bröker et al., 1995, Priebe and Gruyters, 1994, Priebe and Gruyters, 1995, Priebe et al., 2010a). In inpatients, a more positive initial appraisal of treatment was associated with lower symptom levels after one month (Richardson et al., 2011a), at discharge (Bröker et al., 1995), lower social impairment at 3 and 12 months (Priebe et al., 2011a), and lower subsequent involuntary readmission rates (Priebe et al., 2009). Developing a greater understanding of the factors which influence how patients appraise their hospital treatment in the initial stages would help identify those at risk of being less satisfied with their treatment, and could assist in the development of new interventions to maximise patients' initial appraisal of treatment.

Factors which may significantly impact the initial appraisal of inpatient treatment are the symptoms that patients experience at the point of admission. Regarding how symptoms may impact the initial appraisal of treatment, a number of different theories could be considered. One argument is that subjective initial appraisal may be inversely related with mood, given the consistent association detected between depressive symptoms and other patient reported outcomes (Fakhoury et al., 2002, Priebe et al., 1998). However, an alternative argument could be that appraisal of inpatient treatment is closely related to insight, which has been found to be positively associated with positive and negative symptoms, and inversely associated with depressive symptoms (Mintz et al., 2003). This may be significant, as lower insight has been found to be associated with a less positive attitude to treatment such as the medication prescribed (Freudenreich et al., 2004). In an examination of the temporal ordering of symptoms and inpatient treatment satisfaction (Richardson et al., 2011a) inverse correlations were detected between initial appraisal of treatment and positive, manic, and depressive-anxiety symptoms. However, these relationships were not considered in a multivariate model,

so it is unclear whether this association reflects a specific action to that symptom domain, or represents a shared association with other symptom types.

Whilst any links between symptoms and subjective initial response (SIR) may not yet be clear, the association between the appraisal of treatment and the legal status of the hospital admission is a lot more established. In a review comparing involuntary and voluntary hospital treatments, involuntary patients were found to be more dissatisfied with treatment, and were more likely to report that the hospitalisation was not justified (Greenwood et al., 1999, Kallert et al., 2007). This difference does not appear to be attributable to more severe psychopathology, given only minimal differences in the presentation of symptoms have been found at the point of admission (Kallert et al., 2008). However, while the severity of symptoms may be similar between voluntary and involuntary symptoms, their impact on the appraisal of treatment may not be. Experiencing positive symptoms such as paranoid delusions and manic symptoms such as agitation may be more difficult when there is a greater restriction in autonomy. Patients with negative symptoms who experience severe apathy and social withdrawal may struggle with being placed in a busy ward against their will. Consequently, in the analysis the impact of symptoms will be compared between those who are admitted voluntarily and involuntarily.

During an acute episode when schizophrenia patients would typically be admitted, positive symptoms can often dominate the picture, masking other features of the disorder such as negative symptoms (Möller, 2007). In addition, the severity of symptoms experienced is likely to be temporary in nature as symptoms are controlled with drug treatment. Consequently, implementing the inclusion criteria to determine either persistent negative symptoms (Buchanan, 2007) or disentangling primary and secondary symptoms (Carpenter et al., 1985) is highly challenging in newly admitted patients. However, given the aim of this investigation is to examine the impact of symptoms over a very short period (i.e. the point of admission) determining antecedents of negative symptoms may not be of primary importance in this context, whilst conducting multivariate analysis can control for the impact of other symptoms. As a result, no attempt at a distinction between primary and secondary negative symptoms will be made.

In this study the aim is to identify what types of symptoms are associated with the initial appraisal of hospital treatment in patients with schizophrenia, after adjusting for the influence of socio-demographic and other clinical characteristics given their impact on patient reported outcomes.

7.2. Research questions

1) What is the association between negative symptoms and initial appraisal of inpatient treatment, and how does this compare to other symptoms of schizophrenia?
2) Is the association between symptoms and initial appraisal of treatment different in those that were voluntarily and involuntarily admitted?

7.3. Methods

7.3.1. Design

This investigation is an exploratory, cross-sectional study examining the association between symptoms and the initial appraisal of inpatient treatment, after controlling for other sociodemographic and clinical variables. All the assessments took place within the first week following the admission, and were conducted by a researcher not involved in the patients' treatment. The diagnosis was obtained from the participants' medical notes at the point of discharge.

7.3.2. Sample

The current sample was obtained from pooling data from three studies. The InvolvE study (Priebe et al., 2009) assessed characteristics and experiences of in-patients in 22 hospitals across England. The EUNOMIA study (Kallert et al., 2005, Priebe et al., 2010a) was a related study with a similar design conducted at sites in 11 European countries. Both studies had a focus on involuntarily admitted patients, but also included voluntary patients who felt coerced to treatment. The EUNOMIA data from the London site was included as part of the InvolvE study, and so these were omitted from the EUNOMIA sample to ensure that participants were not included twice. The third study, EDEN (Kallert et al., 2007), was a randomised controlled trial comparing outcomes of voluntary patients in day hospitals with those in conventional in-patient settings. Details of the rationale, methods and findings of each of the three studies have been described in in detail in the referenced papers.

All three studies included consecutively admitted patients aged between 18 and 65 who had the capacity to provide informed consent. The exclusion criteria consistent over all three studies included being admitted because of acute intoxication, being a forensic patient, and being transferred from another hospital. In the EDEN study patients requiring 1-to-1

supervision were excluded, whilst in the EUNOMIA and InvolvE studies voluntary patients who did not report a coercion level of at least 3 on the MacArthur Admission Experience Survey were excluded. For this study, only participants with a primary diagnosis of schizophrenia or a related disorder according to ICD-10 (F20-29) were included. Therefore, participants with other psychotic disorders such as schizoaffective disorder were included in this study, unlike with other investigations completed in this body of work. In the previous investigations completed in this study participants were omitted given concerns regarding both the diagnostic stability of schizoaffective disorder (Malhi et al., 2008), and the fact that the disorder appears to follow a different longitudinal course (Harrow et al., 1997). However, given symptoms in the current investigation were only considered cross-sectionally, the longitudinal course of symptoms was not deemed as relevant. With respect to the EDEN study, only patients treated in conventional inpatient hospital settings were included.

Whilst the substantially larger samples that can be derived from pooling multiple studies has benefits in terms of detecting very small effects and interpreting non-significant results, the technique is also considered to have a limitations. The most significant problem is that such a technique can ignore important subgroup characteristics (Bravata and Olkin, 2001), which can in turn result in either generate associations that do not exist, or hide associations that do (Pearson et al., 1899, Robinson, 1950, Yule, 1903). Therefore, in order to test the robustness of the estimates obtained from the pooled analyses, the analysis will also be conducted on the largest single study sample (EUNOMIA).

7.3.3. Measures

An assessment of the initial appraisal of hospital treatment was obtained using the Client Scale for Assessment of Treatment (CAT) (Priebe and Gruyters, 1995). The questionnaire has seven items and asks the patient whether they believe they are receiving the right care, whether their psychiatrist understands them and if other staff are pleasant to them, if they believe they are on the right medication, if they feel well respected and regarded, whether the care received has been helpful, and whether they feel other elements of their care are appropriate. Scores range from 0 (“not at all”), to 10 (“yes entirely”). Patients with missing data on four or more items were excluded from the analysis. Recent factorial analysis supports the use of the CAT as a meaningful unidimensional scale, stable over three different European countries (Richardson et al., 2011b). In previous research the CAT has been found to have excellent internal consistency (α=.90) (Priebe et al., 2009).

Symptom severity was measured on the 24-item version of the Brief Psychiatric Rating Scale (BPRS-E) (Overall and Gorham, 1962). While the scale is recognised to have a number of significant limitations in the measurement of negative symptoms (as summarised in section 1.9.1.2), the instrument was adopted given the need to capture a broader clinical picture, assessing manic, positive and depressive symptoms in addition to negative symptoms. Whilst the scale may not be recommended as a primary outcome for negative symptom trials in either the MATRICS or ISCTM consensus statements (Kirkpatrick et al., 2006, Marder et al., 2011), the scale has been successfully used as a measure of negative symptoms in other recent major investigations (Kring et al., 2013) suggesting the use of the scale is appropriate.

With the BPRS, various 4 and 5 factor models have been proposed, with a summary of these outlined in section 1.9.1.2. In this study, the model proposed by Velligan (Velligan et al., 2005) was adopted, given the study was one of the few to be completed with a sufficiently large sample size in which to conduct factor-analysis, and the fact that both confirmatory factor analysis and exploratory analysis was completed. The Velligan model includes 4 different factors, assessing negative, positive, manic/activation, and affective symptoms separately. The negative symptom subscale comprises of 3 items, including “blunted affect”, “motor retardation” and “social withdrawal”. The positive subscale comprises of 4 items, including “conceptual disorganisation”, “hallucinations”, “bizarre behaviour” and “unusual thought content”. The mania subscale includes 3 items, assessing “excitement”, “motor hyperactivity” and “tension”. Finally, the depressive-anxiety subscale includes the “anxiety”, “depression”, “suicidality” and “guilt” items. In the BPRS a mean of the items in each subscale are calculated to determine a summary score, with scores ranging from 1 (“Not present”) to 7 (“extremely severe”). In the original studies the inter-rater reliability between researchers using the BPRS was high, with researchers on the InvolvE project achieving a Cohen’s Kappa score of .90, while researchers on the EDEN and EUNOMIA studies achieved an intra-class coefficient score of .78.

Socio-demographic details including age, gender, marital status, previous admission history and employment status were obtained using the MANSA (Priebe et al., 1999) in the InvolvE and EUNOMIA studies, and the Clinical History Schedule (Kallert et al., 2000) in the EDEN study. The categories used were identical in the three studies. The employment and marital status the variables were dichotomised i.e. “employed, in training or education” vs. “unemployed/other”, and “married” vs. “unmarried” (which included those divorced, single and widowed). This was done for two reasons. Firstly, in the case of employment the aim was to differentiate between those who did and did not having a regular occupation, rather than focusing on whether participants received a payment for employment. Secondly, a number of

the groups contained only a small number of individuals (i.e. in training or education totalled less than 4% of participants, whilst housewife/househusband totalled less than 3%), meaning the groups would be insufficiently powered to detect small differences.

7.3.4. Analysis

In the first part of the analysis correlations between the different symptom factors were explored, given concerns that symptoms such as depression and negative symptoms can be difficult to distinguish in scales that have not been designed specifically for this purpose (Addington et al., 1993, Collins et al., 1996) (See section 1.3.1.3 for a review). While there is evidence to suggest that the measurement of depression can be conflated with negative symptoms in instruments such as the Hamilton Depression Scale (Addington et al., 1996), this has finding has been inconsistent, with other studies suggesting that these constructs can be measured independently by scales such as the BPRS (Newcomer et al., 1990).

In the next part of the analysis, the association between symptoms and the initial appraisal of impatient was assessed, after controlling for a number of clinical and sociodemographic variables. These included age, gender, employment status, marital status, and the legal status of admission. Any association between symptoms and SIR that were found to approach a level of significance ($P<.10$) were then added to a multivariate model in order to determine whether the association was specific to that symptom cluster. In the final part of the analysis, interaction effects between legal status and each BPRS subscale score were added to the multivariate model separately in order to examine whether the effect of symptom severity on the appraisal of treatment differed between those legally detained and those admitted voluntarily.

The impact of different studies was not controlled for, given one study (EDEN) included only voluntary patients. Since one aim was to assess the impact of legal status, entering this variable would have confounded this part of the analysis. In order to rule out the possibility of any bias in the results occurring due to the heterogeneity of the samples used, a subgroup analysis was conducted on the largest dataset (EUNOMIA).

To tackle any potential issues which could arise through a listwise deletion of incomplete cases (Little and Rubin, 1989) a multiple imputation using a chained equation of 10 cycles was conducted. All values included in the analysis were entered both as predictors and for imputing, other than the dependent variable which was included as a predictor only. Following

the recommendations by Spratt (Spratt et al., 2010), 25 imputations were conducted with the analysis conducted on the pooled data. R^2 scores were obtained from the imputed data in accordance with Rubin's rules by calculating the estimate from each imputed sample and then calculating an overall mean of these estimates (Rubin, 1987). All the analysis was conducted in SPSS version 20.

7.4. Results

7.4.1. Sample characteristics

In total, 2316 patients met the inclusion criteria. 211 patients were omitted due to missing or incomplete CAT scores, leaving 2105 patients in the final sample. The clinical and socio-demographic characteristics of this sample are presented in Table 41. The mean age of participants was 38.5 years (SD=11.24), with a fairly even split between males and females (56.9%-43.1%). Participants experienced a relatively long duration of illness (7.84 years, SD=9.11), most had experienced at least one previous inpatient admission (76.6%), and in the current hospital stay the majority were admitted involuntary (72.7%). The most severe symptoms experienced were positive symptoms (mean=2.92, SD=1.26), and the least severe were manic symptoms (mean=1.97, SD=1.11). Overall, participants reported being moderately satisfied with their treatment (CAT mean=6.00, SD=1.28).

Table 41: Socio-demographic and clinical characteristics of the patients

Characteristics	*n* or mean	% or SD
Patients (N)	**2105**	
% detained involuntarily	1530	72.7%
Age (years)	38.49	11.24
Gender (% female)	906	43.1%
Number married (n, %)	454	22.0%
Employed/training/education	465	22.4%
Previous psychiatric admission (%Yes)	1517	76.7%
Illness Duration (mean, SD)	7.84	9.11
BPRS (mean, SD)		
Depression/anxiety subscale score	2.24	1.08
Mania subscale score	1.97	1.11
Negative subscale score	2.14	1.08
Positive subscale score	2.92	1.26
CAT mean score	6.00	1.28

BPRS= Brief Psychiatric Rating Scale; CAT= Client Assessment of Treatment scale

As stated previously, the sample was pooled from three different studies, with the socio-demographic and clinical breakdown studies presented in table 42. In total, 1556 participants were recruited as part of the EUNOMIA project, 393 as part of the InvolvE study, and 156 as part of the EDEN study. As anticipated, given the nature of the three projects some differences were noted between the studies. In the InvolvE and EUNOMIA studies, a substantial proportion of participants were admitted on an involuntary basis, whilst 100% of the sample was admitted voluntarily in the EDEN study. Although the proportion of participants who had been previously experienced a psychiatric admission (71.4-77.5%), and age (35.83 years – 39.17 years) were similar between studies, a number of other differences were evident. In the EDEN study participants were more likely to be female, either employed and/or in training, married, and with a lower duration of illness. Regarding symptoms, in the EDEN study the sample was found to include experience more severe depressive symptoms, and less severe negative, positive and manic symptoms. In a comparison of the InvolvE and EUNOMIA datasets, manic and negative symptoms were found to be slightly higher in the EUNOMIA

sample, whilst depressive/anxiety symptoms were slightly higher in the InvolvE sample, with positive symptoms being broadly similar. Participants reported being the least satisfied in the InvolvE sample (CAT mean=5.36, SD= 2.91), and most satisfied in the EDEN sample (CAT mean=7.69, SD=1.98)

A missing value analysis indicated that 2.8% of all predictor values (653 in total) were missing, with 21.1% of cases (445) missing at least one. Of the 653 values missing in total, 53.9% (352 in total) related to the duration of illness.

Table 42: demographics by study

Variables	Studies					
	Eunomia		InvolvE		Eden	
	N or mean	% or SD	*N* or mean	% or SD	*N* or mean	% or SD
n	1556		393		156	
% detained involuntarily	1169	75.1%	361	91.9%	156	0%
Age (years)	39.17	11.09	35.83	11.10	38.38	12.15
Gender (% female)	689	44.3%	116	29.5%	101	64.7%
Marital status (% married)	328	21.4%	67	17.5%	59	39.9%
Employed/in training	327	21.3%	71	18.4%	67	43.8%
Prev. admission (%Yes)	1179	77.5%	288	74.6%	50	71.4%
Illness Duration	8.41	9.38	6.91	8.45	4.68	7.05
BPRS						
Depression/anxiety	2.09	1.01	2.43	1.20	3.20	0.90
Mania	1.93	1.00	1.63	0.84	1.55	0.51
Negative	2.27	1.11	1.77	0.92	1.85	0.89
Positive	3.07	1.22	3.01	1.21	1.35	0.50
CAT	6.00	2.69	5.36	2.91	7.69	1.98

BPRS= Brief Psychiatric Rating Scale; CAT= Client Assessment of Treatment scale

7.4.2. Symptoms and other patient characteristics associated with initial appraisal of treatment

Correlations between symptoms and the initial appraisal of treatment are presented in table 43. A moderate negative correlation was detected between the initial appraisal of treatment and positive and manic symptoms (*r*=-.228 and *r*=-.233 respectively). A weak negative correlation was found between negative symptoms and SIR (*r*=-.041), and a weak positive correlation was detected between depressive symptoms and SIR (*r*=.049). Although moderate correlations were detected between some symptoms, these were not of a sufficient level to suggest that collinearity may be an issue in the multivariate analysis. The strongest correlation was detected between positive and manic symptoms (r=.422), whilst the correlation between negative and depressive/anxiety symptoms was much lower than what was originally anticipated (*r*=.127).

Table 43: Correlation table of symptoms subscales and appraisal of treatment

	Subjective initial appraisal (CAT)	Depression/Anxiety symptoms	Manic symptoms	Negative symptoms	Positive symptoms
Subjective initial appraisal (CAT)	**	.049	-.233	-.041	-.228
Depression/Anxiety symptoms		**	-.028	.127	-.080
Manic symptoms			**	.104	.422
Negative symptoms				**	.250
Positive symptoms					**

The associations between symptoms and the initial appraisal of treatment are presented in table 44. After controlling for age, gender, admission history, illness duration, legal status, employment situation and marital status, higher mania and positive symptoms were found to be associated with a lower initial appraisal of treatment (manic symptoms adj. B= -0.474, 95% CI -0.577 to -0.372, P<.001, R^2=.036; positive symptoms adj. B= -0.367, 95% CI -0.460 to -0.274,

P<.001, R^2=.027). A negative relationship between negative symptoms and initial appraisal of treatment was detected, however this was not significant, with the estimates found to be just outside the specified threshold to be included in the multivariate analysis (adjusted coefficient= -0.089, 95% CI -0.197 to -0.019, P=.106). No relationship between depressive/anxiety symptoms and initial appraisal of treatment was found.

In the multivariate analysis, both higher mania and positive symptoms were found to be significantly associated with a lower assessment of the appraisal of treatment (mania adj. B= -.358, -0.469 to -0.247, P<.001; positive symptoms adj. B =-0.250, 95% CI -0.350 to -0.151, P<.001). However, including both symptoms into the model appeared to only explain a relatively small proportion of additional variance (R^2=.045).

Table 44: Associations between symptoms and subjective initial response

Predictor variables[a]	Univariate analysis				Multivariate analysis[B]		
	B	95 %CI	*P*	R^2	B	95 % CI	*P*
Depressive/anxiety	0.028	-0.082 to 0.138	.619	<.001			
Mania	-0.474	-0.577 to -0.372	<.001	.036	-0.358	-0.469 to -0.247	<.001
Negative	-0.089	-0.197 to 0.019	.106	.001			
Positive	-0.367	-0.460 to -0.274	<.001	.027	-0.250	-0.350 to -0.151	<.001

[a]Association between SIR and symptoms, after adjusting for age, gender, admission history, illness duration, legal status, employment status, and marital status.
[B]R^2 change after adding symptoms= .045

In order to ensure the findings are not attributable to subgroup differences between studies (Bravata and Olkin, 2001) a subgroup analysis was completed on just the largest dataset, namely the EUNOMIA study. The findings are presented in table 45. Overall, the findings were broadly consistent with those reported in the pooled analysis. When symptoms were considered separately, a significant negative association was detected between SIR, and mania and positive symptoms (mania adj. B= -0.521, 95% CI -0.633 to -0.408, P<.001, R^2=.050; positive adj. B= -0.416, 95% CI -0.524 to -0.308, P<.001), whilst no relationship between depressive/anxiety symptoms and SIR was detected (adj. B= 0.023, 95% CI -0.111 to 0.158, P=.735). In a slight change to the pooled analysis, the negative symptom subscale was found to be significantly associated with SIR, albeit only explaining a very small proportion of the variance (adj. B= -0.157, 95% CI -0.278 to -0.035, P=.012, R^2=.002). When symptoms were included in the model together, the findings were consistent with the original findings, with significant negative associations detected between mania an positive symptoms (mania symptoms adj. B= -0.401, 95% CI -0.526 to -0.277, P<.001; positive symptoms adj. B= -0.239,

95% CI -0.360 to -0.117, P<.001), whilst the relationship to negative symptoms was non-significant (negative symptoms adj. B= -0.102, 95% CI -0.225 to 0.021, P=.104). In the multivariate model, the symptoms again explained only a relatively small proportion of the total variance in appraisal of treatment (R^2=.061).

Table 45: Associations between symptoms and subjective initial response in the EUNOMIA dataset

Predictor variables[a]	Univariate analysis				Multivariate analysis[B]		
	B	95 %CI	P	R^2	B	95 % CI	*P*
Depressive/anxiety	0.023	-0.111 to 0.158	.735	<.001			
Mania	-0.521	-0.633 to -0.408	<.001	.050	-0.401	-0.526 to -0.277	<.001
Negative	-0.157	-0.278 to -0.035	.012	.004	-0.102	-0.225 to 0.021	.104
Positive	-0.416	-0.524 to -0.308	<.001	.036	-0.239	-0.360 to -0.117	<.001

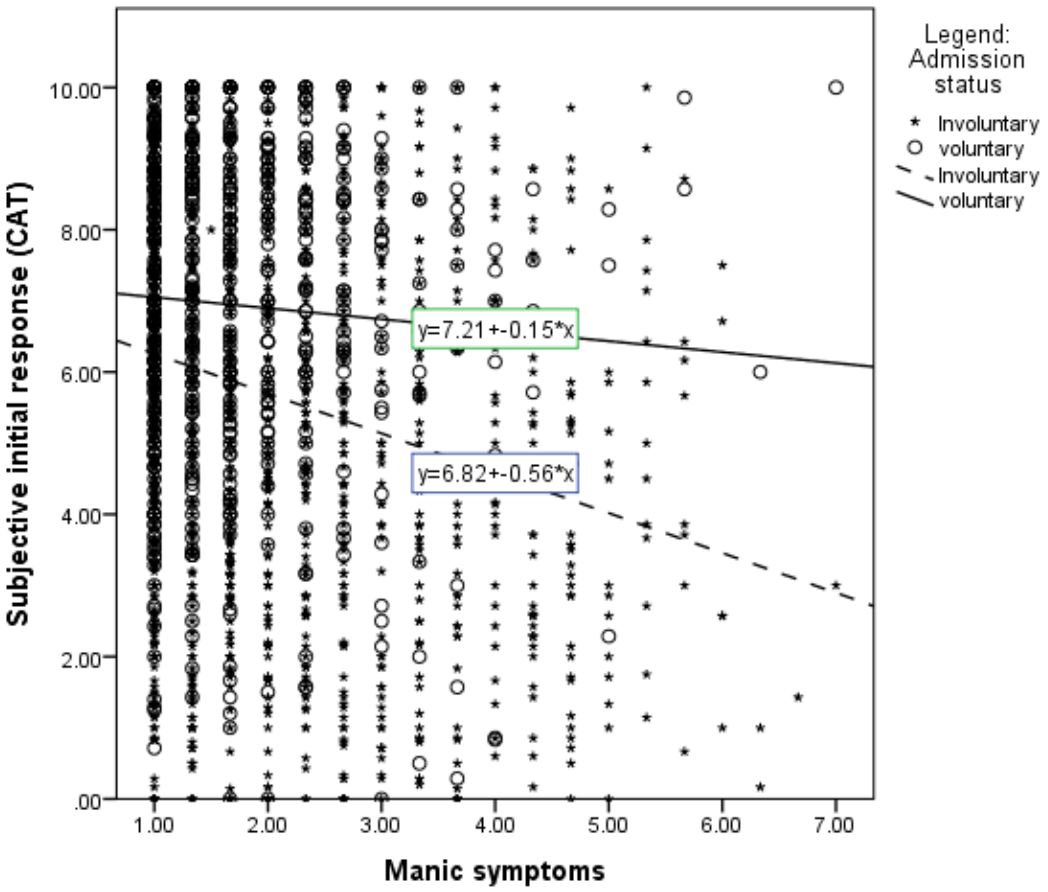
[a]Association between SIR and symptoms, after adjusting for age, gender, admission history, illness duration, legal status, employment status, and marital status.
[B]R^2 change after adding symptoms in the multivariate model= .061

7.4.4 Legal status of admission, symptom severity and initial treatment evaluation

The next stage of the analysis explored whether symptom levels had a different predictive value in voluntary and involuntary patients. In order to achieve this, an interaction effect between legal status and each symptom subscale score was separately entered into the model. Amongst the four symptom subtypes, a significant interaction effect was found for manic symptoms (adj. B=0.407, 95% CI 0.138 to 0.676, P=.003), with the results presented in figure 18. The graph suggests that whilst SIR is broadly similar between voluntary and involuntary patients when manic symptoms were very low; as they increase the appraisal of treatment reduces far more in involuntarily admitted patients, relative to those admitted voluntarily. No difference in the impact of symptoms between those that were and were not admitted involuntarily were detected in positive symptoms (adj. B= 0.116, 95% CI -0.092 to 0.325, P=.274), negative symptoms (adj. B= -0.123, 95% CI -0.365 to 0.119, P=.320) or depressive/anxiety symptoms (adj. B= -0.112, 95% CI -0.343 to 0.120, P=.345).

In a post-hoc analysis separating those admitted involuntarily from those admitted on a voluntary basis, a significant negative association between manic symptoms and SIR was detected in those admitted involuntarily (adj. B=-0.548, 95% CI -0.666 to -0.430, P<.001, R^2 change=.053), whilst the relationship was non-significant in the voluntary sample (adj. B=-0.124, 95% CI -0.340 to 0.093, P=.263. R^2change=.002).

Figure 18: Association between manic symptoms and SIR between those that have been voluntarily and involuntarily admitted.



7.5. Discussion

7.5.1. Main findings

The negative symptoms of schizophrenia were not found to be associated with the subjective initial appraisal of impatient treatment. Instead, manic and positive symptoms were found to be negatively associated how hospital treatment is perceived in the initial stages, after controlling for other clinical and sociodemographic variables. The impact of manic symptoms appeared to be particularly strong in those patients who were detained involuntarily, as opposed to those who are voluntarily admitted. Somewhat surprisingly, no association between depressive symptoms and appraisal of treatment was detected, despite the consistent negative association between patient reported outcomes and mood which has previously been found (Fakhoury et al., 2002, Priebe et al., 1998).

7.5.2. Strengths and limitations

Regarding the strengths of the study, the large sample size (2105 patients) provides sufficient statistical power to detect even small effect sizes, thus allowing the interpretation of negative findings. In this study observer-ratings of symptoms were used to predict patient-rated appraisals of the appraisal of treatment, meaning the associations detected are not a consequence of a generalised tendency to provide more or less positive ratings in different self-reporting measures (Fakhoury et al., 2002, Hansson et al., 2007). In addition, results were consistent in the sensitivity analysis evaluating the EUNOMIA dataset in isolation, suggesting the findings are robust. Finally, the Interrater reliability was high in all three studies. In the InvolvE study all researchers achieved an interrater reliability of Cohen's Kappa =.90 in the BPRS, whilst in both the EDEN and EUNOMIA an interrater reliability score of ICC=.78 was reported.

One significant limitation of the study is the fact that there appears to be a number of differences between the study samples pooled, both in terms of sociodemographic and clinical characteristics. In two of the three studies (InvolvE and EUNOMIA), voluntary patients were included only if they expressed a level of being coerced. In the third study (EDEN) no involuntary patients were recruited. In the EDEN study participants appeared to report lower symptoms in all domains, other than in depression/anxiety, and reported a more positive appraisal of treatment, whilst a number of sociodemographic differences were evident. As highlighted previously, one significant issue with the pooling multiple studies is the fact that it can ignore important subgroup characteristics, which can in turn influence any associations between variables (Bravata and Olkin, 2001, Pearson et al., 1899, Robinson, 1950, Yule, 1903). However, given the findings of the pooled sample were found to be highly consistent with those in an analysis of the single largest dataset (EUNOMIA). it suggests that this may not be as significant an issue as may first have been assumed.

Another significant limitation of the study relates to the context in which participants were recruited. Given the aim of all three studies was to recruit and assess all participants within the first week of an inpatient admission, it is likely that there may have been a small subsample of patients who were too acutely unwell to be eligible for recruitment due to a lack of capacity. Whilst problematic, this particular issue is common to all studies which aim to recruit participants in this phase of treatment. In a related issue, it is also possible that patients who were highly dissatisfied with treatment may be less likely to co-operate in research being conducted in this setting. However, his may not be as significant an issue as first assumed

given all assessors were independent to the clinical team. This being the case, it is quite possible that this sub-group of patients may be more keen to be involved in the research as it provides an independent platform in which to discuss their dissatisfaction with aspects of their treatment.

Another limitation is due to the lack of available data, it was not possible to consider what treatment participants received during the first days of hospital treatment, and whether specific treatments were linked a more positive or negative appraisal of treatment. For example it has been recognised that patients with high positive symptoms are significantly more likely to be prescribed a high dose of antipsychotic medication (Sim et al., 2004), while involuntary admissions have been found to be a significant predictor of antipsychotic polypharmacy and high-dose (Lelliott et al., 2002). High-dose and polypharmacy have been both been recognised to increase adverse side effects (Centorrino et al., 2004), which in turn are considered to be a significant source of discomfort and treatment non-compliance (Cabeza et al., 2000, Fenton et al., 1997), which could in turn impact treatment appraisal. Future work assessing the nature of treatments that participants receive during the initial hospitalisation period may help determine possible mediating factors in associations between symptoms and the appraisal of hospital treatment.

7.5.3. Summary

The findings suggest that patients with different symptom profiles experience and respond to psychiatric hospital treatment in different ways and, as a result, express different appraisals of treatment within a few days after admission. Patients with schizophrenia experiencing more severe manic and positive symptoms, and manic symptoms in particular if detained involuntarily, are more likely to report a more negative initial evaluation of treatment. Higher negative symptoms do not appear to impact the appraisal of inpatient treatment.

The findings underline the importance of assessing patients' initial appraisal of treatment as a relevant process variable in both research and routine practice. Further studies may explore environmental factors, processes of interaction between service users and staff, treatment components and mediating processes as an explanation into the association of manic and positive symptoms with more negative appraisals of hospital treatment after only a few days. In a recent review Mullen (Mullen, 2009) has suggested that acute inpatient settings are at present too custodial and over reliant on medication, and suggests that providing more

psychosocial interventions as an alternative may be a way in which to try and address these issues. If these are problems which disproportionally affect those experiencing higher positive and manic symptoms, then this possible solution may go some way to addressing the more negative experiences these particular patients report.

Chapter 8. Discussion

8.1. Thesis aims

The main aim of this thesis was to explore areas which could either inform the design of negative symptom clinical trials, or build upon the current developments in symptom assessment. This included examining how negative symptoms change over time, the impact of different symptom inclusion criteria adopted in clinical trials, a comparison of different scales designed to measure negative symptoms, and the nature of their association to other constructs such as subjective quality of life and the initial appraisal of treatment.

In the first part of this investigation the aim was to explore the longitudinal course of negative symptoms in stable schizophrenia outpatients over a period of up to 3 years, pooling a broad array of studies by way of meta-analysis. In a meta-regression, study-level variables such as the assessment scale used and the eligiblity criteria adopted were examined as predictors of differing longitudinal course. Despite symptom inclusion criteriafor negative symptom trials being consistently recommended in the literature (Kirkpatrick et al., 2006, Marder et al., 2013, Marder et al., 2011), there has been substantial variation in the manner in which they have been adopted (Dunayevich et al., 2014, Rabinowitz et al., 2013). Therefore, in Chapter 4 the aim was to further explore the impact of adopting differen symptom inclusion criteria on the associations between these negative, and positive and depressive symptoms.

As stated previously, one of the major recent advances in the field has been the development of new instruments to measure negative symptoms, such as the CAINS (Kring et al., 2013) and the BNSS (Kirkpatrick et al., 2011). Whilst it is recognised that CAINS has highly promising psychometric properties (Kring et al., 2013) and represents an important advance on earlier scales such as the PANSS and the SANS from a conceptual point of view (Blanchard et al., 2011), to date little work has been conducted examining the sensitivity of the scale. In chapter 5, a comparison of how the PANSS and the CAINS differentiate between participants that report high and low negative symptoms, and differences in the degree to which both scales report symptom change over time was conducted. In addition, the incrimental validity of the CAINS was compared to the PANSS negative subscales in various indicators of social improvishment. The main aim of this investigation was to determine whether the CAINS is a more sensitive instument than the PANSS negative subscale, and whether the CAINS is a stronger pedictor of outcomes known to be related to the negative symptom construct.

One important feature of the CAINS is the fact that the scale is designed to measure expressive and experiential features of negative symptoms as distinct constructs. Measuring these two features of negative symptoms seperately allows us to examine whether associations between negative symptoms and other constructs may relate specifically expressive or experiential deficits, or both. In chapter 6 the association between subective quality of life and the expressive and experiential components of negative symptom was explored, which has previously been found to be relatively weak (Eack and Newhill, 2007, Priebe et al., 2011b). The aim of this investigation was determine whether the association between SQOL and negative symptoms have previously been underreported due to limitations in existing scales which do not sufficiently tap into the experiential features of negative symptoms (Blanchard et al., 2011).

In the final part of the investigation (chapter 7), the impact of negative symptoms was extended to another patient report outcome, namely the initial appraisal of inpatient psychiatric treatment. Subjective initial appraisal is an important outcome given it has been found to have significant implications on later treatment response (Bartkó et al., 1987, Bröker et al., 1995, Priebe and Gruyters, 1994, Priebe et al., 2009). The aim of this investigation was to determine whether negative, positive, manic or depressive symptoms are associated with SIR.

8.2. Summary of findings and comparisons to the literature

8.2.1. The change in negative symptoms over time in outpatients

The meta-analysis presented in chapter 3 suggests that there is a significant reduction in the severity of negative symptoms over time in all treatment contexts. This finding was supported in the analysis completed in chapter 4, where a reduction in negative symptoms over time was present regardless of the eligibility criteria adopted. In chapter 6, a significant reduction over time was detected in the PANSS negative subscale and the CAINS experiential subscale, but not in the expressive subscale. Collectively, the findings from chapters 3, 4 and 6 all point to the conclusion that there is a significant reduction in negative symptoms over time in stable outpatients diagnosed with schizophrenia, including in samples which are selected to minimise the impact of secondary negative symptoms. However, due to the inconsistent evidence it is unclear whether this reduction is consistent across all types of negative symptoms, or whether expressive and experiential symptoms follow a different trajectory.

The findings that negative symptoms significantly reduce over time are contrary both to the earliest conceptions of schizophrenia, which suggested that negative symptoms follow a path of progressive deterioration (Bleuler, 1950, Kraepelin, 1971), and our current understanding of negative symptoms which suggest that they are highly stable in the non-acute phase (Möller, 2007). Instead, these results appear to mirror the findings of a study by Quinlan (Quinlan et al., 1995), who evaluated the longitudinal course of symptoms in chronic schizophrenic outpatients. Over two years significant reductions in negative symptoms were detected, leading Quinlan to propose that the notion of a progressive downward course of schizophrenia may need to be reconsidered.

In the assessment of individual negative symptoms in chapter 3, the reduction in alogia, anhedonia, blunted affect and avolition all appeared very similar. These findings are in contrast with the findings in chapter 6 where significant reductions in experiential, but not expressive symptoms were evident. The reasons for the differences between these findings are not clear. One possible theory could be that the non-significant reduction in expressive symptoms detected in chapter 6 could be attributable to floor effects, given the level of expressive symptoms were relatively low at baseline (mean= 1.94, SD= 0.92). However, it also possible that the lack of any differences between the types of symptoms uncovered in chapter 3 may be attributable the limitations of the assessment scales used. As stated previously, the SANS and PANSS is recognised to merge conceptually distinct experiential symptom domains into single subscales such as anhedonia-asociality, in addition to including features now not recognised to be part of the negative symptoms construct (Blanchard et al., 2011). In addition, these scales insufficiently tap into experiential symptoms of the disorder (Blanchard et al., 2011, Kring et al., 2013), a theory further supported by the findings presented in chapter 5 which only found a moderate association between the PANSS negative and CAINS experiential subscales (r=.480). This being the case, it is quite possible that a reduction in the experiential symptoms may be under-reported when these scales are used. The third possibility it that expressive symptoms such blunted affect and alogia are more stable than experiential symptoms such as anhedonia, avolition and asociality. Greater stability in expressive symptoms have been reported in the past (Johnstone et al., 1987; Meuser et al., 1991; Dollfus and Petit, 1995; Kelley et al., 2008), possibly because they are less affected by causes of secondary negative symptoms such as positive symptoms and medication side effects (Angrist et al., 1980; Kelley et al., 1999).

Participants who were allocated to receive SGA's or adjunctive medications reported a greater reduction in negative symptoms, relative to those allocated to other conditions. At first glance,

these findings appear to suggest that these medications may be more effective in the treatment of negative symptoms, contrasting with earlier studies which have not found a consistent difference in the efficacy of SGA's over other treatments (i.e. Leucht et al., 2009; see section 1.7 for a review). However, this finding is complicated by the fact that in the placebo/control/treatment as usual samples a greater reduction in negative symptoms were detected in those that were part of a second generation antipsychotic or adjunctive medication drug trial. This suggests that there may be undetermined features of these types of studies which result in a greater change in negative symptoms being detected, rather than the effectiveness of the treatments themselves. Given a number of the SGA and adjunctive drug studies that were completed more recently, it is possible that this finding relates to an increasing placebo effect which has been found in psychiatric pharmacological trials (Kinon et al., 2011, Rutherford and Roose, 2013, Walsh et al., 2002).

8.2.2. The impact of adopting different symptom inclusion criteria in negative symptom trials

In the meta-regression completed in chapter 3, studies that adopted a minimum negative symptom inclusion criterion reported a small but significant increase in the reduction of negative symptoms over time. However, this difference was not significant in the multivariate model. In chapter 4, a substantial reduction in negative symptoms over time was evident as the minimum negative symptom eligibility criteria increased. These reductions were present despite maximum depressive and positive symptom eligibility criteria also being adopted, which should theoretically minimise secondary symptoms and so increase the stability of negative symptoms over time (Möller, 2007). The reason why the minimum negative symptom inclusion criterion appeared to have a much greater impact in the analysis completed in chapter 4, relative to the meta-regression completed in chapter 3 is not clear. One possibility is that in chapter 3 the substantial variation in the manner in which these criteria are implemented, in addition to the large degree of heterogeneity between the pooled studies themselves may have resulted in a number of extraneous factors and a substantial loss of power, masking any differences which may exist. If this is the case, then the findings of chapter 4 may be a closer representation of the impact of adopting such criteria.

Over the different inclusion criteria examined in chapter 4, the association between positive and negative symptoms appeared to be largely consistent regardless of how restrictive the inclusion criteria were. Of the 11 criteria examined, the only difference that appeared to exist

was when predominant criteria were determined by negative symptoms being over positive symptoms by a specified amount. In these cases (Olie et al., 2006, Rabinowitz et al., 2013) the association between positive and negative symptoms substantially increased. These findings are broadly consistent with those reported by Dunayevich (Dunayevich et al., 2014), who found that adopting different inclusion criteria did not minimise the association between positive and negative symptoms . In other work, Stauffer (Stauffer et al., 2012) found that negative symptom change was not different between participant samples that reported prominent or predominant negative symptoms. Whilst these findings merit further exploration, they point to the conclusion that most symptom inclusion criteria adopted in clinical trials may not be effective in reducing the association between positive in negative symptoms and, based on the findings of the current study, may even increase it in some cases.

Regarding the association between depressive and negative symptoms, it is interesting to note that this was reduced both by implementing a minimum negative, and maximum depressive symptom criterion. In the whole sample the association between negative and depressive symptoms was found to be relatively large. This association was found to decrease slightly when all participants with at least moderate depressive symptoms were omitted, which in turn resulted in a small reduction in the severity of negative symptoms. This finding supports earlier work which suggests that high levels of depressive symptoms may either mimic or exacerbate negative symptoms (Carpenter et al., 1985). However, a larger decrease in the association between these symptoms occurred when a minimum negative symptom criterion was implemented, the reason for which is not entirely clear. One theory is that implementing a minimum negative symptom threshold means that participants would be required to present with a broader range of negative symptoms, some of which have not found to be significantly elevated in depressed verses non-depressed schizophrenia patients such as affective flattening (Barnes et al., 1989). A second possibility is that participants may need to present with more severe individual symptoms, making it easier to distinguish between depressive and negative symptoms. One example of this may be in anhedonia, where an inability to experience pleasure is a feature of both negative symptoms and depression. However, in depression this manifests itself as an overall anhedonic deficit, whilst in negative symptoms this is limited specifically to anticipatory pleasure, with the experience of sensory pleasure remaining largely intact (Gard et al., 2007, Strauss et al., 2011). Given this distinction is somewhat nuanced, it is likely to be more challenging to determine when the symptoms experienced are relatively mild. A reduction in the association between negative symptoms and depression was similar when a number of individual negative symptoms were required to be above a mild level of severity, and in criteria that specified an overall negative symptom subscale score be over a

certain threshold, making it difficult to determine whether either (or if indeed both) mechanisms may be involved.

The findings in chapter 4 appear to support the conclusions outlined in the NEWMEDS consensus statement (Marder et al., 2013). In this report it was recommended that participants who present with depressive symptoms that do not overlap with negative symptoms should be excluded from negative symptom clinical trials, whilst no consensus was reached regarding excluding participants with high positive symptoms. This conclusion is in contrast to the NIMH-MATRICS consensus statement (Kirkpatrick et al., 2006), the criteria of persistent negative symptoms outlined by Buchanan (Buchanan, 2007), and the current guidelines of the European Medicines Agency (EMA., 2012) which all recommend excluding participants with at least moderate levels of positive symptoms.

8.2.3. A comparison of the different negative symptom assessment scales.

In chapter 3 participants that were assessed using the SANS were found to report a significantly greater reduction in negative symptoms, relative to those assessed by either the PANSS negative subscale or the BPRS anergia subscale. This difference was relatively large, even after controlling for a range of other study-level factors (ES=0.43). In chapter 5, the CAINS was found to provide a greater differentiation between participants that report high and low symptoms, and reported a greater change in negative symptoms relative to the PANSS as the mean change in both scales increased. In addition, the CAINS was found to be a stronger predictor in a range of outcomes relating to social impoverishment.

The findings in chapter 3 and 5 suggest that different assessment tools can result in a large variation in the severity and change in negative symptoms reported. This supports the conclusions of the recent MATRICS consensus report which suggested that inappropriate scales may act as a significant barrier to the development of new treatments (Kirkpatrick et al., 2006). They concluded that new scales should be developed that adhere to our current conception of the negative symptom construct, and be a more sensitive instrument to detect symptom changes. Prior to developing the CAINS and the BNSS, a review of the negative symptom construct outlined the conceptual requirements of the scales (Blanchard et al., 2011). In follow up work, the CAINS was developed, evaluated and refined, with the final scale being found to have excellent psychometric properties (Forbes et al., 2010, Horan et al., 2011, Kring et al., 2013). In the current study, the findings suggest that the CAINS may be a more

sensitive instrument to detect changes in negative symptoms relative to the PANSS, thus fulfilling the final parameter outlined in the consensus report (Kirkpatrick et al., 2006).

The findings from chapter 3 which suggest that the SANS is a more sensitive instrument to detect negative symptom change over the PANSS and the BPRS is in consistent with recommendations outlined in the MATRICS consensus statement (Kirkpatrick et al., 2006). In the report, they suggest that the SANS may be preferable given multiple items are used to measure separate constructs which should improve the psychometric properties of the scale. However in the same report it is also recognises that the scale has a number of limitations, including items which are not considered part of the negative symptom construct such as attention deficits, inappropriate affect, and poverty of speech content (Buchanan and Carpenter, 1994), and not specifying between anticipatory and consummatory hedonic deficits (Gard et al., 2007). If the advantages of the SANS are attributable to the fact that multiple items are used (as proposed by Kirkpatrick and colleagues) (Kirkpatrick et al., 2006), then it follows that this same advantage would also extend to other scales with adopt multiple items such as the CAINS.

8.2.4. The Impact of adopting different eligibility criteria on the sample pool size

Consistent with the findings from Rabinowitz and Dunayevich (Dunayevich et al., 2014, Rabinowitz et al., 2013), the results of chapter 4 suggest that adopting more restrictive inclusion criteria can result in a substantial reduction in the eligible sample pool. In the current study, adopting the most restrictive criteria (Moller et al., 2004) resulted in only 6.6% of the total sample being eligible. This figure is comparable to similar studies by Dunayevich and Rabinowitz which found that only 6.0% and 8.1% were eligible in the most stringent criteria adopted. This is in stark contrast to the broadest criteria examined in the current investigation, which resulted in 50% of the sample still being eligible. With so many participants deemed ineligible in the most restrictive criteria, this could have two major implications. Firstly, excluding so many potential participants can make it substantially harder to recruit the required number of participants, which is already recognised to be a challenging and complex issue for clinical trials (McDonald et al., 2006). Secondly, it could potentially result in trial samples not being sufficiently generalisable to populations that these treatments would ideally be designed to treat. Over 60% of patients have been found to present with at least one moderate negative symptom in routine care (Bobes et al., 2010), and between 20-30% are thought to present with deficit syndrome (Kirkpatrick et al., 2006). In the current study, the

participants were older (mean age 42.1 years), where the prevalence of deficit syndrome in clinical populations is thought to be even higher (37% in those over 45) (Harris et al., 1991). Therefore, it is likely that implementing such criteria is likely to result in a substantial proportion of participants who either present with persistent negative symptoms or deficit syndrome not being eligible for negative symptom trials that adopt these criteria, despite the fact that the treatments under evaluation would be designed precisely for this patient group. Utilising more broad criteria may aid ease of trial recruitment, whilst also producing study samples which are more generalisable to the treatment target population. It is possible that this lack of generalisability may in part explain why such a difference was found between pragmatic trials which utilised broader criteria such as the CUtLASS (Jones et al., 2006) and the CATIE (Lieberman et al., 2005) studies, compared to the early industry studies.

8.2.5. What is nature of the relationship between the CAINS and PANSS negative subscale?

In chapter 5, the CAINS total and the PANSS negative subscale was found to be highly correlated (*r*=.742). Consistent with earlier studies which examined the relationship between the BPRS and the CAINS (Horan et al., 2011), the PANSS negative subscale was found to relate primarily to the expressive features of negative symptoms (*r*=.754), with only a moderate correlation between experiential subscale and the PANSS negative subscale present (*r*=.480). These findings are consistent with the conclusions outlined in a review by Blanchard and colleagues (Blanchard et al., 2011), which suggested that older scales such as the PANSS insufficiently tap into experiential features of negative symptoms, instead relying primarily on behavioural referents. These referents can include the frequency of activities, interviewer observations, and reports from family members or carers, and mean the experiential features of symptoms such as anhedonia and avolition are not directly addressed. This is important, as it means that link between outcomes with negative symptoms that one would expect to relate more to experiential than expressive deficits may have been under-reported in studies that have used older scales. This conclusion is supported by the findings presented in chapter 6, where significant associations were detected between experiential deficits and subjective quality of life using the CAINS, whilst no relationship was detected using the PANSS negative subscale.

8.2.6. The association between the negative symptom construct and other variables when measured by the CAINS, PANSS and BPRS

In chapter 7, negative symptoms were not found to be associated with subjective initial response. In chapter 5, significant associations between negative symptoms and indicators of social impoverishment such as the number of activities participants took part in over the past week, the number of friend contacts made over the past week, and whether they had anyone they considered a close friend were detected. In the majority of cases, the CAINS was found to be a better predictor of these outcomes than the PANSS negative subscale score. In chapter 6, no relationship was detected between negative symptoms and subjective quality of life when it was measured as a singular construct using the PANSS, however significant associations between experiential deficits and SQOL were present.

In chapter 5, the CAINS total subscale was found to be a better predictor of the number of friends they have made contact with, the number of activities they have taken part in over the past week, and whether participants reported having a close friend. Given the PANSS has been criticised for focusing primarily on behavioural referents (Blanchard et al., 2011), it is somewhat surprising that while the scale explained only a minimal degree of unique variance in the two behavioural outcomes (both =.001), at least some unique variance was explained in the subjective outcome which related to whether participants had somebody they would consider as being a close friend (=.007). This was more apparent in the comparison between the PANSS Marder negative subscale and the CAINS, where similarly little unique variance was explained by the PANSS subscale in the two behavioural outcomes (both <.001), but explained a relatively large proportion in reporting whether they had a close friend (=.017). In this item, the degree of shared and unique variance explain by the PANSS Marder negative subscale was slightly higher than the CAINS total score, with the Marder subscale being dominant in 62.7% of cases.

These findings point to a number of conclusions. Firstly, the PANSS Marder negative subscale was found to be a superior predictor of whether participants have a close friend whilst the PANSS negative subscale was not, lending further support to recommendations which suggest that the Marder subscale may be a more appropriate method to adopt in clinical trials evaluating negative symptoms (Marder et al., 2011, Marder et al., 1997). Secondly, despite the PANSS Marder negative subscale being marginally better than the CAINS at predicting whether participants report have a close friend, in the other 5 comparisons made the CAINS total score was found to be dominant with the PANSS typically explaining little to no additional variance.

This suggests that the CAINS should be considered as superior at predicting functional impairments related to the negative symptom construct. Somewhat contrary to expectations, this advantage appears to be particularly strong in predicting more concrete, behavioural outcomes related to the negative symptom construct. This is important, as determining the incremental validity of new psychometric scales should be considered a crucial step in the scale development process (Hunsley and Meyer, 2003), despite it often being neglected (Haynes and Lench, 2003).

In chapter 7, higher negative symptoms were not found to result in a lower subjective initial appraisal of inpatient psychiatric treatment. Instead, it was found that positive and manic symptoms were associated with a more negative assessment. Given the impact of subjective initial appraisals on various social and psychopathological outcomes (Bröker et al., 1995, Priebe et al., 2010a, Richardson et al., 2011a) this study suggests that a greater consideration of these symptoms during the admission stage may help longer term outcomes. These findings are partly consistent with the results of Richardson and colleagues (Richardson et al., 2011a) who reported a less positive initial treatment appraisal for patients with higher levels of mania, positive and depression/anxiety symptoms. The findings from the current study are in contrast to a body of literature in psychiatry which has typically found that mood symptoms have the greatest impact on patient reported outcomes (Priebe, 2007). It has been suggested that this reflects a negative rating bias of patients with high levels of depression, rather than a specific experience of treatment (Fakhoury et al., 2002, Hansson et al., 2007, Priebe et al., 1998).

One possibility for the finding that positive and manic symptoms lead to a more negative assessment of treatment may relate to how these symptoms might impact upon being placed in the confined environment of a hospital ward. In a qualitative review of involuntary inpatient experiences of treatment (Katsakou and Priebe, 2007), a number of features of treatment were recognised to negatively impact upon a patient's experience of admission. Of these experiences, a number may particularly resonate with those suffering more intense manic and positive psychotic symptoms. Patients experiencing greater levels of positive symptoms such as paranoia or hallucinations may struggle more in an unfamiliar setting which may feel frightening or insecure. Patients with severe manic symptoms are likely to be more agitated, and struggle more with being contained in an enclosed space with rigid rules and limited opportunities for activities. The finding that manic symptoms influence patients' appraisal even more in those involuntarily admitted, who therefore would experience an even greater restriction to their autonomy, lends further support to this argument. Patients who exhibit 'disturbed behaviour' or experience acute positive symptom exacerbation are also more likely

to receive combined antipsychotics and high doses of antipsychotic medication (Paton et al., 2008), which can lead to a higher side effect burden (Centorrino et al., 2004), potentially impacting the appraisal of the treatment they receive further.

8.2.7. The association between negative symptoms and other constructs when expressive and experiential constructs are considered separately

Whilst the relationship between negative symptoms of schizophrenia and subjective quality of life (SQOL) has been examined in the past (Eack and Newhill, 2007, Priebe et al., 2011b) this is the first time the link between SQOL and expressive and experiential deficits as separate constructs have been considered. As anticipated, the association between experiential deficits and SQOL detected in this investigation appears to be significantly stronger than in previous studies which have examined the relationship to negative symptoms as a singular construct. This stronger association was found both cross-sectionally and in changes over time, and in contrast to earlier investigations, remained present after controlling for depressive symptoms. These findings support the current developments in negative symptom assessment which advocate measuring experiential and expressive symptoms as distinct negative symptom constructs (Blanchard and Cohen, 2006, Horan et al., 2011, Kring et al., 2013), suggesting that new insights in the field of negative symptoms may be uncovered by utilising the new CAINS assessment instrument. In addition, this finding suggests that if the primary aim of treatment is to improve the patients' quality of life, then the focus on treatment should be on the experiential, as opposed expressive features of the illness.

In the comparison of the PANSS negative and CAINS subscales, the experiential scale was found to be the strongest predictor of the number of friends contacts and social activities completed in the past week, in addition to whether participants report having somebody they consider to be a close friend. The finding that the expressive subscale explains little variance in these outcomes is not surprising, given the outcomes evaluated would be considered to relate more to experiential deficits, such as asociality and avolition. One interesting finding was that in the outcome concerning the number of reported friend contacts, the experiential subscale was found to explain a slightly greater proportion of variance than the whole CAINS subscale (R^2=.118 in comparison to R^2=.091), further supporting the argument that in some situations it may be beneficial to utilise the subscales separately.

Overall, these findings support an emerging evidence base which suggests that experiential and expressive symptoms represent distinct constructs (Blanchard and Cohen, 2006), and as such should be measured separately (Horan et al., 2011). Not only does assessing these symptoms in this manner better resemble the negative symptom construct as it is currently understood, the findings here suggests that assessing symptoms in this manner may yield new insights which may have previously been missed when negative symptoms were measured as a singular concept.

8.3. Project Strengths and Limitations

One strength of this study is that the investigation comes at a time when there are significant developments in the field of negative symptoms of schizophrenia. Recent consensus statements have placed increasing focus on refining methodological and conceptual issues around trials designed to evaluate treatments for negative symptoms (Marder et al., 2013, Marder et al., 2011). The work of this project builds upon these findings, providing further insight on how negative symptoms may change over time in the context of a research trial, and the impact of different symptom inclusion criteria on the associations between negative symptoms and factors known to exacerbate these symptoms. In addition, the current investigation uses date from one of the first large-scale studies to use the CAINS, which have been considered an important advance in the field. Whilst earlier validation studies suggest that the scale as excellent psychometric properties (Horan et al., 2011, Kring et al., 2013), this investigation suggests the scale be a more sensitive instrument, be a stronger predictor of social and functional impairment, and by disentangling expressive and experiential deficits, may lead to further important insights in the field.

One significant limitation of the investigation as a whole is that all of the analysis has been completed using data from existing studies, either through pooling them by way of meta-analysis, or conducting analysis on datasets obtained from previous studies. Consequently, the scope of the analysis was limited by the nature of the data available. In chapter 3, an insufficient number of studies used a maximum level of EPS as an inclusion criterion for eligibility, meaning the impact of these criteria on negative symptom change could not be included in the meta-regression. In addition, a substantial degree of heterogeneity between the pooled studies was unexplained, which resulted in considerable imprecision in the estimates. This may account for the differences in the findings between chapters 3 and 4, where minimum negative and depressive symptom criteria were evaluated. In chapter 4, whilst the original dataset was relatively large (N=507), there was insufficient power to obtain

meaningful estimates from the most restrictive criteria evaluated due to the fact that the trial had not been powered for this purpose. In addition, the lack of any assessment of EPS meant these could not be considered as a third factor associated with secondary negative symptoms. In this sample the mean DDD was found to be relatively high, meaning it is possible that some participants may have experienced notable EPS. As a result, it is possible that parkinsonian symptoms such as akinesia may have mimicked expressive symptoms, resulting in a higher rating of negative symptoms that may not represent core psychopathology. Finally, using an assessment scale for depressive symptoms designed specifically for schizophrenia populations, such as the Calgary (Addington et al., 1992), would have been preferable given the issues in disentangling depressive and negative symptoms with the PANSS (Collins et al., 1996).

Given the meta-regression from chapter 3 had found that the SANS may be a more sensitive instrument to detect negative symptom change, relative to the PANSS, in chapter 5 it may have been preferable to compare the SANS to the CAINS in the analysis. However, given the extensive use of the PANSS in negative symptom treatment trials, as evidenced in the meta-analysis in chapter 3, determining the relationship between the two scales should still be regarded as an important step forward. In chapter 7, given the BPRS provides a relatively poor coverage of the negative symptom construct, the PANSS may have been a preferable assessment tool, given factor analytic studies have suggested the scale can provide relatively good coverage of various symptom clusters (see section 1.9.1.3. for a review).

Whilst prospective studies designed to address the stated aims would have meant that many of these limitations could have been addressed from the outset, this would have required significant resources far in excess of what would be available in an investigation of this scale.

8.4. Implications

8.4.1. Implications on research

The findings from chapters 3, 4 and 6 all suggest that negative symptoms appear to reduce over time to a greater extent than originally presumed, with the meta-analysis suggesting that there is a substantial degree of heterogeneity in the rate of change that exists between studies. These results could be considered to have a number of important implications to future research. Firstly, these findings underline the importance of comparing outcomes to an appropriate control, and the difficulty in determining whether within-group reductions found

in negative symptoms are attributable to treatment. This is important, given the assumption that negative symptoms are highly stable and treatment-resistant have previously led some researchers to conclude that within-group pre-post reductions suggest a clinically significant improvement as an effect of treatment (Sensky et al., 2000). Secondly, if there is more variability and a greater reduction in negative symptoms over time, and/or a larger placebo effect than previously assumed, then this suggests it may be harder to detect treatment effects than was previously thought, suggesting larger samples sizes may be required in some cases.

Building upon recent developments in our understanding of the negative symptom construct (Blanchard and Cohen, 2006, Blanchard et al., 2011), the CAINS is considered to represent a significant advance on older scales used to measure these symptoms (Kring et al., 2013). In an assessment of incremental validity, the CAINS was found to be more strongly associated to functional impairments related to negative symptoms, relative to the PANSS negative subscale. In chapter 6, the CAINS experiential subscale was negatively associated with subjective quality of life, whilst no relationship to the PANSS negative subscale was detected. In chapter 5, the CAINS was found to be a more sensitive than the PANSS, both in differentiating between participants with high and low negative symptoms, and in measuring changes in these symptoms over time. Given the limitations of earlier negative symptom assessment scales have been identified as a major barrier in the development of new treatments (Kirkpatrick et al., 2006), these findings suggest the CAINS may be a superior scale to adopt in clinical trials for negative symptom treatments. If so, then this may represent an important advance in treatment evaluation in an area which been identified as an unmet therapeutic need (Kirkpatrick et al., 2006). The findings from chapters 5 and 6 also suggest that the ability of the CAINS to evaluate expressive and experiential deficits as separate constructs may open up new insights and opportunities in the research of negative symptoms.

The results of chapter 4 suggest that adopting minimum negative and maximum depressive symptom study inclusion criteria reduces the association between negative and depressive symptoms. This supports the recommendations outlined in both the MATRICS and NEWMEDS reports (Kirkpatrick et al., 2006, Marder et al., 2013), and highlight the importance and effectiveness of adopting such criteria to minimise secondary negative symptoms attributable to depressive symptomology in future clinical trials. By contrast, adopting predominant negative symptom criteria was not found to reduce the association between negative and positive symptoms, and in most cases resulted in a substantial reduction in the sample pool size. If these inclusion criteria are not effective, then it suggests that alternative methodologies

may need to be considered to disentangle co-occurring changes in positive symptoms from negative symptoms in clinical trials for negative symptom treatments. Once such method may be to adopt a path analysis design, which has been adopted in a number of earlier pharmacological studies evaluating SGA's for negative symptoms (Alvarez et al., 2006, Moller et al., 1995, Tollefson and Sanger, 1997). However, such a method comes with the drawback that much larger samples may be required (MacCallum et al., 1996).

The findings in chapter 6 suggest the association between negative symptoms and SQOL may be significantly stronger than previously assumed, however the relationship appears to relate specifically to experiential subdomain of these symptoms. Such findings appear to support a model proposed by Priebe (Priebe, 2007) which suggests that quality of life may be improved by treatment indirectly via an improvement in symptoms. Given improvements in quality of life are considered central to the concept of recovery (Liberman et al., 2002) these findings suggest it is important to develop and evaluate new treatments which focus on the experiential symptoms of the negative symptom construct in particular. Given the initiation and development of social relationships are seen as a key feature of all resource-orientated models of psychiatric interventions (Priebe et al., 2014), such treatments may represent a promising area which could address experiential deficits such as amotivation and asociality, and merit further consideration.

8.4.2. Implications on policy

At present, both the FDA and EMA policy guidelines state that for negative symptom treatments to be considered eligible for approval then their effectiveness needs to be determined in clinical trials which evaluate negative symptoms as a singular construct (Marder et al., 2011). However, there is increasing evidence to suggest that negative symptoms comprise of at least two distinct domains, namely expressive and experiential symptoms (Blanchard and Cohen, 2006, Horan et al., 2011, Kring et al., 2013). In the current investigation completed in chapters 5 and 6, experiential deficits were found to be uniquely associated to objective indicators of social impoverishment, such as the participation of activities and friend contacts made over the past week, in addition to other important outcomes such as impaired subjective quality of life. Such links between experiential deficits and functional disability have been noted elsewhere, and have in turn led to efforts towards developing treatments specifically for experiential symptoms (Reddy et al., 2015). If such treatments prove to be effective at reducing experiential symptoms, and any functional disability which derive from

these symptoms, then the current policy guidelines may merit reconsidering. As outlined in the MATRICS consensus statement (Kirkpatrick et al., 2006), if the subdomains of negative symptoms respond differently to treatment, then it is possible that a combined negative symptom assessment may underreport clinically meaningful improvements in an individual symptom.

The current EMA guidelines require clinical trials evaluating adjunctive medications for negative symptoms to recruit participants that present with predominant, as opposed to prominent negative symptoms (EMA., 2012). The rationale for implementing such a policy is to determine that changes in negative symptoms are not attributable to co-occurring changes in positive symptoms. However, in chapter 4 it was found that adopting various different maximum positive symptom exclusion criteria did not reduce the association between positive and negative symptoms, and in some cases actually increased it. Furthermore, the increasingly restrictive criteria adopted appeared to result in a substantial reduction in the available sample pool which may have implications on trial recruitment and the generalisability of findings. Given that adopting maximum positive symptom criteria was found to be ineffective, these findings suggest that if the aim is to reduce the association between the variables then alternative methods may need to be proposed in new policy guidelines.

8.4.3. Implications on practice

The findings from chapters 3, 4, and 6 all suggest that negative symptoms may significantly reduce over time in stable outpatients, even after adopting criteria which aims to reduce the impact of secondary negative symptoms. Whilst acknowledging that the changes in negative symptoms were relatively small, and the fact it is difficult to determine what the nature of this measured change actually is, this improvement over time appears to lend support to the recovery model of schizophrenia (Warner, 2009), given these symptoms links to functional outcomes (Hunter and Barry, 2012, Lysaker and Davis, 2004, Whitty et al., 2008). Such findings may provide hope to those that experience these symptoms, in addition to those who work with patients to help try and alleviate the impact of this devastating disorder.

The findings in both chapters 5 and 6 suggest that the experiential and expressive subdomains of negative symptoms appear to be related to outcomes differently. In support of these findings, the link between functional disability and experiential symptoms in particular has been noted in the literature (Reddy et al., 2015). In chapter 5, experiential symptoms were

found to have a stronger inverse relationship to how socially engaged the participants reports to be, relative to experiential symptoms. In chapter 6, experiential symptoms were found to be significantly associated to subjective quality of life, whilst no relationship to expressive symptoms was apparent. Given the the ability to maintain satisfying relationships and participate in productive and enjoyable activities are seen as central to the concept of recovery (Liberman et al., 2002), these findings suggest that extra consideration should be given to addressing experiential symptoms in routine practice.

The findings in chapter 7 emphasise the importance of measuring symptoms at the point of inpatient admission, and considering the impact of manic and positive symptoms in particular during the initial phase of acute treatment. Whilst no association between negative symptoms and initial appraisal of impatient was detected, the results underline the importance of assessing patients' initial appraisal of treatment as a relevant process variable in routine practice. In a recent review Mullen (Mullen, 2009) has suggested that acute inpatient settings are at present too custodial and over reliant on medication, and suggests that providing more psychosocial interventions as an alternative may be a way in which to try and address these issues. If these are problems which disproportionally affect those experiencing higher positive and manic symptoms, then this possible solution may go some way to addressing the experiences these particular patients report.

8.5. Future directions

The results in this investigation point to a number of possible future directions for research. The findings in chapter 3, 4 and 6 all suggest that negative symptoms improve during the study period. However, understanding the nature of the improvement in negative symptoms over time requires further attention. The duration between time points was not found to be a significant predictor, but with the considerable variability in treatment duration, post treatment follow-up duration, and post treatment provision between studies, this is perhaps not surprising. In longitudinal studies assessing persistent negative symptoms over very long periods of time, there has been little evidence of a gradual linear improvement towards symptom remission (Strauss et al., 2010), whilst the rate of recovery in schizophrenia remains low (Jääskeläinen et al., 2013). One explanation of the improvement in negative symptoms noted throughout this investigation could be the non-specific effects of being involved in the research, possible related to the "trial effect" (Braunholtz et al., 2001). However, the mechanism that drives change in this context is unclear. One possibility is that a reduction in

negative symptoms found between the first and subsequent assessments may be a consequence of increased familiarity with the assessor and the assessment process itself. If a good rapport was established in the first assessment, then it is possible that this may result in the participant being less anxious in subsequent assessments. This is significant, given symptoms of anxiety in schizophrenia are positively associated with passive withdrawal and poorer psychosocial functioning (Lysaker and Salyers, 2007). If this is the case, then it suggests that the improvement detected between assessments may be secondary rather than primary, in nature. Studies exploring the possibility that secondary negative symptoms may be more prominent in initial assessments may be merited, given the importance attached to minimising transient secondary negative symptoms in clinical trials of treatments for these symptoms (Kirkpatrick et al., 2006).

Another possible reason for the reduction in negative symptoms typically found in research settings, regardless of the type of intervention administered, may be related to the type of social interactions which occur within these studies. If the improvement in negative symptoms is related to increased social contact during studies, then treatments that promote social interactions such as befriending schemes and group psychotherapies may be a possible step forward. Recent findings suggesting a non-specific effect of group therapies on negative symptoms (Orfanos et al., 2015) appear to support this possibility. As a result, additional studies which examine the impact of these more socially-oriented treatments may be informative.

Whilst the meta-analysis did consider studies that implemented criteria which aimed to limit the impact of secondary negative symptoms, none used criteria which would qualify as determining a diagnosis of deficit syndrome (Carpenter et al., 1988, Kirkpatrick et al., 1989). The principle reason for this is that studies that did adopt these criteria often included participants with schizoaffective disorder or inpatients (Buchanan et al., 2007). Amending the inclusion criteria to focus on these particular studies would allow for a greater understanding of any change in primary negative symptoms. Due a lack of available data the impact of extra-pyramidal side effects on the variability of negative symptom change could not be explored, which would be informative in further determining longitudinal course. In addition, as more studies are completed using the newer BNSS and CAINS scales, an evaluation of these tools would be helpful in determining their sensitivity to other assessment tools.

The findings in chapter 4 suggest that adopting a maximum positive symptom exclusion criterion does not appear to result in a reduction in the association between positive and

negative symptoms. However, given much of the criteria evaluated resulted in a substantial number of participants being excluded, the samples on which many of the estimates were based on were small. Therefore, replicating this study in a far larger sample would be informative, particularly given larger sample sizes would allow for a greater comparison between the different R^2 values through calculating narrower confidence intervals. Larger sample sizes would also allow for the possibility of conducting path analysis, looking at the proportion of change in negative symptoms over time associated with co-occurring changes in positive, depressive, and extra-pyramidal symptoms in subsamples obtained using the different eligibility criteria.

The results in chapter 5 suggest that the CAINS may be a more sensitive instrument than the PANSS in measuring changes in negative symptoms. However, given the results from the meta-regression in chapter 3 suggest that the SANS may also be more sensitive than the PANSS, a comparison of the CAINS and the SANS would be informative in determining whether the new scale represents a significant advance over all previously available scales. Another step forwards would be a comparison of the results obtained from different scales within a clinical trial where a treatment effect is present. If the CAINS produces larger effect sizes than other scales used, then this may go some way improving the evaluation of treatments designed to treatment these symptoms.

In chapter 6, the finding that experiential symptoms were primarily linked to subjective quality of life suggest that it may be beneficial to revisit the link between the different subdomains of negative symptoms and other functional outcomes. In addition, it emphasises the pressing need to develop treatments that are particularly effective at treating experiential symptoms, namely asociality, anhedonia and avolition. Following the findings in chapter 7, further studies may explore environmental factors, processes of interaction between service users and staff, treatment components, and mediating processes as an explanation into the association of manic and positive symptoms with more negative appraisals of hospital treatment after only a few days.

8.6. Concluding Statement

Over the years the concept of negative symptoms have undergone a number of important revisions, from the “avolitional syndrome” proposed by Kraepelin (Kraepelin, 1971), to the current model of negative symptoms which include alogia, blunted affect, avolition, anhedonia

and asociality (Blanchard et al., 2011). The findings of this thesis suggest that the CAINS, which was developed to better represent our current interpretation of the negative symptom construct (Kring et al., 2013), may represent a significant advance in older assessment tools. This is important, as the limitations inherent to earlier assessment scales have been identified as a significant barrier in the development of new treatments for negative symptoms (Kirkpatrick et al., 2006).

In this study CAINS was found to be a more sensitive instrument in detecting negative symptom change, reported a greater differentiation between participants who reported high and low symptoms, and reported stronger association to functional outcomes and SQOL relative to the PANSS negative subscale. The fact that the CAINS is designed to measure the expressive and experiential features of negative symptoms as distinct constructs may be particularly important, given the evidence presented here which suggests the subdomains may be independently associated to functional outcomes. The finding that it is only the experiential deficits of the negative symptom construct that are associated to SQOL suggest that more targeted treatments which focus on these particular symptoms may represent a new way forward in supporting the recovery of patients with schizophrenia.

Overall, many of the findings in this investigation could be considered to offer renewed optimism to those who experience the negative symptoms of schizophrenia. Collectively the results suggest that negative symptoms may improve more than was originally assumed, challenging earlier models of schizophrenia which have either suggested negative symptoms are either highly stable, or get progressively more severe. This improvement over time was found in stable outpatient samples with relatively low positive and depressive symptoms, suggesting that improvements in these symptoms may be achievable at all phases of the disorder.

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Appendix I. Meta-analysis examining the course of negative symptoms

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ORIGINAL ARTICLE

Do negative symptoms of schizophrenia change over time? A meta-analysis of longitudinal data

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Background. Negative symptoms are a core component of schizophrenia which can severely impact quality of life and functional outcomes. These symptoms are understood to be highly stable but this has not been tested in a meta-analysis, despite the wealth of longitudinal data available.

Method. A systematic review of the literature was conducted, with eligible studies pooled into a random-effects meta-analysis. Planned meta-regressions were conducted to evaluate the impact of factors known to induce secondary negative symptoms, in addition to other possible sources of heterogeneity.

Results. The main analysis included 89 samples from 41 studies, totalling 5944 participants. Negative symptoms were found to significantly reduce in all treatment interventions, including in placebo and treatment as usual conditions, with a medium effect size (ES) present across all study conditions (ES = 0.66, 95% confidence interval 0.56–0.77, $I^2 = 94.0\%$). In a multivariate meta-regression, only the type of scale used was found to significantly influence negative symptom change. No difference in outcome was found between studies that excluded patients with a high level of positive or depressive symptoms, compared to those that did not.

Conclusions. Negative symptoms were found to reduce in almost all schizophrenia outpatient samples. A reduction was found across all conditions, with effect sizes ranging from small to large depending upon the condition type. These findings challenge the convention that negative symptoms are highly stable and suggest that they may improve to a greater extent than what has previously been assumed.

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Key words: Longitudinal course, negative symptoms, schizophrenia, symptom assessment.

Introduction

Since Bleuler coined the term schizophrenia in the early 1900s negative symptoms have been recognized as a core feature of the disorder (Bleuler, 1950). The symptoms include alogia, asociality, blunted affect, anhedonia and amotivation (Blanchard *et al.* 2011), and have been found to severely impact both quality of life and social functioning (Norman *et al.* 2000).

Historically, negative symptoms were believed to increase over time as patients experience a progressive deterioration in functioning (Kraepelin, 1971). However, in observational studies which evaluated the progressive course of these symptoms the evidence initially suggested that these are largely stable over time (Pogue-Geile & Harrow, 1985; Fenton & McGlashan, 1991; Dollfus & Petit, 1995; Eaton *et al.* 1995). Later work recognized that the course was highly heterogenous, with some negative symptoms improving, often in tandem with improvement in positive symptoms (Addington & Addington, 1991). In an attempt to explain this heterogeneity Carpenter and colleagues proposed a distinction between those attributable to factors such as hospitalization, medication side-effects, depression, and elevated positive symptoms (known as secondary negative symptoms), from primary symptoms which were regarded as a core feature of the disorder itself (Carpenter *et al.* 1985). While secondary symptoms tend to improve relatively quickly once the causes are addressed, primary negative symptoms are thought to be largely persistent (Möller, 2007).

Broadly defined, primary negative symptoms refer to negative symptoms which are present both within and during periods of positive symptom exacerbation. However, distinguishing between primary and secondary negative symptoms can be a complex undertaking given the challenges in obtaining sufficient historical information and the level of clinical expertise required by the assessors. In light of this, Buchanan

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(2007) suggested the alternative, broader distinction of 'persistent negative symptoms', which include negative symptoms which remain present after usual treatments for secondary negative symptoms have failed. In the consensus statement for negative symptoms, it was proposed that distinguishing between primary and secondary negative symptoms was not essential for the purposes of testing therapeutics, as long as studies select participants with persistent symptoms and control for secondary sources of negative symptoms (Kirkpatrick *et al.* 2006).

To date, any advances in the treatment of schizophrenia have been found to provide only limited benefit to negative symptoms. In a meta-analysis which examined the efficacy of different second-generation antipsychotics, most were found not to provide a significant benefit over and above first-generation drugs, and in those that did the effect sizes were small (Leucht *et al.* 2009). Meta-analyses into the efficacy of adjunctive medications such as α_2 receptor antagonists (Hecht & Landy, 2012) and glutamatergic compounds (Tuominen *et al.* 2005) show some promise, while there is some evidence to suggest that adjunctive antidepressant medication may have some limited benefit (Singh *et al.* 2010). In a broader review evaluating the different pharmacological approaches in treating negative symptoms (Arango *et al.* 2013), new drugs that act on the NMDA and α_7 nicotinic receptors are highlighted as promising, but again more research is needed. In a series of meta-analyses on psychotherapeutic interventions, CBT was reported to have a small effect (Jauhar *et al.* 2014), social skills training a moderate effect (Kurtz & Mueser, 2008), while no effect was found for social cognitive training (Kurtz & Richardson, 2012). In a meta-analysis of cognitive remediation therapy which evaluated symptoms overall, a small effect was detected (Wykes *et al.* 2011). In the UK, NICE have previously recommended Arts therapies (NCCMH, 2010); however, this has since been challenged by the non-significant result of the MATISSE trial (Crawford *et al.* 2012). Overall, a lack of treatment efficacy has led to negative symptoms to be recognized as an unmet therapeutic need, and an important target for new interventions (Kirkpatrick *et al.* 2006).

Given the current focus on developing new interventions for negative symptoms, understanding their longitudinal course is important for future study design. Many of the earlier observational studies included inpatients, which is problematic given this population would typically receive far higher doses of antipsychotic medication and experience higher positive symptoms (Kasckow *et al.* 2001), and may reside in an under-stimulating environment (Oshima *et al*. 2003), which may induce negative symptoms secondary to the disorder itself. In addition, a number of the earlier studies included other illnesses such as schizoaffective disorder, which follows a different longitudinal course and can have poorer diagnostic stability, which again may influence symptom change over time (Malhi *et al.* 2008).

The objective of this study was to examine how negative symptoms change over time in schizophrenia outpatients, while exploring the impact of factors known to induce secondary negative symptoms. By pooling a wide variety of studies by way of meta-analysis, the aim was uncover broader trends in how these symptoms may change, as opposed to attempting to identify an estimate of effect size for a particular type of treatment. Following a systematic search, we conducted a meta-analysis of the within-group mean changes in negative symptoms. Only samples comprising exclusively of schizophrenia patients from the first assessment point were considered. Due to the expected heterogeneity between different interventions, separate effect size estimates were calculated for each treatment type. Finally, a series of planned meta-regressions were conducted to explore any impact of factors which may lead to secondary negative symptoms (Carpenter *et al.* 1985), and possible sources of methodological bias.

Method

Research in context

The systematic review was conducted following PRISMA statement guidelines (Liberati *et al.* 2009). An electronic search using the Medline, PsycINFO, EMBASE and CENTRAL databases was conducted dating back to 1962, which was when the Brief Psychiatric Rating Scale (BPRS) was first published (Overall & Gorham, 1962). The search was conducted on 26 April 2014 and contained three parameters. The first related to diagnosis, the second to negative symptoms, and the third an indicator that the study took place over at least two time points.

A hand-search of the *American Journal of Psychiatry, Acta Scandinavica Psychiatrica, British Journal of Psychiatry, Schizophrenia Bulletin, JAMA Psychiatry, The Lancet*, and *Schizophrenia Research* was conducted, either from 1962 or the date of first issue, and reference lists from all selected papers were hand-searched. During extraction, all assessments of negative symptoms, study inclusion/exclusion criteria, demographic details, industry sponsorship, and study methodology details were recorded. When necessary, corresponding authors were contacted for further information. In the case of missing standard deviations, a mean from the existing sample was imputed when possible. M.S.

conducted the abstract screening, 20% of which was duplicated by C.B. with minimal discrepancies in selection detected. In the full paper screening phase M.S. conducted 100% of the screening, duplicated by H.K. and C.B. screening 50% of the sample each. All discrepancies were resolved without the need for S.P. to adjudicate as planned. At the full screening phase, all data were independently extracted onto a piloted extraction sheet.

Eligibility criteria

During the screening phase studies were excluded if they were clearly not relevant, did not have repeated assessments of negative symptoms at set time points, included no usable data on an exclusively schizophrenic sample, children or older adults, or were either under 10 weeks in length or over 3 years in length from the first follow-up assessment. Studies which included inpatients were considered, as long as the study included one time-point where the sample was exclusively outpatients, and then followed up from a standardized time-point from this assessment. Symptoms were required to be measured on a validated scale. Qualitative studies, case reports, letters to the editor, conference abstracts and book chapters were excluded. All articles were required to be published in a language which used Latin-based characters. Due to the analytical strategy adopted and the risk of small samples leading to biased estimates (Morris, 2000), studies with fewer than 50 participants were excluded.

Analysis plan

In the pooled analysis, the measure of effect size for each study was calculated using the standardized mean change (SMC) (Becker, 1988; Morris, 2000). The estimation of the variance was calculated using the large-sample approximation method recommended by Becker (1988), which can provide accurate estimates provided the sample sizes are adequately sized (Morris, 2000). The estimate of the correlation between the baseline and end of study scores was set at 0.633, based upon datasets held at our research group (Priebe *et al.* 2007) and a subsequent sensitivity analysis.

In deciding the appropriate effects model to adopt, the decision was complicated by the likelihood that multiple arms of the same study would be separately eligible for inclusion. One method of addressing this which was recognized in the *Cochrane Handbook* (Higgins & Green, 2011), is to conduct a two-level, fixed-effects meta-analysis across arms within studies, followed by a random-effects meta-analysis across studies, as a way to account for the mix in fixed and random effects that are likely to be present. However, this model adds considerable complexity to the analysis, while the handbook itself acknowledges that 'in practice the difference between different analyses is likely to be trivial' (section 16.5.5). This being the case, the method was not used, and the DerSimonion and Laird random-effects model was adopted (DerSimonian & Laird, 1986). All analysis was completed using Stata version 11 (StataCorp, 2009).

In cases where multiple scales were used to measure negative symptoms, the primary outcome measure was selected. When negative symptoms were measured over more than two time points, only the baseline and the study endpoint data were selected.

In the first stage of the analysis samples were grouped according to whether the intervention involved testing second-generation antipsychotics, first-generation antipsychotics, adjunctive medications, non-drug interventions, or placebo/treatment as usual (TAU) arms. In the next stage a series of planned univariate meta-regressions were conducted, with those found to approach significance ($p < 0.10$) entered into a multivariate model. First, we examined the impact of length of treatment in order to assess whether there was any trend over time. Next, we tested whether there was any difference between studies which incorporated a maximum threshold for positive and depressive symptoms, compared to those that did not, in order to assess whether the degree of change in negative symptoms varied dependent upon how studies dealt with factors which can cause secondary negative symptoms. We also tested the impact of blinding the assessors, a minimum negative symptom inclusion criterion, and whether the study received industry sponsorship.

In any examination of the change in a continuous variable over time which only includes two time points the issue of regression to the mean should be considered (Chiolero *et al.* 2013). This being the case, the mean negative symptoms at baseline were added to the final multivariate model to determine the degree of additional variance that may be explained by a greater reduction in negative symptoms being caused by a higher baseline symptom levels.

Results

A flow diagram depicting the search strategy for studies is included in Fig. 1. Of the 9480 articles screened, 49 articles were found and 41 were included in the final analysis (see Table 1). From these, a total of 89 separate samples were obtained. Of the 41 studies, five came from the USA; four each from Canada, Germany and the UK; three each from India, Spain and Turkey; two each from China, France and Italy;

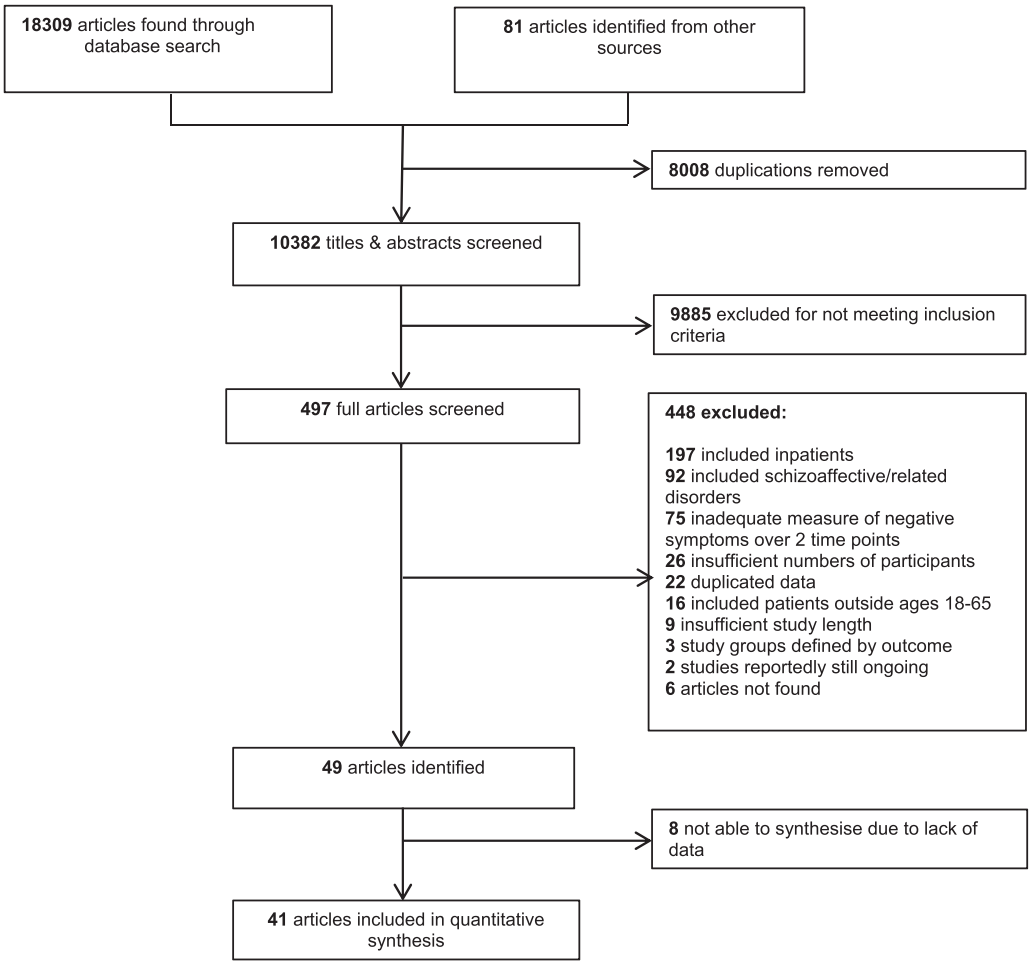

Fig. 1. Flow diagram outlining study selection procedure.

and one each from Brazil, Finland, Israel, Nepal, Poland and Serbia. Four studies were conducted in multiple countries, with sites in Northern America, Europe and Asia. Based on 51 samples, the median of study mean illness duration was 12.4 years (range 0.6–27.5 years). Twenty-three studies measured negative symptoms using the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987), 14 used the Scale to Assess Negative Symptoms (SANS; Andreasen, 1983), and four used the BPRS (Overall & Gorham, 1962). While studies which used alternative scales were screened, none met eligibility criteria. After pooling all 89 samples, a final total of 5944 participants were included in the meta-analysis.

As indicated in the forest plot (see Fig. 2), in all five intervention types a significant reduction in negative symptoms was found between the baseline and the follow-up assessment stage. Large effect sizes (ES) were detected in second-generation antipsychotics [ES = 1.09, 95% confidence interval (CI) 0.86–1.32, I^2 = 95.5%] and the adjunctive medication (ES = 0.97, 95% CI 0.68–1.26, I^2 = 91.7%) arms, while a small effect size was noted in the placebo/TAU group (ES = 0.33, 95% CI 0.17–0.49, I^2 = 91.8%).

Next, a series of meta-regressions were conducted. In the univariate analyses the scale used, intervention type, study duration, and a minimum negative symptoms inclusion criterion were all associated with negative symptom change heterogeneity (see Table 2). A maximum level of positive symptoms and previous non-response to treatment as exclusion criteria were found to approach significance ($p < 0.10$), while other variables were non-significant. In the multivariate model, only the type of scale used and the type of intervention received remained significant. Studies which used the SANS found a significantly greater reduction in negative symptoms relative to those that used the PANSS (SANS: ES = 1.02, 95% CI 0.77–1.28; PANSS: ES = 0.66, 95% CI 0.56–0.77). Collectively, the scale used and the intervention type accounted for 43.65% of the variance. In a sensitivity analysis, the sample-level baseline negative symptoms were added to the model which was found to be a significant predictor (B = 0.01, S.E. = 0.00, 95% CI 0.00–0.02). However,

Table 1. *Characteristics of eligible studies*

Authors	Year	Country	Study duration (weeks)	Outcome measure[a]	Individual symptoms reported	Intervention type[b]	*n*
Addington & Addington (2000)	2000	Canada	130	PANSS	No	TAU	65
Aguglia *et al.* (2002)	2007	Italy	52	SANS	Yes	Non-drug intervention: psychoeducation	69
						TAU	66
Alptekin *et al.* (2005)	2005	Turkey	52	BPRS	No	TAU	382
Alvarez *et al.* (2006)	2006	Spain	48	SANS	Yes	SGA: olanzapine	120
						SGA: risperidone	115
Amell & Llandrich (2008)	2008	Spain	46	PANSS	Yes	Non-drug intervention: skills training group	35
						TAU	22
Bales *et al.* (2009)	2009	Nepal	18	PANSS	No	TAU	30
						TAU + betel nuts	30
Behere *et al.* (2011)	2011	India	16	PANSS	No	Non-drug intervention: yoga group	34
						Non-drug intervention: exercise group	31
						TAU	26
Bhowmick *et al.* (2010)	2010	India	12	SANS	No	SGA: amisulpride	40
						SGA: olanzapine	40
Bio & Gattaz (2011)	2011	Brazil	26	PANSS	No	TAU	57
Bobes *et al.* (2009)	2009	Spain	34	BPRS	No	SGA: risperidone	362
Bodkin *et al.* (2005)	2005	USA	12	SANS	Yes	Adjunctive: selegiline	33
						Placebo	34
Crawford *et al.* (2012)	2012	UK	52	PANSS	No	TAU	137
						Non-drug intervention: activity group	140
						Non-drug intervention: art therapy group	140
Fleischhacker *et al.* (2003)	2003	Multi	52	PANSS	No	SGA: risperidone	120
						SGA: risperidone	228
						SGA: risperidone	267
Gaebel *et al.* (2007)	2007	Germany	52	PANSS	No	SGA: risperidone	77
						FGA: haloperidol	74
Gorna *et al.* (2008)	2008	Poland	52	PANSS	No	TAU	88
Hirsch *et al.* (2002)	2002	Germany	28	PANSS	No	SGA: ziprasidone	110
						FGA: haloperidol	117
Kane *et al.* (2011)	2011	USA	26	PANSS	No	TAU: remained on same drug	194
						Placebo: switched to placebo	192
Kane *et al.* (2012)	2012	USA	24	PANSS	No	Adjunctive: armodafinil	70
						Adjunctive: armodafinil	69
						Adjunctive: armodafinil	71
						Placebo	70
Kaphzan *et al.* (2014)	2014	Israel	12	PANSS	No	Placebo	22
						Adjunctive: entacapone	23
Klingberg *et al.* (2011)	2011	Germany	52	PANSS	Yes	Non-drug intervention: CBT	99
						Non-drug intervention: CRT	99
Lasser *et al.* (2013)	2013	USA	10	SANS	No	Adjunctive: lisdexamfetamine dimesylate	92
Lecrubier *et al.* (2006)	2006	France	26	SANS	No	Placebo	34
						SGA: olanzapine	70
						SGA: olanzapine	70

Table 1 (*cont.*)

Authors	Year	Country	Study duration (weeks)	Outcome measure[a]	Individual symptoms reported	Intervention type[b]	*n*
						SGA: amisulpride	70
Liu *et al.* (2014)	2014	China	16	PANSS	No	Placebo	40
						Adjunctive: minocycline	39
Loebel *et al.* (2007)	2007	India	64	PANSS	No	SGA: ziprasidone	32
						SGA: ziprasidone	30
Loo *et al.* (1997)	1997	France	26	SANS	Yes	Placebo	72
						SGA: amisulpride	69
Meltzer *et al.* (2010)	2010	USA	52	BPRS	No	SGA: clozapine	40
						FGA: various first-generation drugs	45
Olie *et al.* (2006)	2006	Multi	12	PANSS	No	SGA: ziprasidone	59
						SGA: amisulpride	63
Pach *et al.* (1998)	1998	Germany	52	SANS	Yes	FGA: flupenthixol decanoate	63
Peet & Horrobin (2002)	2002	UK	12	PANSS	No	Placebo	31
						Adjunctive: eicosapentaenoic acid	32
						Adjunctive: eicosapentaenoic acid	32
						Adjunctive: eicosapentaenoic acid	27
Purdon *et al.* (2000)	2000	Canada	54	PANSS	No	SGA: olanzapine	21
						FGA: haloperidol	23
						SGA: risperidone	21
Ravanic *et al.* (2009)	2009	Serbia	52	PANSS	No	FGA: haloperidol	70
						FGA: haloperidol	35
						FGA: chlorpromazine	65
						FGA: chlorpromazine	40
						SGA: clozapine	65
						SGA: clozapine	50
Richardson *et al.* (2007)	2007	UK	38	SANS	No	TAU	46
						Non-drug intervention: art therapy group	43
Semiz *et al.* (2007)	2007	Turkey	12	SANS	No	SGA: clozapine	97
Schoemaker *et al.* (2014)	2014	Multi	12	SANS	Yes	Adjunctive: Org25935 low dose	71
						Adjunctive: Org25935 high dose	73
						Placebo	70
Sumiyoshi *et al.* (2007)	2007	USA	26	BPRS	No	Adjunctive: buspirone	30
						TAU	29
Taiminen *et al.* (1997)	1997	Finland	12	PANSS	No	TAU	39
						Adjunctive: citalopram	36
Turkington *et al.* (2008)	2008	UK	78	SANS	No	Non-drug intervention: CBT	46
						Non-drug intervention: befriending	44
Ucok *et al.* (2011)	2011	Turkey	52	SANS	No	TAU	52
						TAU	41
Voruganti *et al.* (2007)	2007	Canada	52	PANSS	No	SGA: olanzapine	42
						SGA: quetiapine	43

Table 1 (*cont.*)

Authors	Year	Country	Study duration (weeks)	Outcome measure[a]	Individual symptoms reported	Intervention type[b]	*n*
Xiang *et al.* (2006)	2006	China	34	PANSS	No	Non-drug intervention: community re-entry	48
						Non-drug intervention: counselling	48
Zoccali *et al.* (2007)	2007	Italy	24	SANS	Yes	Adjunctive: lamotrigine	26
						Placebo	25
List of studies not included in the main analysis due to insufficient data							
Adams *et al.* (2013)	2013	Multi	24	NSA-16	No	SGA: multiple types	130
						SGA: LY2140023	131
Chouinard *et al.* (1975)	1975	Canada	12	BPRS	No	Placebo	24
						FGA: amitriptyline hydrochloride	24
						FGA: perphenazine	24
						FGA: amitriptyline perphenazine	24
Goff *et al.* (2005)	2005	USA	26	SANS	Yes	Adjunctive: D-cycloserine	26
						Placebo	25
Hayes *et al.* (1995)	1995	Australia	44	SANS	No	Non-drug intervention: skills training group	n/s
						Non-drug intervention: discussion group	n/s
Liberman *et al.* (1998)	1988	USA	156	BPRS	No	Non-drug intervention: occupational therapy	n/s
						Non-drug intervention: skills training group	n/s
Lieberman *et al.* (2013)	2013	Multi	12	SANS	No	Adjunctive: TC-5619	94
						Placebo	91
Marder *et al.* (2003)	2003	USA	104	SANS	Yes	SGA: risperidone + skills training	33
						FGA: haloperidol + skills training	30
Pinto *et al.* (1979)	1979	UK	78	BPRS	No	FGA: flupenthixol decanoate	34
						FGA: fluphenazine decanoate	30

[a] PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; SANS, Scale to Assess Negative Symptoms; NSA-16, Negative Symptom Assessment – 16.

[b] TAU, treatment as usual; SGA, second-generation antipsychotic; Adjunctive, adjunctive medication in addition to antipsychotic medication received; FGA, First-generation antipsychotic; CBT, cognitive behaviour therapy; CRT, cognitive remediation therapy.

the additional variance explained was relatively small (4.10%).

Although many of the studies evaluated extra-pyramidal symptoms (EPS) as part of their analysis (53.7%), only three studies specified an EPS maximum threshold as an exclusion criterion (Klingberg *et al.* 2011; Lasser *et al.* 2013; Schoemaker *et al.* 2014). Given the lack of data, this was not included in the meta-regression analysis. Of those studies that did report EPS, they were generally considered to be in the low range at study intake, suggesting that the impact of EPS on negative symptoms was likely to be minimal.

Given the finding that second-generation antipsychotics and adjunctive medication arms resulted in much larger effect sizes than other treatment types, contrary to our expectations based on the existing literature (i.e. Leucht *et al.* 2009; Arango *et al.* 2013), the TAU and placebo control arms that they were compared to were explored in more depth. A substantially larger effect size was detected in TAU/placebo control arms which were part of the drugs trials, in

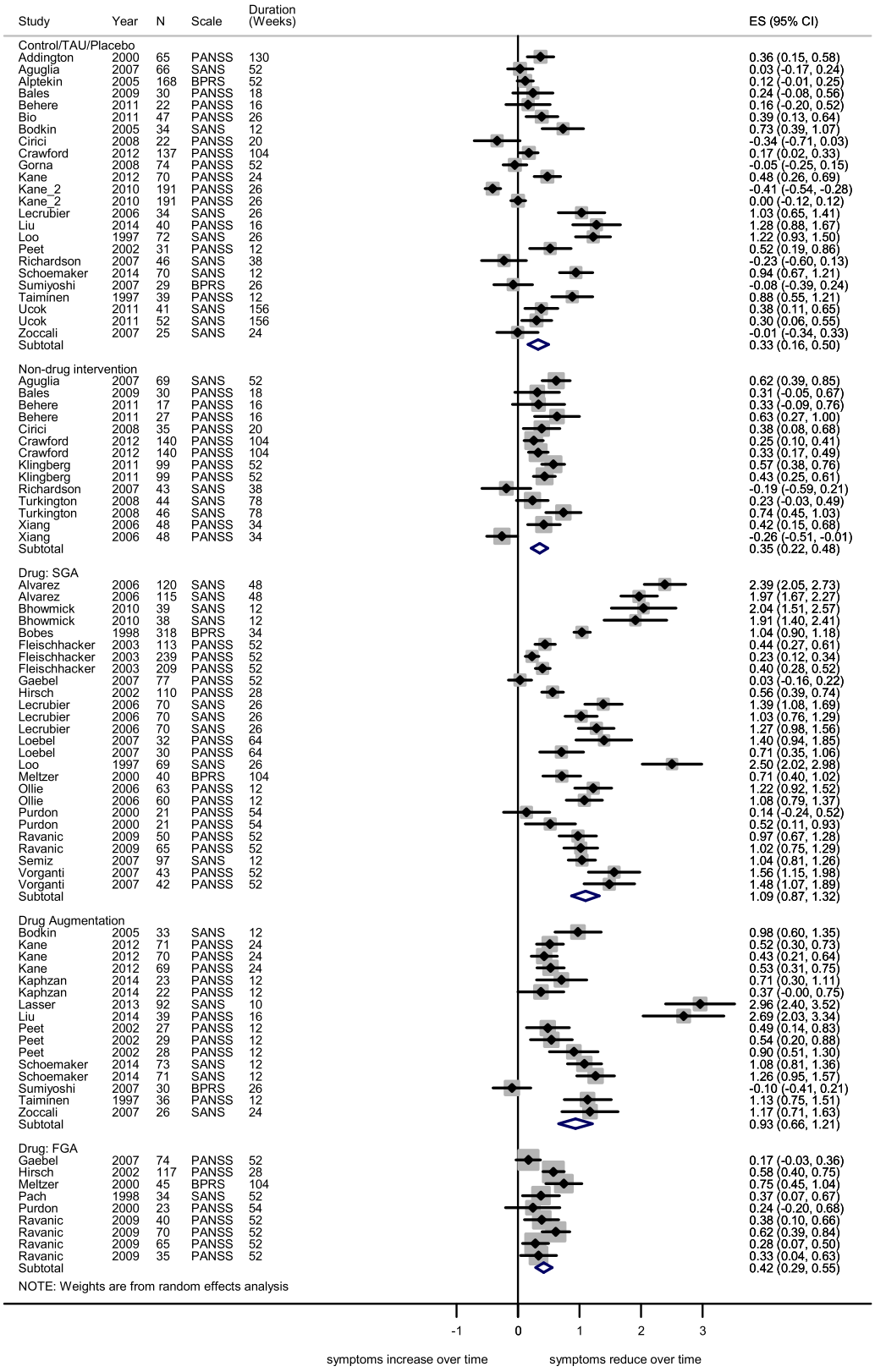

Fig. 2. Forest plot of the change in negative symptoms, by intervention type.

Table 2. *Univariate and multivariate meta-regressions examining the heterogeneity of negative symptom change*

	Univariate analysis			Multivariate analysis		
Predictor of negative symptom change	Coefficient	95% CI	*p*	Coefficient	95% CI	*p*
Study duration	−0.01 (0.00)	−0.01 to −0.00	0.035	−0.00 (0.00)	−0.01 to 0.00	0.388
Scale used (compared to PANSS)			0.002			
SANS	0.49 (0.14)	0.21 to 0.77		0.43 (0.13)	0.16 to 0.70	0.002
BPRS	−0.12 (0.26)	−0.63 to 0.40		−0.07 (0.23)	−0.54 to 0.39	0.760
Intervention type (compared to SGA)			<0.001			
Non-drug intervention	−0.75 (0.18)	−1.11 to −0.38		−0.67 (0.18)	−1.04 to −0.30	0.001
TAU/placebo	−0.76 (0.16)	−1.07 to −0.45		−0.72 (0.16)	−1.04 to −0.40	<0.001
Drug: FGA	−0.68 (0.18)	−1.10 to −0.25		−0.53 (0.20)	−0.93 to −0.13	0.010
Drug: augmentation	−0.12 (0.18)	−0.48 to 0.23		−0.17 (0.18)	−0.54 to 0.19	0.336
Min negative symptoms	0.37 (0.13)	0.10 to 0.63	0.007	0.11 (0.12)	−0.13 to 0.36	0.356
Max positive symptoms	0.26 (0.14)	−0.02 to 0.54	0.071	0.05 (0.13)	−0.21 to 0.32	0.685
Study supported by industry sponsorship	0.15 (0.14)	−0.14 to 0.43	0.309			
Exclusion: previous non-response	0.42 (0.18)	0.07 to 0.78	0.019	0.05 (0.17)	−0.29 to 0.40	0.752
Raters blinded to allocation[a]	−0.18 (0.15)	−0.47 to 0.12	0.234			
Exclusion: moderate levels of depression	0.13 (0.17)	−0.21 to 0.46	0.452			

CI, Confidence interval; PANSS, Positive and Negative Syndrome Scale; SANS, Scale to Assess Negative Symptoms; BPRS, Brief Psychiatric Rating Scale; SGA, second-generation antipsychotic; TAU, treatment as usual; FGA, first-generation antipsychotic.

Values within parentheses are standard errors.

[a] One study not included due to lack of data.

comparison to those that were not (ES = 0.67, 95% CI 0.41–0.93, in comparison to ES = 0.15, 95% CI 0.04–0.25). In a subsequent meta-regression this difference was found not to be attributable to either higher negative symptoms at baseline, or the type of assessment tool used, which were significant predictors in the full model.

Examination of individual negative symptoms

In 18 samples over nine studies the change in individual negative symptoms were also reported (see Table 1). Seven studies used the SANS as the rating tool, while two used the PANSS. Scores from different scales were combined using the method proposed by Lyne and colleagues (2012). A significant reduction was found in all four of the symptoms measured (affective blunting, alogia, avolition-apathy, anhedonia-asociality). Of the four, alogia appeared to reduce the least (ES = 0.64, 95% CI 0.45–0.83) and avolition-apathy the most (ES = 0.77, 95% CI 0.53–1.01); however, the difference between the items appeared minimal.

Eligible studies not pooled into the main analysis

Eight studies were found to be eligible, but could not be included in the main analysis (see Table 1). In line with the main results, 11 samples found some form of reduction in negative symptoms from baseline to end of study, five saw no change, and in two the change was not specified.

Discussion

Main results

The meta-analysis provided a clear result; negative symptoms of schizophrenia tend to improve significantly in an outpatient setting. A reduction in negative symptoms found across all intervention types, with the effect sizes ranging from small to large. A significant reduction was found in all four of the separate negative symptoms examined, covering both experiential and expressive features of the disorder. While substantial heterogeneity was present in the sample, a series of planned meta-regressions indicated that there was no difference in the reduction between studies which did and did not exclude participants with higher levels of positive or depressive symptoms. In addition, study-level methodological differences such as whether assessors were blinded, the symptom eligibility criteria, or whether the study received industry sponsorship did also not appear to influence the result.

Strengths and limitations

One of the main strengths of the study is that, despite the broad range of study interventions considered, the

findings are consistent. Of the 89 study arms included, only one found a clear significant increase in symptoms. In this case, the sample was part of a continuation study where patients who had previously responded well to their SGA medication were then switched to a placebo (Kane *et al.* 2011). In addition, when testing for the effect of regression to the mean, adding baseline negative symptoms to the multivariate model appeared to add relatively little additional explanatory power of the variance (4.1%), suggesting the findings are relatively robust. A further strength of this study is that despite the broad study inclusion criteria, removing samples which included inpatients at baseline, and other psychotic diagnoses, meant the participant inclusion criteria were relatively stringent in comparison to other observational studies that have looked at how negative symptoms change over time (i.e. Pogue-Geile & Harrow, 1985; Fenton & McGlashan, 1991; Dollfus & Petit, 1995; Eaton *et al.* 1995). When testing for heterogeneity, no difference in the effect size was detected between studies which excluded participants with elevated positive and depressive symptoms, which suggests the change unlikely to be attributable to a reduction in these factors which can induce secondary negative symptoms.

One limitation of the study is that because of the variance estimation method adopted a number of studies were excluded due being too small. However, given there is evidence to suggest that smaller studies can often present larger effect sizes (i.e. Zhang *et al.* 2013), our findings may have led to a more conservative estimate of the effect size. Another limitation is that, despite the number of studies included in the analysis ($n = 41$), the final sample of 5944 patients was smaller than what was anticipated. This was due to a number of the larger studies either containing inpatients (Lieberman *et al.* 2005), not using a validated negative symptoms scale (Dossenbach *et al.* 2004), or including patients with other psychotic disorders.

Another important issue to consider is that it is difficult to assess to what extent the reduction in severity is attributable to improvements in primary or secondary negative symptoms. However, difficulties making this distinction in research trials is not new (Buchanan, 2007), and the consensus statement suggests that such a distinction is not essential in trials as long as the symptoms are persistent and causes of secondary negative symptoms are adequately controlled for (Kirkpatrick *et al.* 2006). In this analysis, the eligible studies typically reported participants as being highly chronic in nature, reflected in the large median duration of illness (12.4 years), and many defined their sample as treatment-resistant, stable, non-acute, or in a maintenance period. Regarding whether secondary negative symptoms can be adequately controlled for using study-level inclusion/exclusion criteria in a meta-regression of the heterogeneity present in a meta-analysis, this is also up for debate. However, despite these issues the high consistency of the directional change in negative symptoms in an outpatient sample, and the fact that there was no difference in this change between studies which did and did not control for factors which induce secondary negative symptoms does suggest that the improvement appears to occur to a greater extent to what was previously assumed. Further work examining the longitudinal course of negative symptoms in a study with clearly defined inclusion criteria relating to the persistence of negative symptoms, with appropriate controls for secondary negative symptoms, would provide stronger evidence for whether primary negative symptoms of the disorder are less stable than previously assumed.

Another limitation is that due to the substantial heterogeneity of the study designs, the fact that multiple arms of single studies were included which would naturally cluster together, and possible issues relating to the regression of the mean complicating the interpretation further, it was recognized that conducting an examination of publication bias important in typical meta-analytical studies (Higgins & Green, 2011) would have limited utility in this context. This being the case, such analysis was omitted so we cannot be certain as to whether publication bias influenced the results significantly. However, given a number of the studies were non-inferiority trials, dose–response studies, observational studies, and that control arms were used in this study as equivalent to experimental conditions, it would be unlikely that any publication bias would systematically inflate the overall effect sizes in the same manner as would typically be expected in a normal meta-analysis.

Finally, due to the lack of data, no-medication as a therapeutic option could not be evaluated, meaning it is not clear whether a reduction in negative symptoms would also occur in non-medicated patients. It is possible, however, that such an improvement could occur given there is some evidence to suggest that patients who do not immediately relapse upon termination of their antipsychotic regimen may experience improved global functioning over time (Harrow & Jobe, 2007).

Interpretation

These findings are contrary both to the earliest conceptions of schizophrenia, which suggested that negative symptoms follow a path of progressive deterioration (Bleuler, 1951; Kraepelin, 1971), and our current understanding of negative symptoms which suggest that they are highly stable in the non-acute phase (Möller, 2007). While acknowledging that the improvement in

negative symptoms were relatively small in the TAU, non-drug intervention arms and typical antipsychotic study arms, the improvement of negative symptoms over time appear to lend support to the recovery model of schizophrenia, particularly given the relationship of these symptoms to psychosocial functioning (Norman *et al*. 2000; Warner, 2009).

Given the limitations of the within-group design, the effect sizes presented cannot be used as an assessment on the effectiveness of any one treatment. As highlighted earlier, a series of meta-analyses have been conducted to evaluate treatments for schizophrenia using more appropriate designs (i.e. Kurtz & Mueser, 2008; Leucht *et al*. 2009; Jauhar *et al*. 2014). Overall, these reviews have detected relatively limited treatment benefits for negative symptoms, contrasting with the large within-group effect sizes noted here in the example of second-generation antipsychotic and adjunctive drug medication trials. Further investigation into the TAU and placebo study arms indicate that the effect sizes of drug study control arms are substantially larger than non-drug study controls , which suggest there is something inherent in the methodologies employed which makes these drug studies more likely to detect and report symptoms improvements. Many drug studies used placebo, as opposed to TAU, so a placebo effect may account for at least part of this difference. However, while it has been noted that the placebo effect is an increasing issue in schizophrenia drug trials (Kinon *et al*. 2011), given the effect size differences between drug and non-drug studies are so large (ES = 0.67, in comparison to ES = 0.15) it suggests that other factors inherent to the design and assessment may also be important. Regardless, the highly varied nature and outcomes study arms which fall under the heading of TAU and placebos merits further investigation.

Disentangling how regression to the mean issue relates to negative symptoms in an exclusively outpatient sample is complex issue worthy of further consideration. Higher mean levels of negative symptoms at baseline did predict a greater reduction. However, the additional proportion of the variance explained over and above the intervention type and assessment scale used was fairly small (4.1%), suggesting that the regression to the mean may not be as large as one might typically expect. This could be due to a number of factors. First, primary negative symptoms are thought to be highly stable (Möller *et al*. 2007) so it is perhaps unlikely that a substantial fluctuation around the mean level of symptoms over time would be expected, presuming secondary factors are appropriately considered. Second, by omitting samples which contained inpatients at baseline (but not necessarily at study end), the patients were a lot less likely to have been recruited during their most severe phase of their disorder, further minimizing the regression to the mean effect (Morton & Torgerson, 2003).

When testing for sources of heterogeneity in the course of negative symptoms, only the impact of assessment scale type remained significant, after controlling for intervention type. In comparison to studies which used the PANSS or the BPRS, a significantly greater change in negative symptoms was detected in studies that used the SANS. The finding that the SANS is a more sensitive instrument to detect change is in line with recommendations outlined in the MATRICS consensus statement (Kirkpatrick *et al.* 2006) and is perhaps unsurprising given the scales focus on negative symptoms, despite the conceptual and methodological issues that the scale is recognized to have (Blanchard *et al*. 2011). No eligible studies used either the Clinical Assessment Interview for Negative Symptoms (Horan *et al.* 2011) or the Brief Negative Symptom Scale (Strauss *et al*. 2012), therefore it is unknown how these new scales compare.

Understanding how negative symptoms change over time requires further attention given the duration between time points was not found to be a significant predictor. However, with the considerable variability in treatment duration, post-treatment follow-up duration, and post-treatment provision between studies, this is perhaps not surprising. In longitudinal studies assessing negative symptoms over very long periods of time, there has been little evidence of a linear improvement towards symptom remission (Strauss *et al.* 2010), while the rate of recovery in schizophrenia remains low (Jääskeläinen *et al*. 2013). Overall, this suggests that the trajectory of this improvement may be complex. One possible explanation of the improvement uncovered could be the non-specific effects of increased attention derived from being involved in research. Patients with prominent negative symptoms are typically very socially isolated, so increased contact time with researchers in itself may provide some therapeutic benefit.

Conclusions

Based on the available data of almost 6000 outpatients, negative symptoms of schizophrenia do not tend to be stable or deteriorate, but are instead likely to improve over time. This finding offers a further critique of the historical argument which suggests schizophrenia is a disorder of continual decline (Bleuler, 1950; Kraepelin, 1971) and instead provides further support to the recovery model of schizophrenia (Warner, 2009). Overall, these findings suggest that negative symptoms may not be as resistant to change as what has previously been assumed, and perhaps offer new hope to those who may experience such symptoms.

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Declaration of Interest

None.

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Appendix II. Symptom levels and initial appraisal of inpatient treatment

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Symptom levels and initial appraisal of hospital treatment in patients with schizophrenia

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ABSTRACT

The initial appraisal of treatment by inpatients with schizophrenia has been found to be a significant predictor of clinical outcomes. The study aim was to examine whether specific types of symptoms are associated with the initial appraisal of treatment after controlling other patient characteristics. Data of 2105 inpatients with schizophrenia (ICD-10 F20-9) were pooled from three national and international multi-centre studies. Patients were interviewed within the first week of their inpatient admission. Higher levels of manic and positive symptoms were significantly associated with a less favourable initial appraisal of treatment, whilst no association was found with depression/anxiety and negative symptoms. Detained patients had more negative initial treatment appraisals, and the association with manic symptoms was significantly stronger in detained patients compared to those admitted voluntarily. Whilst patient reported outcomes in psychiatry are usually associated with mood symptoms, this appears not to be the case for the initial appraisal by inpatients with schizophrenia. The association with manic and positive symptoms may be explained by the influence of such symptoms on the hospital experience. Focusing on the initial management of mania and positive symptoms might improve patients' appraisal of treatment in the inpatient environment.

1. Introduction

Evidence indicates that patients with schizophrenia who have a more positive initial appraisal of their treatment are likely to benefit more from that treatment eventually. This applies to pharmacological treatment (Van Putten and May, 1978; Van Putten et al., 1978; Bartkó et al., 1987; Awad et al., 1995) and complex interventions (Priebe and Gruyters, 1994, 1995a; Bröker et al., 1995; Priebe et al., 2009, 2010c). In inpatients, a more positive initial appraisal of treatment was associated with lower symptom levels after one month (Richardson et al., 2010), at discharge (Bröker et al., 1995), lower social disability at 3 and 12 months (Priebe et al., 2010a), and lower subsequent involuntary readmission rates (Priebe et al., 2009). Developing a greater understanding of the factors which influence how patients initially appraise their hospital treatment would help identify those at risk of being less satisfied with their treatment, and could assist in the development of new interventions to maximise patients' initial appraisal of treatment.

Whilst previous studies have controlled the predictive association of initial treatment assessments with later clinical outcomes for socio-demographic and clinical characteristics, at present it is unclear whether specific types of symptoms are associated with a more or less favourable initial assessment of treatment. The importance of analysing the influence of symptom types, rather than global levels of psychopathology, has been emphasised in the literature (Shafer, 2005; Richardson et al., 2010). Previous findings suggest other patient reported outcomes, including patients' overall appraisal of psychiatric treatment, are negatively associated with mood, and that this could be due to a negative rating bias in people with higher levels of depressive symptoms, as opposed to specific experiences of treatment (Priebe et al., 1998; Fakhoury et al., 2002; Hansson et al., 2007). In this study we aimed to identify what types of symptoms are associated with the initial appraisal of hospital treatment in patients with schizophrenia, after adjusting the influence of socio-demographic and other clinical characteristics.

2. Methods

An exploratory cross-sectional study examining the association between patients' initial appraisal of inpatient treatment and various socio-demographic and symptom severity measures, analysing a pooled data set specifically collated

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for this purpose. All the data was obtained within the first week of treatment apart from the diagnosis, which was recorded from patient notes at the point of discharge.

2.1. Sample

The current sample was obtained from pooling data from three studies. The InvolvE study (Priebe et al., 2009) assessed characteristics and experiences of in-patients in 22 hospitals across England. The EUNOMIA study (Kallert et al., 2005; Priebe et al., 2010b) was a related study with a similar design conducted at sites in 11 European countries. Both studies had a focus on detained patients but also included voluntary patients who felt coerced to treatment. The EUNOMIA study's data from London was included as part of the InvolvE study, and so these were omitted from the EUNOMIA sample to ensure that participants were not included twice. The third study, EDEN (Kallert et al., 2007), was a randomised controlled trial comparing outcomes of voluntary patients in day hospitals with those in conventional in-patient settings. Details of the rationale, methods and findings of each of the three studies have been described elsewhere.

All three studies included consecutively admitted patients who had the capacity to provide informed consent, aged between 18 and 65. Consistent exclusion criteria were as follows: admitted because of acute intoxication, being a forensic patient, and being transferred from another hospital. In the EDEN study patients requiring 1-to-1 supervision were excluded, whilst in the EUNOMIA and InvolvE study voluntary patients who did not report a coercion level of at least three on the MacArthur Admission Experience Survey were excluded. For this study, only patients with a main diagnosis of schizophrenia or a related disorder according to ICD-10 (F20-29, WHO, 1998) were included. With respect to the EDEN study, only patients treated in conventional hospital settings were included.

2.2. Measures

Initial appraisal of treatment was obtained using the Client Scale for Assessment of Treatment (CAT; Priebe and Gruyters, 1995b; Richardson et al., 2011). The questionnaire has seven items and asks the patient whether they believe they are receiving the right care, whether their psychiatrist understands them and if other staff are pleasant to them, if they believe they are on the right medication, if they feel well respected and regarded, whether the care received has been helpful, and whether they feel other elements of their care are appropriate. Scores range from 0 (''not at all''), to 10 (''yes entirely''). Patients with missing data on four or more items were excluded from the analysis. Recent factorial analysis supports the use of the CAT as a meaningful unidimensional scale, stable over three different European countries (Richardson et al., 2011), and in previous research the CAT has been found to have excellent internal consistency (α=0.90, Priebe et al., 2009).

Symptom severity was measured on the 24-item version of the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993). Scores range from 1 (''not present'') to 7 (''extremely severe''). In examining the severity of symptoms at a sub-syndrome level with the BPRS a number of different 4 and 5 factor models have been postulated (Van der Does et al., 1995; Berger et al., 1997; Ventura et al., 2000; Velligan et al., 2005). Of those, Velligans 4-factor model was selected. Inter-rater reliability was high in all the three studies, with researchers on the InvolvE project achieving a Cohen's Kappa score of 0.90, whilst researchers on the EDEN and EUNOMIA studies achieved an intra-class coefficient score of 0.78.

Socio-demographic details including age, gender, marital status, previous admission history and employment status were obtained using the MANSA (Priebe et al., 1999) in the InvolvE and EUNOMIA studies and the Clinical History Schedule (Kallert et al., 2000) in the EDEN studies. The categories used were identical in the three studies.

All the assessments took place within the first week following the admission (in the EDEN study always within the first two days), and were conducted by a researcher not involved in the patients' treatment.

2.3. Analysis

In univariate analyses linear regressions were conducted with the initial appraisal of treatment as the dependant variable. In addition to the BPRS subscale scores, the following variables were tested as potential predictors: age, gender, employment status, marital status, and the legal status of admission. For the employment and marital status the variables were dichotomised i.e. "employed" vs. "unemployed" (students were treated as employed for this analysis), and "married" vs. "unmarried" (which included those divorced, single and widowed). The patient was defined as involuntarily held if they were initially admitted on a voluntary basis but later detained within the first week, prior to the research assessment taking place. We did not test whether differences in the initial appraisal of treatment were explained by the study from which the data were taken, because in one of the three studies (EDEN) there were only voluntary patients. Since we aimed to analyse the impact of legal status, we did not enter study as a predictor as it would have confounded part of the analysis.

In the next step a multiple linear regression was conducted with all the considered predictor variables entered into the model simultaneously. In the final part of the analysis, interaction effects between legal status and each BPRS subscale score were added to the multivariate model separately in order to examine whether the effect of symptom severity on the appraisal of treatment differed between those legally detained and those admitted voluntarily. In order to rule out the possibility of any bias in the results occurring due to the heterogeneity of the samples used, a subgroup analysis was conducted on the largest dataset (EUNOMIA).

To tackle any potential issues which could arise through a listwise deletion of incomplete cases (Little and Rubin, 1987) a multiple imputation using a chained equation of 10 cycles was conducted. All values included in the analysis were entered both as predictors and for imputing. Twenty-five imputations were conducted (Spratt et al., 2010), with the analysis conducted on the pooled data. R^2 scores were obtained from the imputed data using the method outlined by Harel (2009), which involves conducting a Fisher's r-to-z transformation for each imputed R score, combining them in accordance with Rubin's rules (Rubin, 1987), before transforming them back to R^2. All the analysis was conducted on SPSS version 18.

3. Results

3.1. Sample characteristics

Around 2316 patients met the inclusion criteria. Of which about 211 patients were omitted due to missing or incomplete CAT scores, leaving 2105 patients in the final sample. The clinical and socio-demographic characteristics of this sample are presented in Table 1. Of the final total, 1556 were recruited as part of the EUNOMIA project, 393 as part of the InvolvE study, and 156 as part of the EDEN study. A missing value analysis indicated that 2.8% of all predictor values (653 in total) was missing, with 21.1% of cases (445) missing at least one. Of the 653 values missing in total, 53.9% (352 in total) related to the duration of illness.

3.2. Symptoms and other patient characteristics associated with initial appraisal of treatment

The univariable and multivariable associations of symptoms and other patient characteristics with the initial appraisal of treatment are shown in Table 2.

Higher levels of mania and positive symptoms, lower levels of depression/anxiety symptoms, being involuntarily admitted, unemployed and unmarried were all significantly associated with a less favourable initial appraisal of treatment in univariable analyses. After simultaneously adjusting for potential confounding by other variables; older age, being male, not being detained,

Table 1
Socio-demographic and clinical characteristics of the patients.

Characteristics	*n* or Mean	% or SD
Patients (*N*)	**2105**	
% Detained involuntarily	1530	72.7%
Age (years)	38.49	11.24
Gender (% female)	906	43.1%
Marital status (% married)	454	22.0%
Employment		
Standard paid employment	385	18.5%
Unemployed (incl. disability benefits)	1554	74.9%
Other (e.g. student, home-maker)	138	6.7%
Previous psychiatric admission (%yes)	1517	76.7%
Illness duration	7.84	9.11
BPRS		
Depression/anxiety subscale score	2.24	1.08
Mania subscale score	1.84	0.96
Negative subscale score	2.14	1.08
Positive subscale score	2.92	1.26
CAT mean score	6.00	1.28

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Table 2
Univariate and multivariate analysis of variables associated with patients' initial appraisal of treatment.

Predictor variables	Univariate analysis			Multivariate analysis		
	B	95% CI	*p*	*B*	95% CI	*p*
Socio-demographic data						
Age	0.010	0.000 to 0.020	0.061	0.021	0.009 to 0.033	0.001
Female vs. male	−0.214	−0.450 to 0.022	0.076	−0.346	−0.581 to −0.111	0.004
Past admission (Yes/No)	−0.178	0.235 to −0.473	0.235	−0.022	−0.338 to 0.293	0.889
Illness duration	−0.014	−0.028 to 0.000	0.056	−0.012	−0.030 to 0.005	0.172
Detained legal status	−1.207	−1.464 to −0.949	<0.001	−0.984	−1.247 to −0.722	<0.001
Unemployed	−0.441	−0.726 to −0.156	0.002	−0.305	−0.589 to −0.021	0.036
Married	0.319	0.034 to 0.604	0.028	0.135	−0.155 to 0.426	0.360
BPRS symptom clusters						
Depressive/anxiety subscale	0.130	0.021 to 0.239	0.019	0.017	−0.091 to 0.125	0.758
Mania subscale	−0.674	−0.794 to −0.554	<0.001	−0.490	−0.620 to −0.360	<0.001
Negative subscale	−0.190	−0.218 to −0.000	0.051	−0.005	−0.114 to 0.104	0.929
Positive subscale	−0.465	−0.557 to −0.372	<0.001	−0.226	−0.330 to −0.122	<0.001

being employed, and having a low level of manic and positive symptoms were associated with a more favourable appraisal of treatment. The variance explained by the multivariable model was $R^2=0.106$, with manic symptoms, with a detained legal status of admission and mania symptoms explaining the greatest proportion.

In the subgroup analysis with data from the EUNOMIA study only, the effect of the variables remained broadly consistent, with all of the 95% confidence intervals falling inside those from the full sample and with the same variables significant and in the same direction. The only exception to this was 'employment status' ($B=-0.305$, 95%, CI$=-0.589$ to -0.021, $P=0.036$ in the full sample, in comparison to $B=-0.230$, 95%, CI$=-0.561$ to 0.100, $P=0.172$).

3.3. Legal status of admission, symptom severity and initial treatment evaluation

The next stage of the analysis explored whether symptom levels had a similar predictive value in voluntary and involuntary patients. An interaction effect between legal status and each symptom subscale score was separately entered into the existing multivariable model (presented in Table 2). Such interaction effect was found only for manic symptoms ($B=0.372$, 95%, CI$=0.067$–0.677, $P=0.017$). A post hoc analysis was conducted in order to identify the direction of the interaction. In detained patients the association between more manic symptoms and less positive treatment appraisal was stronger ($R^2=0.062$, $P<0.001$) than in voluntary patients ($R^2=0.012$, $P=0.009$).

4. Discussion

4.1. Main findings

Mania, depression/anxiety and positive BPRS subscale scores were significantly associated with patients' initial appraisal of treatment in the univariate analysis. When the influence of all tested variables was considered however, only two types of symptoms remained significant: patients with higher levels of mania and positive symptoms tended to appraise hospital treatment more negatively. Younger age, female gender, being unemployed and being detained involuntarily were also linked with less positive appraisals in multivariable analyses.

4.2. Strengths, limitations and methodological considerations

Whilst previous research emphasised the importance of patients' initial appraisal of treatment as a predictor of treatment outcome, this is the first large study focusing on understanding the factors that determine more or less favourable initial appraisals of hospital treatment. The sample size (2105 patients) provides sufficient statistical power to detect even small effect sizes, thus allowing the interpretation of negative findings. We tested observer-ratings of symptoms as predictors of the patient-rated initial appraisal of treatment. This avoided obtaining associations as a mere effect of a generalised tendency to provide more or less positive ratings in different self-reporting measures (see Hansson et al., 2007; Fakhoury et al., 2002). The same measures of symptoms and treatment appraisal were used in all studies from which the data were pooled, and that all ratings were provided by well trained researchers who were not involved in treatment.

The major limitation of the study is a potential selection bias. In two of the three studies (InvolvE and EUNOMIA), voluntary patients were included only if they expressed a level of being coerced. In the third study (EDEN), there were no involuntary patients. Also, not all eligible patients could be recruited in the three studies. This may have influenced the absolute levels of symptoms and initial treatment appraisals, however associations between variables are assumed to be more robust against a selection bias, and exploring associations was the aim of this analysis. Another limitation is that we did not consider in the analysis what exact treatment was administered during the first days of hospital treatment and whether specific treatment components were linked with patients' appraisal of treatment. We did not have consistent data on what type and dose of antipsychotic medication patients had taken at the time of the interview, so that medication was not examined as a possible influencing or mediating factor. Finally, the multivariable model explained only about 10% of the variance of the initial assessment of treatment. Whilst such an amount of explained variance is common for this type of research, it still leaves about 90% of the variance unexplained.

4.3. Comparison with previous research

Patients' initial statements about the appropriateness of their psychiatric treatment have been the subject of research for more than 30 years. They have been referred to using terms such as initial subjective response (Van Putten and May, 1978), early subjective reactions (Priebe, 1987), and initial treatment satisfaction (Priebe et al., 2009). In this study, we used initial appraisal.

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It reflects the type of questions asked in the CAT and mirrors the nature of assessing a treatment that has just started and is unlikely to have yet had a major effect. However, when comparing the findings with the literature, one has to consider that other studies may have used a different terminology.

The literature on treatment satisfaction in psychiatry, i.e. not initial but later appraisals of treatment, suggests that mood symptoms have the greatest impact on patients' ratings. Patients who are more depressed tend to express a more negative view of their treatment. It has been suggested that this reflects a negative rating bias of patients with high levels of depression rather than a specific experience of treatment (Priebe et al., 1998; Hansson et al., 2007; Fakhoury et al., 2002; Fakhoury and Priebe, 2002). In this study, the multivariable analysis did not identify depression, but mania and positive symptoms as influential. This is unlikely to be explained by a mood dependent rating bias, but may reflect how patients with different symptoms of schizophrenia experience the in-patient setting. Given patients level of insight into their disorder has been found to negatively correlate with both positive and negative symptoms (Minz et al., 2003; De Hert et al., 2009), whilst in our study negative symptoms were found to have no impact on treatment appraisal, the finding is also unlikely to be attributable to simply how aware the patients were of their illness and the need for treatment.

The finding is partly consistent with the results of Richardson and colleagues (2010) who reported a less positive initial treatment appraisal for patients with higher levels of mania, positive and depression/anxiety symptoms. That analysis however had a different focus, used a smaller sample of exclusively involuntary patients, a different factor analysis of the BPRS to define the subsyndromes, and did not adjust for other symptoms and patient characteristics.

Patients with higher levels of manic and positive symptoms may have greater difficulty in coping with being placed in the confined environment of a hospital ward. In the ward they have reduced autonomy and limited space. They have to conform to the organisational requirements of the ward and are surrounded by other patients who are also acutely ill, many of whom can be noisy and aggressive. Manic and positive symptoms may lead to less satisfactory interactions with other service users and staff members and greater conflict, which in turn may negatively impact upon their perception of treatment still further. Patients who exhibit 'disturbed behaviour' or experience acute positive symptom exacerbation are also more likely to receive combined anti-psychotics and high doses of antipsychotic medication (Paton et al., 2008), which can lead to a higher side effect burden (Centorrino et al., 2004), which could result in a lower appraisal of the treatment they receive. In a qualitative review of experiences of involuntary inpatient treatment (Katsakou and Priebe, 2007) a number of features were highlighted that can negatively impact upon a patient's experience of admission, and these may particularly resonate with those suffering from more intense manic and positive psychotic symptoms. Patients experiencing greater levels of positive symptoms such as paranoia or hallucinations may struggle more in an unfamiliar setting which may feel frightening or insecure. Patients with severe manic symptoms are likely to be more agitated, and struggle more with being contained in an enclosed space with rigid rules and limited opportunities for activities. The finding that manic symptoms influence patients' appraisal even more in those involuntarily admitted, who therefore would experience an even greater restriction to their autonomy, lends further support to this argument.

4.4. Implications

The findings suggest that patients with different symptom profiles experience and respond to psychiatric hospital treatment in different ways and, as a result, express different appraisals within a few days after admission. Patients with schizophrenia experiencing more severe manic and positive symptoms, and manic symptoms in particular if detained involuntarily are more likely to report a more negative initial evaluation of treatment. This suggests that it is symptom characteristics which may relate specifically to being in a ward environment that have a greater impact on the initial appraisal of treatment, as opposed to mood which has been found to be the most important in predicting a range of other patient self-reported outcomes (Priebe et al., 1998; Fakhoury et al., 2002).

The findings underline the importance of assessing patients' initial appraisal of treatment as a relevant process variable in both research and routine practice. Further studies may explore environmental factors, processes of interaction between service users and staff, treatment components and mediating processes as an explanation of the association of manic and positive symptoms with more negative appraisals of hospital treatment after only a few days. In a recent review Millon (2009) has suggested that acute inpatient settings are at present too custodial and over reliant on medication, and suggests that providing more psychosocial interventions as an alternative may be a way to try and address these issues. If these are problems which disproportionally affect those experiencing higher positive and manic symptoms, then this possible solution may go some way in addressing the more negative experiences these particular patients report.

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Appendix III: Systematic review protocol

Systematic review protocol

Objectives:

1) What is the course of negative symptoms in stable schizophrenia patients over a standard treatment period (i.e. 10 weeks-36 months)?
2) On a study-group level, what changes in negative symptoms can actually be achieved?
3) Do any patient or treatment characteristics influence the course of negative symptoms?
4) Does the method of assessment impact upon how stable the course of negative symptoms is recorded to be?
5) Is there any variation between the courses of individual negative symptoms?

Search process:

Electronic databases: MEDLINE, PsychINFO, EMBASE, CENTRAL.

Reference lists from selected papers hand-searched

Key journal search: American Journal of Psychiatry, Acta Scandinavica, British Journal of Psychiatry, Schizophrenia Bulletin, Schizophrenia Research, The Lancet. Hand-searched, back to 1962:

Selection Criteria:

Database selection:

Diagnosis: 100% of sample diagnosed with Schizophrenia.

Patient status: assessments conducted exclusively with outpatients

Age: 18-65

Sample size: minimum 50 participants total.

Length of time between first and last assessment points: minimum 10 weeks.

Methods: Quantitative research only. Not reviews, case-studies, or papers which have not used a validated symptom measurement scale.

Assessment methods: Any peer reviewed assessment tool used to establish the severity of specific negative symptoms of schizophrenia (including motor retardation), or the severity of a general schizophrenia negative symptom subscale. Examples measuring negative symptom as a singular subscale include (but are not exclusive to): BPRS, PANSS, SANS, NSA-16, NSA-4, PNS-Q. Measures of individual symptoms include (but not excluded to): SANS, Emotional Blunting

scale, Chapman Anhedonia scales, TEPS, Fawcett-Clark Pleasure scale, Snaith-Hamilton Scale or individual items on the above subscale measures.

Publication date: Start from when standardised assessment of negative symptoms was initiated (i.e. BPRS, 1962).

Language: Include non-English papers where possible (German, Italian, French, Spanish). Articles written in non-Latin characters excluded

Abstracts and 'Grey literature' excluded.

Search terms:

1 + 2 + 3

Medline search terms:

1. Disorder	2. Symptoms	3. Treatment /Duration
*Schizophren$	Negative symptoms	Change$
Deficit syndrome	Reduced affect	Effect$
	Flattened affect	Therap*
	Blunted affect	Intervention /Intervention studies
	Emotional experience	Efficacy
	Emotional expression	Impact
	Alogia	Treatment / *therapeutics
	Anhedonia	Medication
	Avolition	*Longitudinal
	Asociality	*Follow up /*Follow up studies
	Motor retardation	course
	Amotivation	Stability
	Apathy	Time
		Progress$
		Persist$
		Year$ */treatment outcome

* denotes an exploded term
$ denotes open
/ denotes a meshed term

PsychINFO variation in mesh terms:

Efficacy: efficacy, * Treatment effect evaluation
Intervention: intervention, /intervention
Treatment: treatment, /treatment
Medication: Medication, *drug therapy

EMBASE variation in mesh terms:

Deficit syndrome, *negative syndrome/
Blunted affect, /blunted affect
Motor retardation, /motor retardation
Anhedonia, /anhedonia
Effect, *therapy effect/

Intervention, *intervention study/
Efficacy, *drug efficacy/
Treatment, /treatment outcome*
Medication, /drug therapy*

CENTRAL full search terms list:

(schizophren* OR deficit syndrome) AND (negative symptoms OR reduced affect OR flattened affect OR blunted affect OR emotional experience OR emotional expression OR alogia OR anhedonia OR avolition OR asociality OR motor retardation OR amotivation OR apathy) AND (change* OR effect* OR therap* OR intervention OR efficacy OR impact OR treating OR medication OR longitudinal OR follow up OR course OR stability OR time OR progres* OR persist* OR year*):ti,ab,kw in Clinical Trials

-Screening (3 stage process: title, abstract, and full paper screen)

Exclude if:
- Non-human, neuro-imaging or neurobiology study
-If the title indicates it is clearly not relevant (i.e. nothing to do with topic area, schizophrenia, negative symptoms etc.)
-Study published in a non-Latin character language
-The study is a case report, letter to the editor, conference abstract, book chapter, qualitative study, or review[†]
-Clearly no repeated assessments (i.e. straight comparison between two samples in one time period)
-includes inpatients
-No repeated assessments of schizophrenia symptoms OR repeat defined by outcome rather than standardised time-point (i.e. re-admission)
-<50 participants total
-A structured assessment of negative symptoms was not undertaken, using a psychometrically validated assessment tool.
-No details on exclusively schizophrenic samples presented
-total study length <10 weeks, or no details reported within 3 year interval
-Child/older adult (ie >65 years old) included in sample

* Note; if the study is a review concerning the longitudinal course of negative symptoms then source data should be obtained, and reference list screened.

Appendix IV: Systematic review extraction sheet

Indentification features									**Study Characteristics**			
#	Screener	date	Authors	Year	Title	Journal	**Included?**	Reason for exclusion	Design	Inclusion/exclusion criteria		
										1	2	3

							Country	Total	Method ofDx	Randomised?	participants blinded	
4	5	6	7	8	9	10		participants		if so, how?		

			Data at each level: measure 1							
Assessors blinded?	Multiple Raters?	management of drop out?	Symptoms measured	intervention	recruited number	T1				
						timepoint	assessment method	mean	std dev	no# parts

					Data at each level: measure ….							
T…					Symptoms measured	intervention	recruited	T1				
timepoint	assessmen	mean	std dev	no# parts			number	timepoint	assessment method	mean	std dev	no# parts

					Participant characteristics							
T...					Age		Gender	Ethnicity %				
timepoint	assessmen	mean	std dev	no# parts	Mean	std dev	(% male)	1- White	2- Black Carribean	3- Black African	4- Black other	5- Indian

				Group level	Co-morbidity %			
6-Pakistani	7- Bangladeshi	8- Chinese	9-Other	co-morbidities	Anxiety Disorder	Depressive disorder	Substance abuse disorder	Personality Disorder

% employed	length of education		Illness duration		Age of onset		no# prev admis		Anti-psychotic med	Stated conflict of	
	mean	std dev	mean	std dev	mean	std dev	mean	std dev	(chlorprom equiv, mg)	Interests?	