Latent growth curve modelling of positive and negative symptom trajectories in first-episode psychosis from baseline to long-term follow-up

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Abstract

Background:

Comparatively little is known about the way in which the positive and negative symptoms of psychosis change in the first year following the initial psychotic episode. The importance of these short-term trajectories (STT) as a predictor of long-term symptomatic outcomes has not been widely explored. Furthermore, the role of short-term change as a mediator of effects of patient presenting features, such as gender, age at onset of psychosis, duration of untreated psychosis, premorbid functioning, and of DSM-IV psychotic diagnosis, on long-term symptom levels, is unclear. Any mediating role of short term changes are of interest because they may help explain the mechanism by which presenting factors affect long-term symptoms. This thesis modelled trajectories of positive and negative symptoms following an initial psychotic episode in 413 first-episode patients to better understand the mechanisms underlying course of recovery.

Methods:

Latent growth curve (LGC) methodologies were used to model the data. These methods offer a contemporary approach for the analysis of longitudinal data. LGC models address the pitfalls associated with the longitudinal designs that conventional methods cannot, including attrition, missing data and variability in follow-up assessment intervals between individuals, and additionally, are able to deal with zero-inflated models and non-normal data. LGC methods also offer other advantages, including explicitly modelling change both within and between individuals, and allows for potential predictors of variability in symptom trajectories to be identified.

Results:

Change in positive symptoms conformed optimally to a non-linear trajectory, whilst changes in affective flattening, alogia, avolition, and anhedonia, were linear. Individuals varied significantly in their values at the beginning of the trajectory on the four negative symptom subscales, and on positive symptoms, and in their rates of change over the short-term trajectory on alogia, avolition and anhedonia. Short-term symptom change was partly accounted for by clinical presenting features. The most notable finding was the pivotal role played by the STTs in predicting long-term symptoms levels, independently of the effects of DUP, premorbid functioning, gender, age at onset of psychosis, admission symptom levels,

and baseline DSM-IV diagnosis. The association between the STTs and long-term negative symptoms, in particular, was notable. Higher initial trajectory levels, and increasing change over the 1-year interval subsequent to initial recovery, predicted worse long-term symptomatic outcomes. The STTs also mediated the effects of participant presenting features on long-term symptomatic positive and negative symptom outcome.

Conclusion:

These findings imply that symptom changes in the period after admission to the service is critical to how a young person's symptoms continue to evolve in the longer term. It suggests that the STT may be a sentinel for long-term negative symptoms. The importance of the STT is underlined, particularly when considered alongside its role as a causal pathway for the effects of DUP, premorbid functioning, age at onset of psychosis, and baseline DSM-IV diagnosis, on long-term symptomatic outcome. Greater focus on the treatment of negative symptoms in psychotic disorders is long overdue, in contrast to the range of relatively established treatments for positive symptoms. New, smaller studies, with frequent assessments, are required to investigate the development, course, and interaction amongst negative symptoms. This is necessary to develop an appreciation of the underlying processes that might inform new treatment strategies.

Declaration

This is to certify that

i. the thesis comprises only my original work towards the PhD,

ii. due acknowledgement has been made in the text to all other material used,

iii. the thesis is less than 100,000 works in length, exclusive of tables, references and appendices, and

iv. the research reported in this thesis was conducted in accordance with the principals of the ethical treatment of human subjects as approved for this research by Human Research Ethics at the University of Melbourne.

Susan Harrigan

Date: 18th May 2017

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1 INTRODUCTION

Longitudinal investigations of the course of psychosis are essential in understanding the evolution of the illness, and to the development of effective, well-timed interventions designed to optimise treatment outcomes. This thesis examines the patterns of evolution of symptomatology in psychotic disorders, in particular, issues relating to change in symptoms and the degree of individual variation in the rate and shape of change over the 1-year interval subsequent to the initial episode. The effects of participant presenting characteristics on short-term and long-term outcome will be investigated, with a focus on mediation analysis to determine whether any effects identified are direct or indirect in nature. The data modelled were taken from a large, broad-based and representative first-episode psychosis (FEP) sample, allowing findings to be generalised across the comprehensive diagnostic spectrum of all functional psychotic disorders.

The symptoms of psychosis – positive and negative symptoms – are introduced in Chapter 2. Generally, it is claimed that there is a dramatic decline in the severity of positive and negative symptoms over the short-term course of first-episode schizophrenia, although this finding has not been universally endorsed. In fact, it is likely that there is substantial variability between individuals in the rate and shape of symptom change over this interval, issues beyond the focus of studies such as these. Previous findings are also limited by several weaknesses, including diagnostic homogeneity, small sample size, and failure to consider latent heterogeneity in the investigation of the course of illness over time. Key questions relating to rate and nature of change in symptoms over the course of recovery from psychosis continue to be largely unanswered.

Chapter 3 formalises the investigations proposed in the previous chapter. There are 16 research questions in total for each of the five symptoms under investigation: positive symptoms, and the four negative symptoms: affective flattening, alogia, avolition, and anhedonia symptoms. These investigations focus on three principal aspects of positive and negative symptomatology of the first psychotic episode. The first is concerned with the rate and shape of change in positive and negative symptoms over the 1-year interval subsequent to the initial psychotic

episode, and identifying the degree to which there is individual variability in these short-term trajectories (STT).

The second aspect concerns the role played by the STT as (i) an independent predictor of long-term symptomatic outcome, and/or (ii) potential mediator of the participants' presenting features on long-term outcome. Similar investigations will be conducted for baseline DSM-IV diagnosis of the initial psychotic episode to assess whether the effects of diagnosis on long-term outcome are direct, or mediated by the STT. Thirdly, effects of participants' presenting features and baseline DSM-IV diagnosis on the STT and on symptoms at service entry will be examined.

Chapter 4 describes the study methodology. The context for the study is presented, followed by an overview of the sample, and study design. The primary psychopathology measures used to assess positive and negative symptoms – the Brief Psychiatric Rating Scale (BPRS), and the Schedule for the Assessment of Negative Symptoms (SANS) – are presented, along with predictors of psychopathology, and the measures used to assess them. One of these predictors is duration of untreated psychosis (DUP). This variable is considered pivotal in prediction of outcome studies, since it is one of the few potentially modifiable risk factors for poor outcome. As such, a special section in this chapter is given to DUP, its definition and measurement, and the reasons for wide variability in DUP findings across different studies. Latent growth curve (LGC) analyses were used to model the data. LGCs are a contemporary approach for the analysis of longitudinal data. These models can help address the pitfalls associated with the longitudinal designs that conventional methods cannot, including attrition, missing data and variability in follow-up assessment intervals between individuals, and additionally, are able to deal with zero-inflated models and non-normal data. LGCs also offer a number of advantages, including explicitly modelling change both within and between individuals, and allows for the investigation of potential predictors of variability in symptom trajectories to be identified

Chapter 5 provides an account of the statistical methods used to model the data. The meaning of the term 'trajectory' is defined, followed by a discussion of forms of functional change, and coding of time for linear and non-linear models. Details are provided regarding model fitting and the MLR estimator used for the initial unconditional model, and for the assessment of direct effects in subsequent conditional models. The MLR estimator is contrasted with the use of a different method of inference for the detection of indirect effects, the bias-corrected

bootstrap. Evaluation of model fit, and an overview of selected goodness of fit indices, is followed by a brief explanation of model modification via the use of modification indices.

A comprehensive description of the logic behind the stepwise fitting of sequential models is also given. For each of the positive and negative symptom measures, a latent growth curve model was developed in four incremental stages in order to sequentially address the research questions in Chapter 3. Each stage built on the preceding stage by incorporating additional observed variables and parameters, with each stage adding a particular set of research questions. Predictors of the short-term trajectories, and long-term symptomatic outcome were: gender, age of the onset of psychosis, duration of untreated psychosis (DUP), and pre-morbid functioning. The degree to which DSM-IV diagnosis of the initial episode predicted the course of positive and negative symptoms was also examined.

Several research questions in this thesis address the general hypothesis that the effects of independent variables (for instance, DUP, or premorbid functioning) on dependent variables such as long-term outcome may be mediated by other variables. The concept of mediation is simple– that a third variable (the mediating variable) is part of a causal 'chain' in the effect of one variable on another; the mediator 'transmits' an effect. Mediation is explored in Chapter 6. Possible mediators in this study include severity of symptoms at admission, and the short-term trajectory (STT), represented by the intercept and slope latent variables. These mediational pathways are of particular interest because they may help explain the process or mechanism by which hypothesized predictor variables impact long-term symptomatic outcome. This aspect of the research requires consideration of how to best evaluate whether mediation is occurring, and is followed by a brief overview of the mediation model for a single mediator and the regression equations which underpin it, followed by a description of the most widely used method of assessing mediation and its limitations, concluding with a recommended approach to establishing the presence of mediation.

Chapter 7 describes the sample of 413 young people experiencing their first psychotic episode. Descriptive material relating to the changes in BPRS and SANS symptom data over the five assessment points, from service admission (T1) to 7.3 year long-term follow-up (T5), is presented, along with graphs displaying the individual short-term growth trajectories. This chapter also covers the issue of missing data. In longitudinal research, participants may be present for some waves of data collection and missing for others. It is not uncommon for

participants to be absent for a particular assessment and then to reappear for later assessments. Maximum likelihood (ML) modelling of longitudinal data is suggested as a highly efficient way of using all available data, however even sophisticated techniques such as ML rest on a number of crucial assumptions. Possible missing data mechanisms are presented and considered. It is important to distinguish between different missing data mechanisms, because different methods used to deal with missing data may be based, either implicitly or explicitly, on the assumption of a particular missing data mechanism.

Chapter 8 reports on the investigation of characteristics and predictors of the short-term positive symptom trajectory and long-term (7.3 year) outcome. The nature of the effects of these predictors on short-term and long-term outcome will also be identified. The chapter is partitioned in four sections: Section 1 identifies the unconditional structure of the positive symptoms data over the 1-year interval subsequent to initial recovery from the first psychotic episode, specifically, the shape of change in the short-term trajectory, and the degree to which individual variability exists in these patterns. Section 2 focuses on the prediction of the short-term symptom trajectories and long-term outcomes by incorporating one predictor, admission symptom severity, and one observed outcome variable, long-term (7.3 year) symptom severity. Section 3 examines the nature of the effects of four patient presenting features on short-term and long-term symptoms; gender, age at onset of psychosis, DUP and pre-morbid functioning. Section 4 introduces baseline DSM-IV psychotic diagnosis as a final predictor of short-term and long-term outcome.

Characteristics and predictors of the short-term trajectory, and long-term outcome for four negative symptom subscales, are presented in Chapter 9. These are: affective flattening, alogia, avolition and anhedonia. The modelling strategy for each of these subscales is similar to that presented for positive symptoms in Chapter 8; a latent growth curve model was developed in four incremental stages to sequentially address the research questions in Chapter 3.

The final chapter draws the findings from Chapters 8 and 9 together, and comprises five sections. Firstly, a summary of the research findings is presented, followed by comparison with previous research. The implications of the findings are then discussed, and the limitations of the study are acknowledged. Following on, future research directions are proposed; specifically, the type and scope of work necessary to bring about general advancement in this area. This chapter concludes with a brief summary of what has been found in this study.

2 BACKGROUND

2.1 Introduction

Symptoms of psychosis can be divided into two categories: positive and negative symptoms. Positive symptoms represent the presence of distinct abnormality in thought or perception, including hallucinations, delusions, and grossly disorganised thought (Möller, 2007). These are thoughts and feelings that are 'additional' to normative experience and thought. Conversely, negative symptoms involve the absence or attenuation of attributes that are ordinarily present in normal function in thoughts, feelings and behaviours. Negative symptoms commonly experienced by patients include affective flattening (reduction in range of facial or vocal expression, little emotion), alogia (diminished amount or content of speech), avolition (loss of initiative, motivation), and anhedonia (inability to experience pleasure). Negative symptoms are often less apparent than positive symptoms, the latter of which can make treatment seem urgent, however negative symptoms are often the principal reason that individuals with psychotic disorders experience difficulty in living independently, have poor quality of life, and problems managing everyday social situations. Thus, although positive symptoms are the most conspicuous symptoms in psychotic illness, negative symptoms have long been regarded as a core feature of the disorder (Bleuler, 1950; Foussias & Remington, 2010; Kraepelin, 1919).

Some studies have suggested that there is a dramatic decline in the prevalence of positive and negative symptoms over the 10-year course of first-episode schizophrenia (Eaton, Thara, Federman, Melton, & Liang, 1995), although this finding has not been universally endorsed. Other longitudinal research has presented evidence of the relative stability of negative symptoms over time compared with positive symptoms, which tend to be regarded as less stable (Arndt, Andreasen, Flaum, Miller, & Nopoulos, 1995; Quinlan, Schuldberg, Morgenstern, & Glazer, 1995; Ventura et al., 2004). It has been claimed that negative symptoms are more treatment-resistant than positive symptoms. However, results from a large recent meta-analytic study (Savill, Banks, Khanom, & Priebe, 2015) concluded that negative symptoms decreased significantly over the course of follow-up in all but one of 89 studies, which ranged in duration from 10 weeks to three years. The finding of a reduction in

severity of negative symptoms is also contrary to the earliest conceptions of schizophrenia that posited negative symptoms as following a path of progressive deterioration: a form of dementia (Bleuler, 1950; Kraepelin, 1919).

Although these findings offer important insights into the course of first-episode psychosis, it is likely that there is substantial variability between individuals in the rate and shape of change of symptoms over time, issues that were beyond the focus of most previous studies (Arndt et al., 1995; Eaton et al., 1995; Marengo, Harrow, Herbener, & Sands, 2000). Furthermore, the nature of the temporal relationship between positive and negative symptom domains remains unclear, despite a profusion of research supporting the conceptualisation of positive and negative symptoms as independent syndrome factors of schizophrenia (Ventura et al., 2004). One reason for this lack of clarity is that the majority of research has modelled the structure of positive and negative symptoms using cross-sectional designs (Grube, Bilder, & Goldman, 1998), leaving open questions of stability and independence of the symptom factor structures over time. Longitudinal designs are essential to answer questions such as these. However, even when longitudinal studies are implemented in psychosis research, primary outcomes often focus on levels of psychopathology and functioning at a predetermined time point, thus providing essentially cross sectional information (Austin et al., 2015). Understanding the longitudinal course of psychosis is crucial to acquiring an understanding of the evolution of the illness, and the development of effective, well-timed interventions designed to optimise treatment outcomes.

The importance of this principle was well understood by Emil Kraepelin, one of the earliest proponents of longitudinal observation in understanding psychosis and its outcomes (Kraepelin, 1919). As a pioneer of modern psychiatry, Kraepelin formulated a nosology of psychiatric illness that laid the foundation for every major diagnostic system today. His fundamental concepts were based on his belief that the classification of psychiatric disorders should be based on common patterns of onset, illness course and outcome, rather than merely the similarity of observed symptoms on any single occasion. Despite the significant heterogeneity acknowledged as inherent in the course of schizophrenia and other psychotic illnesses, it is perhaps surprising that until relatively recently, cross-sectional approaches have prevailed (Tschacher, Scheier, & Hashimoto, 1997), or in the case of intervention studies, simple pre-post designs. Neither approach is designed to capture the fluctuating nature of

psychopathology in psychotic disorders, or to capture non-linear change processes (Peer & Spaulding, 2007 42).

These aforementioned deficiencies in study design and analysis, and the failure to consider individual heterogeneity, are not the only issues. The principal symptomatology of positive and negative symptoms has rarely been examined in a broad-based and large first-episode psychosis (FEP) sample (P. D. McGorry, Bell, Dudgeon, & Jackson, 1998), with the majority of factor analytic studies focusing almost exclusively on schizophrenia samples. As pointed out by McGorry et al. (1998), '*Studies using broader samples of psychotic patients can identify dimensions of psychosis, including subtypes of 'schizophrenia' if it proves to be a valid subcategory, whereas studies using only schizophrenia patients can only characterise the dimensions within schizophrenia…*' (P. D. McGorry et al., 1998). The clinical heterogeneity found within the full-spectrum of functional psychotic disorders would therefore appear to be integral to the conceptualisation of the dimensions of symptomatology in early psychosis. The current literature may have also been shaped by sample representativeness issues as well as by the implementation of narrow diagnostic inclusion criteria. For instance, it has been pointed out that studies have commonly included participants at different stages of illness, with chronic and treatment refractory patients being over-represented, and have been subject to substantial attrition of those who have done well but would have met initial diagnostic criteria for schizophrenia (Menezes, Arenovich, & Zipursky, 2006). These factors potentially lead to biased results, leading to a pessimistic view of the prognosis of schizophrenia.

2.2 Existing Longitudinal Research

The assembled longitudinal psychosis research can be classified into three broad non-exclusive categories. The first category includes factor analytic and related studies that examine how the structure of positive and negative symptoms changes over time, and whether symptoms tend to vary in a systematic manner (Arndt et al., 1995; Eaton et al., 1995; Marengo et al., 2000; Ventura et al., 2004; Ventura et al., 2015). The duration of observation of these studies ranges from 1 to 10 years. These longitudinal studies are particularly noteworthy for their testing of the enduring conceptualisation—derived from predominantly cross-sectional studies—that positive and negative symptoms are independent syndrome factors of schizophrenia (Grube et al., 1998). However, although these symptom studies have examined the stability and independence of the factor structure of symptoms over time, and assessed

whether systematic covariation exists between different syndromes, none have modelled the rate of change over time and the individual variability in that rate of change. The second category of studies comprises research with a specific focus on outcome and course of illness over the long-term, see, for example (Harrison et al., 2001; Thara & Eaton, 1996; Thara, Henrietta, Joseph, Rajkumar, & Eaton, 1994). This class of research will be discussed in Section 2.2.2.

The third category of longitudinal research comprises studies with specific diagnostic inclusion criteria and thus a restrictive focus on particular psychotic disorders. For example, Eaton et al (Eaton et al., 1995), Savill et al (Savill et al., 2015) and Ventura et al. (Ventura et al., 2015) investigated only those patients with an initial diagnosis of schizophrenia, Marengo et al (Marengo et al., 2000) and Ventura et al (Ventura et al., 2004) included only participants with schizophrenia and schizoaffective disorders, and Arndt et al (Arndt et al., 1995) included only subjects with schizophrenia and schizophreniform disorders. Few longitudinal studies have used inclusive diagnostic criteria which would permit findings to be generalised across the comprehensive diagnostic spectrum of all functional psychotic disorders, especially those in affective psychoses. This is important, given the fluidity of psychotic diagnosis early in the course of illness (Fusar-Poli et al., 2016).

2.2.1 Longitudinal Research I: Symptom Stability and Fluctuation

Studies in the first category, focusing on patterns of positive and negative symptom change, have demonstrated disparate findings regarding symptom stability. For example, data were presented from a 10-year follow-up study (Eaton et al., 1995) indicating that positive and negative syndromes declined markedly in first year following the initial hospitalisation, with symptoms stable thereafter. There was no evidence to support an increase in negative symptoms after the subsidence of the first episode, as suggested previously (Pogue-Geile & Harrow, 1985). Another study reported relative stability in negative symptoms over a similar time period, with only a slight improvement in positive symptoms (Marengo et al., 2000), whilst other research has presented evidence that positive and negative symptoms appeared to be independent, with a decrease in negative symptoms over a two-year course, and an increase in positive symptoms (Quinlan et al., 1995). A further study found that positive symptom exacerbations were significantly more common than negative symptom exacerbations when measured at six discrete time periods (defined in relation to psychotic exacerbation or relapse)

throughout the duration of the study, with an average monitoring period of three years (Ventura et al., 2004). A more detailed synopsis of positive and negative symptom stability over longitudinal psychosis follow-up studies follows.

2.2.1.1 Stability of Positive Symptoms

Positive symptoms are usually not regarded as having long-term prognostic value and are thought to be more variable than negative symptoms (Pogue-Geile & Harrow, 1985; Quinlan et al., 1995), although this assumption has not always been supported, as evidenced by the findings such as those of the Madras longitudinal study (Eaton et al., 1995). One of the strengths of this 10-year follow-up study was the frequency of assessments (monthly). These indicated that much of the decline in positive symptoms occurred in the first six months following the first hospitalisation. The prevalence of positive symptoms was 52.9% at year 1, decreasing to 18.8% in year 6, and 21.3% at year 10 (Eaton et al., 1995). This pattern is not dissimilar in other long-term research. Another 10-year follow-up study of 71 young people in the early stages of schizophrenia/ schizoaffective disorder found the prevalence of positive symptoms was around 40-50% at 2 year follow-up, with only a slight decline (of 10%) observed in later years (Marengo et al., 2000). A recent 10-year follow-up study from the OPUS cohort in Denmark confirmed that a pattern of reduction in positive symptoms, followed by stabilisation, was displayed in 59% of the sample, with the time taken to achieve this reduction ranging from one to five years (Austin et al., 2015).

Conversely, other follow-up studies have supported the assumption of variability in positive symptom patterns of course. For example, Quinlan et al. (Quinlan et al., 1995) reported that positive symptoms increased significantly over the course of two-year follow-up, whilst Arndt et al. (Arndt et al., 1995) found that positive symptoms improved considerably (i.e., almost halved) over two-year follow-up, and showed greater instability as compared with negative symptoms, which was supported by Addington and colleagues, who observed that positive symptoms improved significantly over a six-month period (Addington & Addington, 1991).

2.2.1.2 Stability of Negative Symptoms

Early conceptions of schizophrenia suggested that negative symptoms increased over time, as individuals were seen as following a path of progressive, inevitable deterioration in functioning (Bleuler, 1950; Kraepelin, 1919). This view was later challenged by studies which observed that negative symptoms were relatively stable over time, for instance, (Dollfus &

Petit, 1995; Mueser, Douglas, Bellack, & Morrison, 1991; Pogue-Geile & Harrow, 1985; Ventura et al., 2015). Other researchers reported significant improvement in negative symptoms, thus disputing the notion that negative symptoms form a trait (Addington & Addington, 1991). Fenton et al. noted that many short-term studies found that negative symptoms have limited stability during the acute stage of illness, with increasing stability over time (Fenton & McGlashan, 1991). In their Chestnut Lodge study of 187 schizophrenia patients, Fenton et al. reported that negative symptoms were moderately stable between first and index hospitalisation (mean interval of 4.5 years).

Of the longer term studies, Eaton et al. reported that, following a marked decline in the first 6 months, negative symptoms were present in approximately one third of the sample (30.6%) in year 1; decreasing to 13.0% in year 6, and 16.9% in year 10 (Eaton et al., 1995), thus demonstrating a reduction in symptoms from baseline to mid-course of the study, followed by a period of stability. Marengo et al. ((Marengo et al., 2000) found that negative symptoms tended to be reasonably stable over the 10 year follow-up: at 2 year follow-up the prevalence of individual symptoms ranged from 5-36%; at 4.5 years 4-28%, at 7.5 years, 14-34%, and 6-37% at 10 years. Studies conducted over shorter intervals have revealed similar patterns of change: Arndt et al. demonstrated that negative symptoms were prominent at index hospitalisation, with only modest improvement at discharge, then tending towards stability at one-year and two-year follow-up (Arndt et al., 1995), whilst Ventura et al. reported moderate stability of negative symptoms in the first outpatient year, with a subgroup of individuals exhibiting fluctuating symptoms (Ventura et al., 2015). Addington et al. found that all negative symptoms, with the exception of avolition, significantly improved over a six-month course (Addington & Addington, 1991).

Recent findings from a large meta-analytic study have mounted a convincing challenge to the conception that negative symptoms are highly stable. Based on data from nearly 6000 outpatients with schizophrenia, assessed at two time points (which ranged in duration from 10 weeks to three years apart), Savill et al. (Savill et al., 2015) reported that negative symptoms declined in almost all of the 89 included study arms, with only one showing an unequivocal increase in negative symptoms between baseline and endpoint. The authors concluded that negative symptoms do not tend to follow a stable or deteriorating course, but are likely to improve over time. Even in studies of chronic outpatients, it has been reported that negative symptoms decrease significantly over a two-year period, which Quinlan et al. argued showed

support for reconsideration of the notion of 'progressive downward course' in schizophrenia (Quinlan et al., 1995). On the other hand, another recent large meta-analysis of negative symptom treatment RCTs found that although most treatments reduced negative symptoms in pre-post studies relative to placebo, no change met the threshold for clinically meaningful improvement, as assessed by the Clinical Global Impressions (CGI) scale (Fusar-Poli et al., 2015).

2.2.1.2.1 Individual Negative Symptoms

It has been pointed out (Evensen et al., 2012) that few long-term longitudinal studies of schizophrenia and FEP populations have investigated individual negative symptoms, instead focusing on overall negative symptom counts or severity. Over the course of 10 years, Evensen et al. followed the symptomatic development of affective flattening in a sample of FEP patients, which was inclusive of the full diagnostic spectrum of psychosis. Of 184 participants, 71% had clinically significant flat affect on at least one of the six assessments over the 10 year follow-up, with a minority (5%) classified as experiencing enduring flat affect. The authors found that affective flattening fluctuated more than expected, given the emphasis of the literature on the relative stability of affective flattening over other symptoms; two-thirds of the sample experienced improving, deteriorating, or fluctuating affective flattening. This contrasts with the general assumption that negative symptoms tend towards stability. In particular, it has been noted that affective flattening is the most stable symptom over time, as it is considered less responsive to medication (Kelley, van Kammen, & Allen, 1999). A recent publication by the European First Episode Schizophrenia Trial (Galderisi et al., 2013) reported that affective flattening was the most persistent negative symptom over the one year course of the study.

Conversely, Kelley et al. (Kelley, Haas, & van Kammen, 2008), in their study of chronic and FEP schizophrenia samples assessed on four occasions over the course of one year, found that only avolition changed significantly, decreasing initially, then levelling off. Affective flattening and alogia showed a lack of change, with anhedonia showing change only when treated as a continuous variable using linear analysis, as opposed to a categorical approach, where negative symptoms were treated as binary variables (Kelley et al., 2008). The authors suggested that it was possible that levels of affective flattening and alogia were too low to determine reasonable change over time, however they noted that the literature tends to regard these symptoms as being more stable. Another study assessed individual negative symptoms

in schizophrenia patients twice over the course of one year, and reported no significant change in anhedonia, blunted affect, and alogia (Mueser et al., 1991). In direct contrast, Addington et al. (Addington & Addington, 1991) reported significant improvement in each of the negative symptoms over six months, with the exception of avolition. It was suggested that this change showed little support for the idea that negative symptoms are trait symptoms, as opposed to state symptoms (for instance, which positive symptoms are conceived as).

In a two-year follow-up, Quinlan et al. reported that although the overall severity of negative symptoms decreased over this period, only affective flattening and alogia symptoms decreased, whilst avolition increased (Quinlan et al., 1995). Anhedonia demonstrated a significant interaction with diagnosis, increasing over time in the schizophrenia group but decreasing in the non-schizophrenia group. In a three-year follow-up, Dollfus et al. (Dollfus & Petit, 1995) found that affective flattening and avolition did not vary over time, but that anhedonia worsened. These authors ruled this out as being due to the stage of illness, since the aggravation of anhedonia occurred across both chronic and post-acute groups.

The recent meta-analytic study of 89 study arms from 41 studies by Savill et al. examined how negative symptoms change over time in schizophrenia patients (Savill et al., 2015). Only baseline and study endpoint were used. These ranged from 10 weeks to three years apart. Five interventions were assessed: first generation antipsychotics, second generation antipsychotics, adjunctive medications, non-drug interventions, and placebo/TAU arms. Regardless of intervention type, negative symptoms declined in nearly all the 89 study arms. Large effects were detected for second generation antipsychotics and adjunctive medication, with small effects in the placebo/TAU arms. The type of scale used and intervention type contributed significantly to heterogeneity observed in symptom change. Studies that used the Scale for the Assessment of Negative Symptoms (SANS) (N. Andreasen, 1983) found a significantly greater reduction in negative symptoms than those which used the PANSS or BPRS. The authors noted that the finding that the SANS is a more sensitive instrument in detecting change was unsurprising, given the focus of the SANS on negative symptoms, as opposed to a range of symptoms. Of the 89 included samples in Savill et al., 18 samples reported change in individual negative symptoms. A significant reduction was noted in each of affective flattening alogia, avolition, and anhedonia. Alogia declined the least, with an effect size of 0.64, and avolition reduced the most, with an effect size of 0.77. Differences between the symptoms were reported to be minimal, and duration between time points did not significantly predict

change over time in multivariate analyses examining heterogeneity of negative symptom change (Savill et al., 2015).

2.2.2 Longitudinal Research Categories II: Predictors of Outcome and Course of Illness

Of the studies in the second category— those focusing on outcome and course of illness over the long-term—Eaton et al. (Eaton et al., 1995) examined potential predictors of positive and negative symptoms, assessed monthly over a 10-year course**.** This study found that male subjects were more likely to have positive symptoms than females over the course of follow-up, with no effect of gender on negative symptoms. Later onset of psychosis was associated with more positive symptoms and fewer negative symptoms. Insidiousness of onset was related to the presence of both positive and negative symptoms. A related study (Thara et al., 1994) identified later age of onset, longer duration of illness at intake and insidious onset as risk factors for poor course of illness over the 10-year period. In their review paper, McGlashan et al. (T. H. McGlashan & Fenton, 1992) concluded that research is not consistent regarding the association of sex and age of onset with positive and negative symptoms in schizophrenia. A long-term follow-up study (Bottlender et al., 2003) found evidence that the adverse effect of longer DUP on a range of 15-year outcomes in schizophrenia was independent from competing factors such as gender, mode of onset, age at first admission, and pre-morbid functioning. Significant 15-year outcome domains included positive and negative symptoms, as measured by the SANS.

A recent long-term study (Ventura et al., 2015) assessed a group of 53 recent-onset schizophrenia patients with the SANS every three months during the first year, and followed them up eight years later. The authors reported that severity of early negative symptoms predicted negative symptoms at eight-year follow-up, however they cautioned that since potential confounding variables such as pre-morbid functioning and DUP were not included, they could not rule out that the correlations might be accounted for by third variables. On the other hand, Fenton et.al. (Fenton & McGlashan, 1991) found that affective flattening and anhedonia were independent predictors of long-term outcome regardless of pre-morbid functioning, however they also noted that as predictors, negative symptoms showed less prognostic significance when assessed early in the course of illness than when assessed several years after the illness had been established. Addington et al. (Addington & Addington, 1991)

found that negative symptom levels at hospitalisation were highly predictive of negative symptoms at 6-month follow-up, whereas positive symptoms yielded little predictive information.

The International Study of Schizophrenia (ISoS) coordinated by the World Health Organization (WHO) attempted to reconcile divergent long-term study findings in their 15-year follow-up study of 18 diverse treated incidence and prevalence cohorts (Harrison et al., 2001). Predictive relationships between baseline and early course variables, and long-term outcome, as assessed using the Global Assessment of Functioning Disability and Symptoms scales (GAF-D and GAF-S), were examined in a sample of 461 individuals in the early stages of illness who had a sufficiently complete set of data. The authors discovered two findings of note: firstly, the percentage of time experiencing psychotic symptoms in the first two years was the strongest predictor of both 15-year GAF outcomes (although recovery varied significantly by location), and, secondly; participants with a baseline diagnosis of schizophrenia were significantly worse on GAF-D outcome than those with acute schizophrenia and bipolar/ depressive disorder. Other baseline variables considered were: age at first contact, gender, marital status, contacts with close friends, history of drug or alcohol use, and type of onset. DUP was unavailable due to insufficient data.

2.2.2.1 Predictors of Positive and Negative Symptom Outcomes

2.2.2.1.1 Gender

Early research was inconsistent with regard to the effect of gender on negative symptoms, however when present, these effects were invariably in the direction of males having more negative symptoms (T. H. McGlashan & Fenton, 1992), with no evidence for a gender effect on positive symptoms. Later studies have provided evidence to the contrary. For instance, Eaton et al. (Eaton et al., 1995) found that male subjects were more likely to have positive symptoms than females over the course of follow-up, with no effect of gender on negative symptoms, whilst Chang et al. reported that being male was associated with persistent negative symptoms over a 3-year follow-up (Chang, Hui, Tang, Wong, & Lam, 2011). Another study found evidence that most study participants with persisting affective flattening at 1-year follow-up were male (Galderisi et al., 2013). Another study (Austin et al., 2015) found that male gender was not significantly associated with 10-year positive symptom trajectory class membership, but did predict poorer longitudinal negative symptom trajectory outcomes.

2.2.2.1.2 Age at onset of psychosis

The association of age at onset of psychosis with positive and negative symptoms has been reported as inconsistent, with no discernible pattern of findings apparent (T. H. McGlashan & Fenton, 1992). However Eaton et al. later found that individuals with an age at onset of < 20 years were significantly more likely to experience negative symptoms than those aged > 25 years at onset, whilst those aged 20-24 years at the onset of psychosis were half as likely to experience positive symptoms than the older group (Eaton et al., 1995). Another paper based on the Madras longitudinal study reported that being older at the onset of psychosis significantly predicted poorer illness course over the 10-year follow-up, with three older onset categories (20-24 years; 25-29 years; and 30 years and over) experiencing significantly poorer course than those aged >20 years at the onset of psychosis (Thara et al., 1994).

2.2.2.1.3 Duration of Untreated Psychosis

Many studies have reported that an association exists between duration of untreated psychosis (DUP) and outcome in first-episode psychosis (Beiser, Erickson, Fleming, & Iacono, 1993; Bottlender, Straub, & Moller, 2000; Drake, Haley, Akhtar, & Lewis, 2000; Haas, Garratt, & Sweeney, 1998; Helgason, 1990; T. Larsen, McGlashan, Johannessen, & Vibe-Hanson, 1996; T. K. Larsen, Moe, Vibe-Hansen, & Johannessen, 2000; Loebel et al., 1992; T. McGlashan, 1999; R. Norman & Malla, 2001; Scully, Coakley, Kinsella, & Waddington, 1997; Wyatt, 1991) though this is not beyond dispute (Barnes et al., 2000; Craig et al., 2000; B. Ho & Andreasen, 2001; B. C. Ho, Andreasen, Flaum, Nopoulos, & Miller, 2000). DUP is an important variable because it is one of the few risk factors for poor outcome that is potentially modifiable via early detection strategies (Harrigan, McGorry, & Krstev, 2003). Potentially malleable risk factors for poor outcome contrast with the fixed nature of most predictors, such as gender, age of onset of psychotic symptoms, pre-morbid functioning, and diagnosis. The extent of any confounding of DUP by other predictors of outcome such as pre-morbid functioning, level of education, and gender, third variables, is of critical importance, (R. Norman & Malla, 2001) as it has implications for the viability of early detection programs in early psychosis. If DUP is merely a proxy for other predictors of outcome, then establishing early intervention services to reduce DUP would be of uncertain value in improving outcome. On the other hand, if it can be established that prolonged DUP influences patient outcome independently of other factors, then it becomes imperative to develop early detection strategies (Harrigan et al., 2003).

A large systematic review provided convincing evidence of a moderately strong association between DUP and a range of short-term outcomes at 6 and 12 months of follow-up (Marshall et al., 2005). The association was not usually apparent at the time of presentation but emerged after treatment administration. The association between DUP and outcome domains was robust when pre-morbid functioning was controlled for, with only four of 16 analyses no longer significant. The authors noted that three of these four analyses were suboptimal according to predetermined quality criteria. There was a particularly robust association between DUP and positive symptoms. At 24 month follow-up the association between DUP and outcome was weaker, however 15-year follow-up data (Bottlender et al., 2003) continued to show support for a relationship between DUP and overall functioning, positive symptoms, and negative symptoms (as measured by the SANS, but not the PANSS). Even though the findings were consistent throughout the Marshall et al. meta-analysis, three important American studies concluded that there was no association between DUP and outcome e.g., (Craig et al., 2000; B. C. Ho et al., 2000; Loebel et al., 1992). Marshall et al. claimed that on closer scrutiny, the results of these studies were consistent with the findings of the meta-analytic review.

Additional support for the impact of DUP on outcome has been forthcoming from other sources. For instance, a recent 10-year follow-up (Austin et al., 2015) reported that prolonged DUP was associated with an increased risk of a worse positive symptom prognosis for each of four classes of positive symptom trajectories as compared to the reference class (positive symptoms response) when other baseline variables such as diagnosis, substance abuse, and global functioning were taken into account (pre-morbid academic functioning and gender were not included as covariates since they were not associated with positive symptom trajectories in univariable analyses). Likewise, Addington et al. (Addington, Van Mastrigt, & Addington, 2004) reported that prolonged DUP was significantly associated with high levels of positive symptoms at one and two years following admission to an FEP program, after controlling for other factors including age and pre-morbid functioning. However, DUP failed to significantly predict negative symptoms, a finding echoed by Austin et al., who confirmed that although DUP was significantly associated with increased risk of worse 10-year negative symptom trajectory profiles in a univariable model, it dropped out as a significant predictor when the effects of other baseline variables, including pre-morbid social functioning and diagnosis were controlled.

These findings are supported by other studies. For example, Malla et al. (Malla et al., 2002) found that DUP predicted positive symptoms at 1-year follow-up independently of pre-morbid functioning, however negative symptoms was influenced by longer term characteristics such as pre-morbid functioning, earlier age at onset, gender and prodromal duration. The authors concluded that negative symptoms may, therefore, not be as responsive to effects of early intervention as positive symptoms. Another study conducted over an 8-year follow-up confirmed that DUP independently predicted positive symptoms, but did not predict negative symptoms (Crumlish et al., 2009). Conversely, other studies have reported that DUP is a significant predictor of negative symptoms, with two recent studies showing that DUP was significantly associated with persistent negative symptoms (Chang et al., 2011; Galderisi et al., 2013).

2.2.2.1.4 Pre-morbid functioning

One of the factors consistently associated with good outcome in first-episode psychosis is good pre-morbid adjustment (Haas et al., 1998; Johnstone, Macmillan, Frith, Benn, & Crow, 1990; T. K. Larsen et al., 2000). DUP appears to be consistently associated with both patient outcome and pre-morbid adjustment, with debate surrounding the question of whether DUP is simply an epiphenomenon of pre-morbid adjustment (T. K. Larsen et al., 2000; P. McGorry, Krstev, & Harrigan, 2000). It is possible that poor pre-morbid functioning could result in a reduced likelihood of detection and receipt of appropriate treatment, thus resulting in longer duration of untreated illness. DUP, according to this perspective, has only a spurious association with outcome, a view seemingly supported by some studies (Verdoux et al., 1998; Verdoux et al., 2001) but not others (Haas et al., 1998; T. K. Larsen et al., 2000). The question of whether DUP is an epiphenomenon of pre-morbid functioning was addressed by Larsen et al. (T. K. Larsen et al., 2000). In their study, DUP was significantly associated with positive symptoms, but not negative symptoms, independently of gender and pre-morbid functioning at one-year follow-up. On the basis of these findings, the authors ruled out the possibility that DUP was simply a mediator between pre-morbid functioning and 1-year outcome.

Addington et al. (Addington & Addington, 2005) investigated different patterns of pre-morbid development prior to the onset of acute psychosis and their relationship with one- and two-year outcome. Individuals with a deteriorating or poor-deteriorating course of pre-morbid functioning had significantly higher levels of positive and negative symptoms at one-year follow-up, the latter of which remained significant at two-year follow-up. This finding was

supported by Chang et al. (Chang et al., 2011) who reported that participants with stable-poor pre-morbid social functioning had significantly higher levels of negative symptoms at two- and three-year follow-up even when the effect of DUP was taken into account. However, a recent 10-year follow-up (Austin et al., 2015) found that pre-morbid functioning was not associated with positive symptom trajectory class membership, but was linked with poorer negative symptom trajectory class membership.

2.2.2.1.5 Diagnosis

Austin et al. (Austin et al., 2015) ascertained that a baseline diagnosis of schizophrenia was associated with an increased risk of a worse positive symptom prognosis for each of four positive symptom trajectory classes assessed over the course of 10 years, when other baseline variables were taken into account. Schizophrenia diagnosis also discriminated between different negative symptom trajectory classes in multivariable analyses. An earlier 10-year follow-up, the Chicago study (Herbener & Harrow, 2001), reported diagnostic differences in frequency of negative symptoms between schizophrenia/schizoaffective and depressed groups at 7.5-year and 10-year follow-up, however no differences were detected between 'other' psychotic disorders and either of the other two diagnostic groups. Persistence of negative symptoms significantly differed between the schizophrenia/schizoaffective disorder and depressed groups, and between the 'other' psychotic and depressed groups. In terms of severity of negative symptoms, no diagnostic differences were identified at any follow-up point. The authors concluded that diagnosis appears to add additional vulnerability to later negative symptoms even after the effects of early negative symptoms are considered.

2.2.3 Impact of Symptom Fluctuations on Long-Term Outcomes

Few studies have investigated the short-term trajectory of positive and negative symptoms and their impact on long-term outcomes. One exception is a recent study (Ventura et al., 2015) which investigated the stability, exacerbation and remission of negative symptoms in the first year after medication stabilisation in a sample of 149 recent-onset schizophrenia patients. Analyses were also performed which examined the degree to which negative symptoms at specific time periods in the first year were correlated with 8-year symptomatic and functional outcome in a subsample of 53 individuals. Negative symptom levels, averaged across the first year, were significantly correlated with negative symptoms at 8-year follow-up, with

correlation coefficients ranging from 0.32 to 0.54. The authors observed that the significant correlations between negative symptom levels in the first year and 8-year symptoms implied that negative symptoms do not appear to remit spontaneously. However, it was acknowledged that potential confounding variables such as DUP and premorbid functioning were not included, hence these results could be spurious. The authors reported moderate stability in fluctuations in negative symptoms in the 1-year interval from medication stabilisation, with 24% of participants exhibiting one or more periods of symptom exacerbation. This figure is surprisingly similar to that found for positive symptoms in another study (Neuchterlein et al., 2006) which reported that 21% of early course schizophrenia patients demonstrated positive symptom exacerbations over a similar time period.

The study of Austin et al. (Austin et al., 2015) investigated the long-term trajectories of positive and negative symptoms in a large FEP sample over a 10-year follow-up. The aim was to identify distinct groups of individuals with homogeneous longitudinal symptom profiles on each of positive and negative symptoms, using latent class analysis. Austin et al. used symptom scores on each of the available time points for each individual to produce an estimate of the probability of group (i.e., latent class) membership. Five longitudinal symptom trajectory classes were generated for positive symptoms: response (47%); delayed response (12%); relapse (15%); non-response (13%), and episodic response (13%). Predictors of poorer classes of positive symptom trajectories included prolonged DUP and a baseline diagnosis of schizophrenia. For negative symptoms, four classes of symptom trajectories were generated: response (28%); delayed response (19%); relapse (26%); and non-response (27%). Baseline predictors of negative symptom trajectory classes included poor pre-morbid social functioning, male gender, and a diagnosis of schizophrenia.

2.3 Limitations of Existing Research

Although the findings of studies focusing on the prevalence, stability and independence of positive and negative symptoms (Arndt et al., 1995; Eaton et al., 1995; Marengo et al., 2000; Savill et al., 2015; Ventura et al., 2004; Ventura et al., 2015) offer important insights into the course of first-episode psychosis, the extent of individual variability in the rate and shape of symptom change over time has remained largely unexplored. Furthermore, previous findings are limited by a number of potential limitations or weaknesses, including diagnostic homogeneity, small sample size and the failure to consider latent heterogeneity when

investigating the course of illness over time. Thus, the key questions relating to rate and shape of change in symptoms over the course of recovery from illness continue to be largely unanswered. These deficiencies raise a number of questions regarding the mutability of symptoms over the course of recovery from the first psychotic episode and the extent to which this varies, both within and across individuals. Leading logically from this objective is the identification of potential explanatory variables that may account for heterogeneity in symptom fluctuation. Whilst previous research has examined predictors of the prevalence of positive and negative symptoms over the longitudinal course, such as gender, age of onset of psychosis and insidiousness of onset (Eaton et al., 1995), potential predictors of divergence in positive and negative symptom trajectories have rarely previously been examined. A recent exception is the OPUS study research by Austin et al. (Austin et al., 2015), in their investigation of predictors of latent classes of positive and negative symptom trajectories in a first-episode psychosis sample over a 10-year follow-up.

Apart from longitudinal studies such as these (Arndt et al., 1995; Austin et al., 2015; Eaton et al., 1995; Evensen et al., 2012; Marengo et al., 2000; Ventura et al., 2004; Ventura et al., 2015), relatively few studies in psychosis research have investigated change in symptom severity over time. This is probably because, as Arndt et al (1995) points out, longitudinal studies are difficult to do well, with a long-term commitment required and a slow return on the investment. However, longitudinal designs are essential to investigations relating to the patterns of evolution of symptomatology in psychotic disorders, in particular, issues relating to the stability, independence and variation in symptoms over time (Marengo et al., 2000).

Not only are longitudinal studies difficult to do well, there are a plethora of traps, even for the seasoned longitudinal researcher, in the analysis of data emanating from such designs. Firstly, failure to minimize and deal adequately with participant attrition over time constitutes a source of potentially serious bias; secondly, ignoring multilevel structures inherent in longitudinal data can lead to incorrectly specified models and threaten the viability of the findings; thirdly, statistical techniques most appropriate to the analysis of longitudinal data have, until recently, remained relatively inaccessible to many researchers in psychiatric studies; and fourthly, statistical power is often hampered by the modest sample sizes typically found in such studies. Consequently, much information contained in individual change data is obscured by the application of standard statistical techniques such as repeated-measures analysis of variance, which ignores the complexity, richness and individual heterogeneity

inherent in such data. Traditional techniques tend to be inflexible and make a number of untenable assumptions regarding the attributes of longitudinal data. For example, repeated-measures analysis of variance is not able to deal with missing assessments, nor can it accommodate variability in follow-up assessment intervals between individuals, which is common in longitudinal studies of psychosis.

2.4 Longitudinal Data Modelling: New Frontiers in Psychosis Research

Although heterogeneity in the course of schizophrenia and other psychotic disorders is acknowledged in the literature, longitudinal psychosis research has rarely examined fluctuations or non-linear change processes in symptoms (Peer & Spaulding, 2007). This may be at least partly accounted for by the preponderance of cross-sectional designs, or in the case of intervention trials, pre-post assessments. Neither of these allows a description of how and when symptom changes occur (Peer & Spaulding, 2007). Understanding the longitudinal course of psychosis is crucial to acquiring an understanding how the illness evolves over time, and hopefully in developing effective, well-timed treatment interventions which will advance current treatments and outcomes.

A sophisticated class of modelling techniques has become more accessible to psychosis researchers for the analysis of longitudinal data, and has exciting implications for longitudinal psychopathology research. These techniques are broadly known as latent growth curve (LGC) models (Curran, Obeidat, & Losardo, 2010), individual growth curve (IGC) analyses, and are also described variously as multilevel models, hierarchical linear models and random coefficient regression models, amongst others (Lenzenweger, Johnson, & Willett, 2004). The LGC approach can accommodate most of the pitfalls associated with longitudinal designs that traditional methods cannot, including subject attrition, missing follow-up assessments and variability in follow-up assessment intervals between individuals. Growth curve models also offer a number of key advantages, including using data on all individuals at every time point to explicitly model change both within and between individuals, in an attempt to estimate between-person differences in within-person change (Curran et al., 2010). Amongst other terms, these patterns of change are known as growth curves, or latent trajectories, and are likely to take on different forms that vary between individuals. Trajectories may increase or decrease over time, or they might be flat; additionally, trajectories might be linear, or non-

linear. A particular advantage of growth models is that they usually offer higher levels of statistical power than traditional analytic techniques (Curran et al., 2010).

Despite their increasing availability, growth curve methodologies are not widely used in psychopathology research (Curran & Hussong, 2003). Indeed, it has been pointed out as an unfortunate feature of psychiatric research (Gibbons et al., 1993) that the statistical methods for analysing longitudinal psychiatric data are rarely commensurate with the effort involved in their acquisition. Whilst some areas of psychiatric research have applied these approaches, for example, in longitudinal studies of stability of personality disorders (Lenzenweger et al., 2004), the flexibility and utility of these approaches in detecting and describing individual change over time has not yet been realised by longitudinal studies of symptomatology in psychosis research.

2.5 Aims of the Thesis

The research reported in this thesis examines the patterns of evolution of symptomatology in psychotic disorders. In particular, it focuses on issues relating to the degree of individual variation in the rate and shape of change over the 1-year interval subsequent to initial recovery/stabilisation of the initial episode. The effects of presenting characteristics of study participants on short-term and long-term symptomatic outcome will be investigated, with mediation analysis used to investigate whether effects are direct or indirect in nature. Models will be developed and tested using a large, broad-based and representative first-episode psychosis (FEP) sample, which will allow findings to be generalised across the comprehensive diagnostic spectrum of all functional psychotic disorders.

Broadly, this thesis has four primary aims; firstly, to examine the pattern and rates of change in positive and negative symptoms in 413 patients with first-episode psychosis at three time points over the 1-year interval subsequent to initial recovery/stabilisation of the initial episode (defined as the short-term trajectory); secondly, to identify potential predictors of heterogeneity in symptom fluctuation over the short-term trajectory; thirdly, to investigate the role played by the short-term symptom trajectory in predicting long-term (7.3 year average) symptomatic outcome, and; fourthly, to identify participant attributes that may predict long-term symptomatic outcome, and whether any such effects are mediated by the short-term trajectory and/or early symptoms. The data will be modelled using LGC methods,

thus dealing with issues commonly occurring in longitudinal studies including subject attrition, missing data, and variable time to follow-up. Following previous research, predictors of rates of change in symptoms over the 1-year interval subsequent to recovery from the initial episode will include gender, age of the onset of psychosis, duration of untreated psychosis (DUP), and pre-morbid functioning. The degree to which DSM-IV diagnosis of the initial episode predicts the course of positive and negative symptoms will also be examined. The analyses of individual growth trajectories seeks to illuminate the evolution of symptomatology over the course of first-episode psychosis and help identify factors underlying heterogeneity in symptom course.

2.5.1 Clinical Relevance of the Short-Term Symptom Trajectory

The time period of the short-term trajectory (STT) is particularly relevant in a clinical sense. The critical period for vulnerability to symptomatic deterioration, relapse and the development of disability is thought to occur during the early phase of psychosis, with relative stability in symptoms and disability levels subsequently (Birchwood, Todd, & Jackson, 1998). The "critical period" is so named because of its relationship to the timing of the development of disability (P. D. McGorry, Edwards, Mlhalopoulos, Harrlgan, & Jackson, 1996). It is hypothesised that intervention in the early years after onset of psychosis, whether biological or psychosocial, is likely to have a substantially greater impact compared with interventions later in the course of illness. Crumlish et al. (Crumlish et al., 2009) state that:

> *"The critical period hypothesis proposes that the early phase of psychosis, including any period of initially untreated psychosis, is a 'critical period' during which symptomatic and psychosocial deterioration progresses rapidly. Afterwards, progression of morbidity slows or stops, and the level of disability sustained, or recovery attained, by the end of the critical period endures into the long term".*

It is unclear what role, if any, is played by the psychopathology STT in the first year post-recovery in the prediction of long-term symptomatic outcome, whether as a direct predictor, and/or as a mediator of the effects of participant presenting attributes such as gender, age at onset of illness, premorbid functioning, and DUP on long-term outcome. The critical period hypothesis proposes that interventions which shorten DUP and arrest the putative "progressive deterioration" suggested in earlier conceptions of schizophrenia (Bleuler, 1950; Kraepelin, 1919) may have long-term benefits (Crumlish et al., 2009).

The uncertainty regarding the role played by short-term symptom trajectories in determining long-term (7.3 year) outcomes is key to the research questions under investigation. It is possible that the effects of patient presenting attributes on long-term outcome might be direct in nature, or they might be mediated by other variables. For instance, short-term outcomes such as the STT, or symptom levels at admission, might act as a causal pathway for the effects of particular participant presenting attributes on long-term outcome. The concept of mediation is simple—that a third variable (the mediating variable) 'transmits' the causal effect of one variable to another. It will be shown that mediation analysis helps explain the process by which hypothesized predictors impact long-term symptomatic outcome.

The degree to which the evolution of symptoms over the 1-year interval subsequent to initial recovery is impacted by presenting attributes of the participants is similarly uncertain. It is hoped that this research will assist in clarifying the nature of the role played by the STT as a portent of long-term symptomatic outcome, and also help identify whether there are particular participant presenting attributes which account for variability in symptom trajectories.

2.5.2 Research objectives of this thesis:

1. Firstly, to investigate the degree to which positive and negative symptoms change over the short-term course of illness from stabilisation/remission of the initial psychotic episode (i.e., the initial recovery point) up to 1-year follow-up in a sample of 413 FEP patients. Identification of the unconditional structure of positive and negative symptomatology over this phase of illness will set the scene for identification of predictors of variability in symptom trajectories in subsequent aims. The key component of this research question is: How is the change in symptoms over short-term follow-up best represented? The focus of this question is on identifying the average shape of change in symptoms over the 1-year course from initial recovery, and the degree to which individual variability exists in these patterns.

2. Leading logically from the first objective is the question of whether there are potential explanatory symptom variables that may account for heterogeneity in growth trajectories over the 1-year interval subsequent to initial recovery. That is, does symptom severity at service admission predict initial status at the starting point of the growth trajectory (i.e.,

initial recovery), and patterns of change in the specified growth structure over the subsequent 1-year trajectory. Furthermore, investigations will be undertaken to assess the extent to which individual variability in short-term symptom trajectories can account for long-term symptomatic outcome, and whether symptom change over the 1-year interval fully or partly mediates the effect of symptom severity at service admission. Thus, aspects to this research are threefold:

a. Can individual heterogeneity in symptom course over the short-term be accounted for by symptom severity at index presentation?

b. To what degree does variability in the short-term symptom trajectory account for long-term (7.3 year) severity in positive and negative symptoms?

c. Are the effects of symptom severity at admission on long-term outcome fully or partly mediated by the short-term growth trajectories? In other words, does symptom severity at presentation exert an effect on long-term outcome only through its effects on the symptom change that occurs in the 1-year interval subsequent to stabilisation/remission from the first psychotic episode?

3. The third research objective builds on preceding modelling, with the introduction of additional candidate predictors: namely, presenting features of study participants. The predictive utility of gender, age at onset of psychosis, premorbid functioning, and DUP on short-term and long-term outcomes will be investigated. The first question relates to short-term outcome; whether these presenting features can account for heterogeneity in growth trajectories over the 1-year interval subsequent to stabilisation/remission of the initial psychotic episode. The nature of these effects on the short-term trajectories is also of interest, in particular, whether these candidate predictors directly predict the latent growth factors, or whether their effects are mediated by symptom levels at admission.

Secondly, the impact of participants presenting features on long-term outcome, and the nature of any predictive relationship, will be assessed by via mediation analysis. Questions such as these will be investigated: is the effect of DUP on long-term outcome a direct one? Is the presence of any effect of DUP on long-term outcome fully or partially mediated by the short-term trajectory latent growth factors or by severity of symptoms at index presentation? In other words, does DUP exert an effect on long-term symptomatic outcome only through its effects on symptom levels at initial admission, or the short-term

trajectory? Similar questions apply to the other presenting features (gender, pre-morbid functioning, and age at onset of psychosis) as potential predictors of long-term outcome.

4. The final section of this thesis introduces baseline DSM-IV psychotic diagnosis as a predictor of short-term and long-term outcome. Diagnosis has the potential to differentiate positive symptom trajectories and final long-term outcome, over and above other participant attributes. Similar questions to those posed for the participant attributes in the third research objective will be investigated in this section.

These research objectives are formalised as specific research questions in the next chapter.

3 RESEARCH QUESTIONS

The purpose of this chapter is to formalise the investigations proposed in Chapter 2 (Background) as a series of research questions. There are 16 research questions in total for each of the five symptoms under investigation: positive symptoms, and the four negative symptoms: affective flattening, alogia, avolition, and anhedonia symptoms.

These investigations focus on three principal aspects of positive and negative symptomatology of the first psychotic episode. The first is concerned with the rate and shape of change in positive and negative symptoms over the 1-year interval subsequent to the initial psychotic episode, and identifying the degree to which there is individual variability in these short-term trajectories (STT). Secondly, the role played by the STT as (i) an independent predictor of long-term symptomatic outcome, and/or (ii) potential mediator of the participants' presenting features on long-term outcome, will form a central focus. Similar investigations will be conducted for baseline DSM-IV diagnosis of the initial psychotic episode to assess whether the effects of diagnosis on long-term outcome are direct, or mediated by the STT. Thirdly, effects of participants' presenting features and baseline DSM-IV diagnosis on the STT and on symptoms at service entry will be examined. The data will be modelled within a large, broad-based and representative first-episode psychosis (FEP) sample, which will allow findings to be generalised across the comprehensive diagnostic spectrum of all functional psychotic disorders.

These research questions are drawn together by an integrated methodology that is well suited to addressing the questions in a consistent way. It should be noted that the formal research questions are necessarily repetitive – "same form, different variables." This is an inevitable consequence of the application of this structured, model building approach. To avoid unnecessary repetition, each of the research questions refers to the positive symptoms and four negative symptoms in generic terms. For instance, rather than referring to positive symptoms specifically, each question refers to it as 'symptoms', or similar. The representation of these research questions as formal models will be elucidated in Statistical Methods, Chapter 5.

The research questions for each model follow. Where a research question is straightforward, it is simply listed without further explanation.

Model 1: Growth Characteristics of Positive Symptoms over Short-Term Follow-up

This initial model sets the framework for subsequent stages by fitting an unconditional growth curve (the model with no predictors) to the psychopathology data at initial recovery/stabilisation (T2), 6-month (T3) and 1-year follow-up (T4). A representation of the linear model is depicted in Figure 3.1. Two questions are embedded within the unconditional model framework: the first relates to the characteristics of the mean psychopathology growth trajectory for the overall group, whilst the second question relates to the degree to which there is individual variability in psychopathology trajectory estimates across individuals. Each question can be further delineated:

RQ 1.1 What is the overall short-term trajectory for the sample?

This question aims to identify, when aggregating over all 413 first-episode psychosis individuals, the mean trajectory of the severity of each symptom assessed across T2, T3 and T4. It comprises three components: (i) the average level of severity at the starting point of each symptom trajectory (T2); (ii) whether the average symptom severity changes significantly over the 1-year interval subsequent to the starting point, and if so (iii) whether change over time is best described as linear or non-linear.

RQ 1.2 What is the nature of variation of short-term trajectories between individuals?

Of particular interest is the degree to which there is evidence of meaningful variability of individual trajectories from the overall population mean trajectory. For instance, some individuals may have initial levels of symptom severity well above or well below the average initial level of severity. Furthermore, some may exhibit increases or decreases in symptom severity at a more rapid rate over time compared with the average rate of change. If the only variations can be attributed to sampling or measurement error, it could be concluded that there is no evidence of individual differences in trajectories and the mean trajectory can be considered representative of each individual trajectory. On the other hand, if there is meaningful variability of individual trajectories around the mean intercept and slope, this raises a third question about whether it might be possible to model individual variability in trajectories and predict individuals who start high versus low and who change over time more or less rapidly than average. The incorporation of predictors to account for individual

variability in severity of symptoms via conditional models will be presented in subsequent stages of the model.

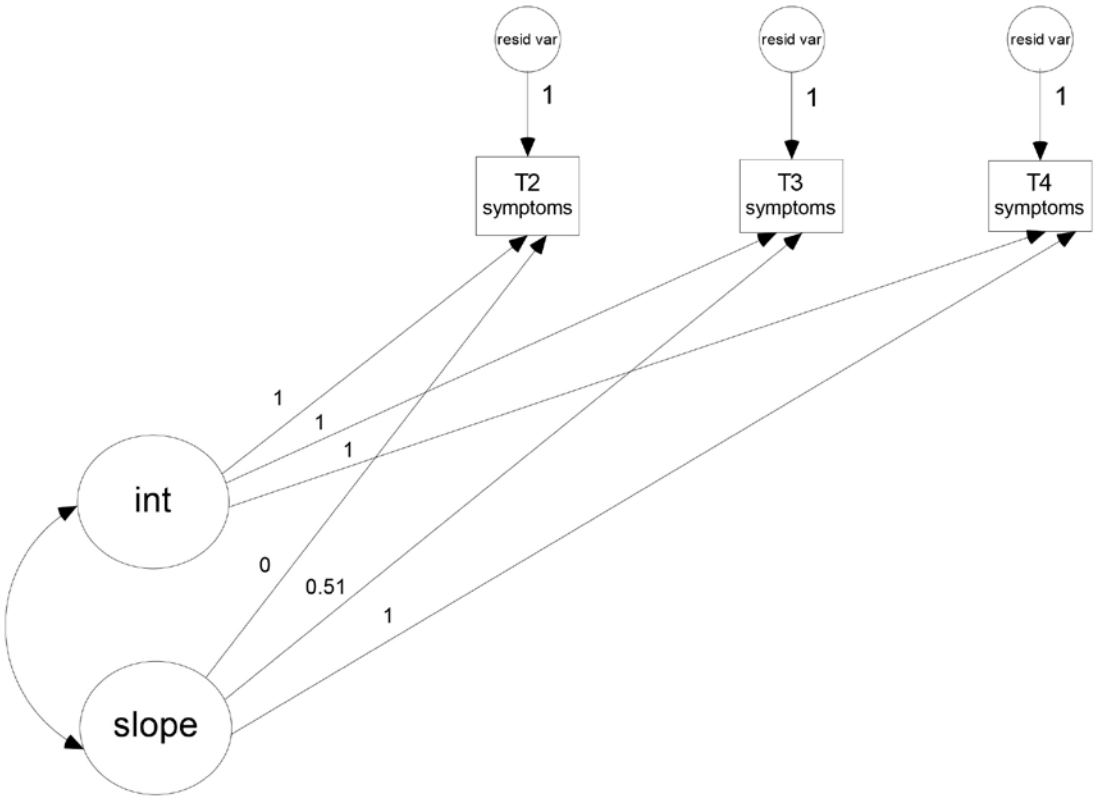


Figure 3.1. Unconditional linear latent trajectory model for symptoms measured at initial recovery, 6-month follow-up and 1-year follow-up.

The latent growth factor model depicted in Figure 3.1 includes symptom measures observed on three occasions over a 1-year interval subsequent to initial recovery: T2 (the starting point of the trajectory at initial recovery), T3, and T4; along with two latent growth factors. Further detail regarding this model specification will be provided in Chapter 5.

Model 2: Symptoms at Admission and Long-Term Follow-up

Measurements of symptoms made on two other occasions — admission (T1) and long-term follow-up (T5) — were added to the unconditional model established in Model 1. Severity of symptoms at admission, a time when participants are typically floridly psychotic, is specified as an exogenous covariate to the short-term growth trajectory. Severity of symptoms score at long-term follow-up (T5) is included as a distal outcome variable, and is predicted by

symptoms at admission (T1) and by the two latent growth trajectory factors, the intercept and slope. The covariance between the disturbance terms of the intercept and slope was initially constrained to zero (unless otherwise indicated), since correlated disturbance terms might imply the presence of another common factor. A representation of this model is depicted in Figure 3.2.

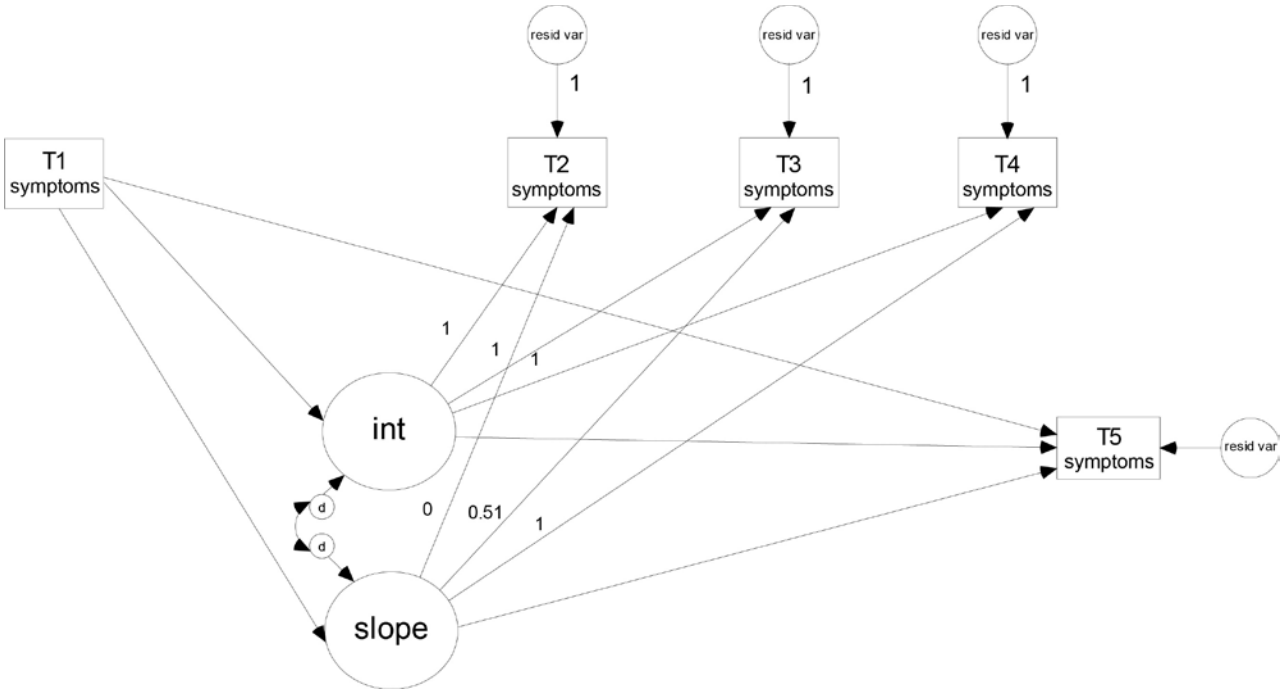


Figure 3.2. Conditional linear latent trajectory model for severity of symptoms, incorporating symptoms at admission (T1) as a covariate and long-term symptoms (T5) as an outcome variable.

Model 2 research questions

The main question addressed by this model relates to whether the effect of symptoms at admission on distal long-term symptom levels is mediated, either fully, partly, or not at all, by the initial level and change (intercept and slope latent trajectory variables) that represent the short-term growth trajectory in the 1-year interval subsequent to initial recovery. If some form of mediation is found, this would imply that symptom severity at admission (T1) transmits its effect on long-term outcome (T5) solely, or partly, through the short-term change following initial recovery. These mediational possibilities are further elaborated below (see RQ 2.4). Additional to these questions concerning indirect effects, there are three research questions of interest concerning direct effects for this model, specifically:

Direct Effects

RQ 2.1 Does symptom severity at admission directly predict the short-term trajectory?

This question seeks to identify whether admission symptom levels predict:

a) Initial symptom levels at the starting point of the trajectory (i.e., intercept) and/or:
b) the short-term change (i.e., slope) that occurs over the subsequent 1-year interval.

RQ 2.2 Does symptom severity at admission directly predict long-term outcome?

RQ 2.3 Does the short-term trajectory directly predict long-term symptom severity?

This question addresses whether either of the latent variables predict long-term outcome:

a) Initial symptom levels at the starting point of the trajectory (i.e., intercept) and/or;
b) the short-term change (i.e., slope) that occurs over the subsequent 1-year interval.

The magnitude and direction of direct effects will be presented as regression coefficients linking severity levels at admission, each of the intercept and slope latent growth factors, and observed long-term symptoms.

Indirect Effects

RQ 2.4 Is the effect of severity of symptoms at admission on long-term symptom levels mediated in full or in part by the latent trajectory variables?

This question is concerned with whether admission symptoms indirectly affects long-term symptoms, via its effect on the short-term change (represented by the intercept and/or slope latent variables) that occurs after initial recovery/stabilisation.

(i) If full mediation is occurring, (that is, admission symptoms at T1 does not predict long-term outcome whilst accounting for the mediator, but does predict either or both intercept and/or slope, which in turn predict(s) long-term outcome), this would imply that the severity of an individual's symptoms at admission transmits its effect on long-term outcome solely through the short-term change that has occurred after initial recovery.

(ii) If partial mediation is occurring (that is, admission symptoms at T1 predicts intercept and/or slope, which in turn predict long-term outcome, and admission also predicts long-term outcome whilst accounting for the mediator), then this indicates that severity of symptoms at admission transmits its effect on long-term outcome both

directly, and indirectly. The indirect effect is manifested via the impact of admission symptom severity on the short-term change that occurs after initial recovery, which transmits the effects on to long-term symptom levels.

Two other possibilities are: inconsistent mediation; and no mediation. These will be discussed in Mediation (Chapter 6).

Model 3: Effects of Participants' Presenting Features on Short and Long-term Follow-up

The preceding conditional model (Model 2) will be further developed by integrating four exogenous baseline predictors of the following outcome measures: (i) symptom levels at admission; (ii) the short-term trajectory, and; (iii) long-term outcome. These predictors are:

1. Gender;
2. Age at onset of psychosis;
3. Duration of untreated psychosis (DUP);
4. Pre-morbid functioning.

A representation of this model is depicted in Figure 3.3. These new variables are exogenous and are not predicted by any variable in the model. All paths in the preceding conditional model 2 are retained. Long-term symptom levels are now also being predicted by gender, age at onset, DUP and pre-morbid functioning. Symptom levels at admission becomes an endogenous variable in these models, and is predicted by gender, age at onset, DUP, and pre-morbid functioning. The short-term growth trajectory is predicted by gender, age at onset, DUP, and pre-morbid functioning. Further detail regarding this model specification will be provided in Chapter 5.

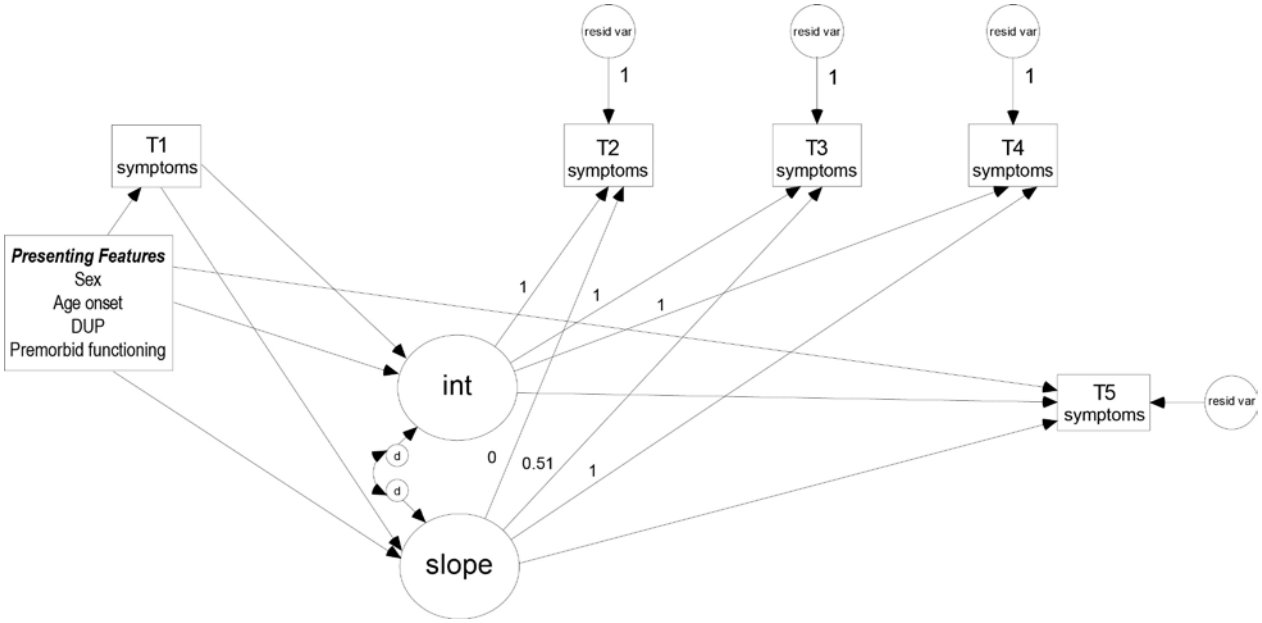


Figure 3.3. Conditional linear latent trajectory model for severity of symptoms, incorporating effects of gender, age at onset of psychosis, DUP and pre-morbid functioning as predictors of symptom severity at admission, short-term trajectory and long-term outcome.

Model 3 Research Questions

The main question addressed by this model is whether the effects of the participants' presenting features on distal symptom severity levels (T5) are mediated either fully or partly, or not at all, by the intercept and slope latent trajectory variables which represent the short-term trajectory in the 1-year interval subsequent to initial recovery (T2), and/or mediated by symptom levels at admission (T1). This question is of particular interest given that research has suggested that these presenting features are significantly associated with both short-term and long-term outcome even after the effects of known confounders are taken into account (Addington et al., 2004; Harris et al., 2005; T. K. Larsen et al., 2000; Marshall et al., 2005). If some form of mediation is found, then it would imply that the particular characteristic transmits its effect on long-term outcome solely, or partly, through the short-term change that has occurred after initial recovery, and/or by the severity of symptoms at admission. In addition to these indirect effects, which are presented in RQ 3.4 and RQ 3.5, there are three research questions of interest concerning direct effects for this model, specifically:

Direct Effects

RQ 3.1 Do the four key presenting features (gender, age of onset, DUP or pre-morbid functioning) directly predict symptom levels at admission?

RQ 3.2 Is there a direct effect of any presenting feature on the latent growth factors?

This question investigates whether these four baseline characteristics directly predict:

a) Initial symptom levels at the starting point of the short-term trajectory (i.e. intercept) and/or;
b) the short-term change (i.e. slope) that occurs over the 1-year interval subsequent to the starting point.

RQ 3.3 Do the four presenting features directly predict long-term outcome?

Indirect Effects

RQ 3.4 Are the effects of gender, age of onset, DUP and pre-morbid functioning on the short-term symptom trajectories mediated in full or in part by level of symptoms at admission?

This question investigates whether certain presenting features indirectly affect the short-term symptom trajectory, via their effects on level of symptoms at admission.

RQ 3.5 Are the effects of gender, age of onset, DUP and pre-morbid functioning on long-term symptom levels mediated in full or in part by either the latent trajectory variables or by symptom levels at admission?

This question investigates whether particular baseline characteristics indirectly affect long-term symptoms. Indirect effects of presenting features can occur via two possible pathways, either: (a) via their effect on short-term change (represented by the intercept and/or slope latent variables) that occurs after initial recovery, or (b) via their effect on level of symptoms at admission. As detailed previously, there are four possibilities: complete mediation, partial mediation, inconsistent mediation, and no mediation.

The research questions posed in Model 2 remain relevant. Brief commentary will be made

regarding whether the presence or absence of direct and indirect effects identified in Model 2 remained robust when the effects of the presenting features of the study participants were introduced in Model 3.

Model 4: Effect of DSM-IV Baseline Diagnosis on Short-term and Long-Term Outcome

The final model includes a further refinement of the preceding conditional model, achieved by including DSM-IV diagnosis of the first episode of psychosis as a predictor of symptom levels at admission, of the short-term trajectory, and of long-term outcome. Although potentially an important predictor, there is some circularity in the inclusion of this variable, since the duration criteria for specific diagnoses are inherently linked with clinical predictors such as DUP, and symptom severity at T1. The effects of these predictors on short-term and long-term outcomes could therefore be expected to be attenuated as a result. A representation of this model is depicted in Figure 3.4.

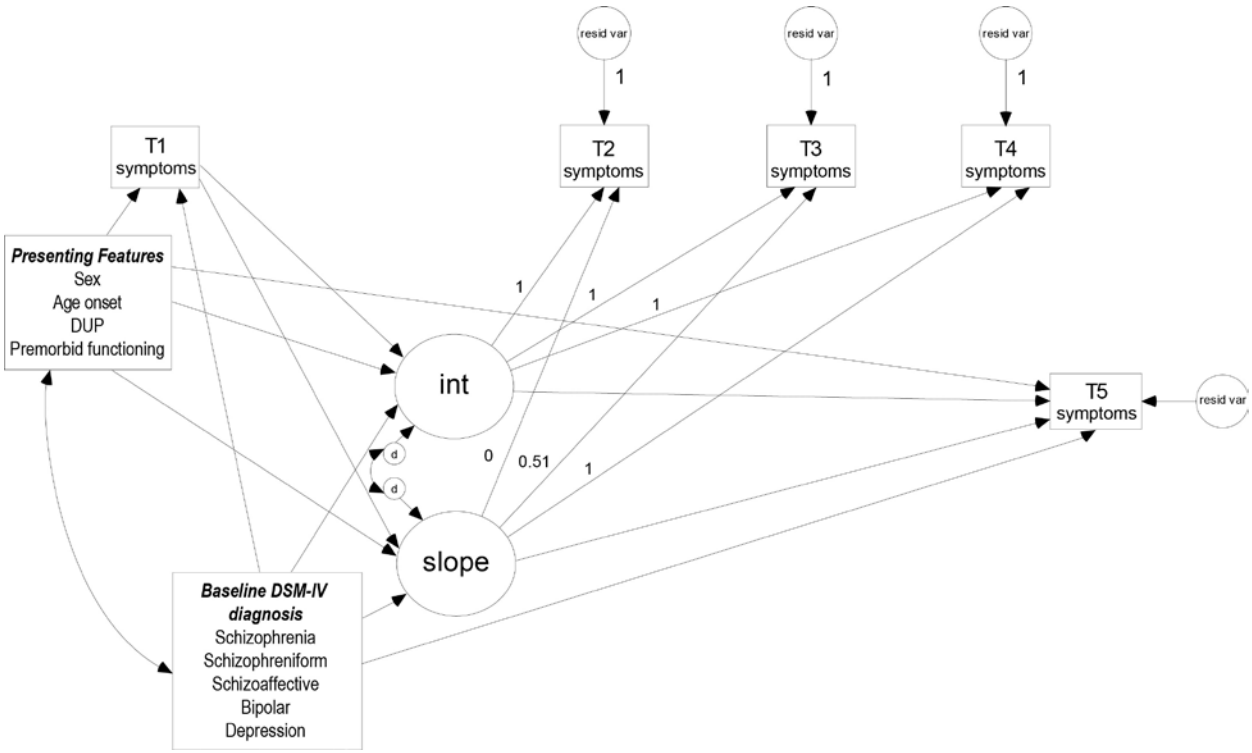


Figure 3.4. Conditional non-linear latent trajectory model, incorporating direct effects of DSM-IV diagnosis (bolded), gender, age at onset of psychosis, DUP and pre-morbid functioning as predictors of severity of symptoms (i) at admission; (ii) across the short-term growth trajectory and (iii) at long-term follow-up. Each arrow actually represents multiple paths from the multi-category DSM-IV diagnosis predictor to each dependent variable.

Model 4 Research Questions

The principal question addressed by this model is whether the effect of DSM-IV diagnosis on distal symptom severity levels (T5) is mediated either fully or partly, or not at all, by the intercept and slope latent trajectory variables which represent the short-term change that occurs in the 1-year interval subsequent to initial recovery, and/or mediated by symptom levels at admission (T1). If some form of mediation is found, then it would imply that the diagnosis transmits its effect on long-term outcome solely, or partly, through the short-term change that has occurred after initial recovery, and/or by the severity of symptoms at admission. In addition to these indirect effects, which are presented in RQ 4.4 and RQ 4.5, there are three research questions of interest concerning direct effects for this model, specifically:

Direct Effects

RQ 4.1 Does baseline diagnosis directly predict symptom levels at admission?

RQ 4.2 Does baseline DSM-IV diagnosis directly predict the latent growth factors?

This question seeks to identify whether particular psychotic diagnoses directly predict:

a) initial symptom levels at the starting point of the trajectory (i.e. intercept) and/or;
b) the short-term change (i.e. slope) that occurs over the subsequent 1-year interval.

RQ 4.3 Does baseline DSM-IV psychotic diagnosis directly predict long-term outcome?

Indirect Effects

RQ 4.4 Are the effects of baseline psychotic diagnosis on the short-term symptom trajectories mediated in full or in part by level of symptoms at admission?

This question seeks to identify whether the type of DSM-IV psychotic diagnosis at baseline indirectly impacts on the short-term negative symptom trajectory (represented by the intercept and/or slope latent variables) via its effect on level of symptoms at admission.

RQ 4.5 Are the effects of baseline diagnosis on long-term symptom levels mediated in full or in part by either the latent trajectory variables or by symptom levels at admission?

This question concerns whether particular psychotic diagnoses indirectly impact on long-term symptoms via two possible pathways: (a) its effect on short-term change (represented by the intercept and/or slope latent variables) that occurs over the 1-year interval subsequent to initial recovery, or (b) via its effect on level of symptoms at admission. The impact of each of the diagnostic categories is evaluated relative to a diagnosis of schizophrenia.

4 METHOD

In this chapter, the study methodology will be described. First, the context for the study will be presented in Section 4.1, followed by an overview of the sample and a description of the study design in Sections 4.2 and 4.3. A summary of the measures used and their psychometric properties will follow in Section 4.4. These include the primary psychopathology instruments used to assess severity of positive symptoms (BPRS) and negative symptoms (SANS), along with predictors of psychopathology: gender, age at onset of psychosis, pre-morbid adjustment (PAS), DSM-IV diagnosis, and duration of untreated psychosis (DUP). Special emphasis will be placed on DUP, considered pivotal in prediction of outcome in psychosis research, since it is one of the few potentially modifiable risk factors for outcome. A special section will therefore be devoted to DUP in Section 4.5. Issues regarding its definition and measurement will be examined in detail, and the reasons for wide variability in DUP findings across different studies will be explored. Inter-rater reliability aspects of the study will also be reported in Section 4.6, along with Ethical Approval information in Section 4.7, and Intellectual Property aspects in Section 4.8. The chapter will conclude with a Summary in Section 4.9.

4.1 Context

The Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, Victoria, provides innovative clinical care to patients aged 14-30 years experiencing their first psychotic episode, whilst devoting significant resources to running a comprehensive research program investigating the area of early psychosis. Established in October 1992, the aim of EPPIC was to address early detection, prevent secondary morbidity and to optimise the young person's social and occupational functioning during the initial two years following entry to treatment, the so-called early 'critical period'. EPPIC covers a tightly defined catchment area of approximately 800,000 people in the inner and Western areas of Melbourne, a relatively socioeconomically disadvantaged area.

The EPPIC program evolved from the specialised model of care offered by the Aubrey Lewis Unit for First-Episode Psychosis located at the Royal Park Psychiatric Hospital, which provided primarily inpatient-based care. In addition to a 14-bed inpatient unit, EPPIC offered a range of outpatient services, including an outpatient clinic, a mobile home treatment team,

day program, family work and specific therapies designed to optimise the patient's course of recovery. These components were framed around a treatment model that emphasises rapid assessment, use of neuroleptic medication in low doses and the integration of psychosocial and biological interventions, intensive case management, continuity of care, close follow-up of relapsing patients and a close involvement with the patient's family (Carbone, Harrigan, McGorry, Curry, & Elkins, 1999; P. D. McGorry et al., 1996).

A research protocol was developed for the EPPIC service model. Baseline psychotic diagnoses were systematically assessed using standardised diagnostic assessment tools administered by trained interviewers with a 4-year minimum psychology research degree. Subsequent assessment schedules and instrument batteries varied between some EPPIC studies, however the majority of participants were assessed with a core package containing demographic, clinical, symptom and functioning measures which were administered at multiple time points.

This PhD candidate was responsible for constructing and overseeing the EPPIC research databases and study protocols from June 1993 until April 2016. A total of 723 participants with first-episode psychosis were enrolled in the research programs between April 1989 and January 2001, during active periods of recruitment. Each participant was recruited to a specific cohort, with each cohort affiliated with a defined research objective and study design. Long-term follow-up assessments (median 7.4years) were subsequently conducted on the 723 research participants between January 1998 and April 2005 in chronological order from the date of baseline using an eight-step tracing algorithm (Henry et al., 2007) to standardize the procedure for tracing and locating participants and to maximize case re-identification.

Since the inception of these pre-EPPIC and EPPIC research enterprises, numerous research papers have been published, each based on different cohorts comprising the overarching research studies. Selection of study samples for these publications was usually guided by available data from participants who shared a common set of measures and time points relevant to the proposed analysis. Therefore, different research publications are often based on different subsets of the overall sample of 723 research participants. Each study cohort comprising the overall sample of 723 participants received Human Research Ethics Committee approval. Further detail regarding Research and Ethics approval will be provided later. Written, informed consent was obtained from participants after a complete discussion of the study with subjects, including a detailed explanation of the study aims and procedures.

4.2 Sample

The current study sample consisted of 413 young people consecutively admitted to EPPIC between January 1993 and September 1997 who consented to assessment over the course of their first psychotic episode and to follow-up assessment over the 12 months after their illness recovery or stabilisation. Long-term follow-up assessments were subsequently conducted several years later. Each participant was assessed on up to five occasions from baseline to long-term follow-up. This particular subset of 413 research participants was selected from the total cohort of 723 participants because they shared a common set of measures and assessment points, for which details are provided in Section 4.4. Other cohorts were considered (for instance, the pre-EPPIC cohort, recruited between April 1989 and April 1992, and other EPPIC cohorts, recruited between 1998 and 2001) and ultimately rejected, due to incompatible follow-up designs and/or instrument batteries.

In addition to the current study sample of 413 participants, another group of patients failed to consent to any assessment. Available data indicate that the refusal rate was ≤ 25%. The subjects who consented to participate in the research constituted a broadly representative first-episode psychosis sample, which is detailed elsewhere (Harrigan et al., 2003). EPPIC is the only facility in the catchment area for the target population, with virtually no private psychiatrists and little, if any, leakage to private facilities located outside of the catchment area, hence this study sample is a truly epidemiologically based sample. Participants met the following inclusion criteria at baseline:

1. Aged between 15 and 30 years;
2. A DSM-III-R (Association, 1987) and from 1995, a DSM-IV (Association, 1994) diagnosis of a psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, bipolar psychotic disorder, major depressive disorder with psychotic features, brief reactive psychosis/brief psychosis and psychosis not otherwise specified);
3. Informed consent for research participation;
4. Living in the geographical catchment of the EPPIC service;
5. Adequate English language comprehension;
6. Experiencing their first treated episode of psychosis with less than 6 months of prior neuroleptic medication.

Individuals with primary organic mental syndrome (which may resemble psychosis), intellectual disability, drug and/or alcohol induced psychosis, or epilepsy were excluded.

4.3 Procedure

4.3.1 Study Design

This study is a naturalistic, prospective multiwave longitudinal design, with the 413 participants assessed on up to five occasions over an average 7.3 year study period. Assessments were designed to be conducted at:

T1: admission to EPPIC;
T2: initial recovery/stabilisation of symptoms from the initial psychotic episode (time point not fixed);
T3: 6 months subsequent to initial recovery/stabilisation;
T4: 1 year subsequent to initial recovery/stabilisation;
T5: final long-term assessment at a mean 7.3 years (SD=0.92; median 7.3; range 5.6 - 10.6 years) following initial recovery/stabilisation.

The Royal Park Multidiagnostic Instrument for Psychosis (RP-MIP) (P. D. McGorry, Copolov, & Singh, 1990; P. D. McGorry, Singh, et al., 1990) was used to assess all patients as soon as possible after service admission. Multiple sources of information were obtained by interviewing patients and close relatives between T1 and T2, and this information was then merged to produce an accurate record of the onset, evolution and duration of the illness. Along with administration of the RP-MIP at T1, interviews were conducted using the BPRS, SANS and Premorbid Adjustment Scale. Interviews with consenting patients (and possibly close relatives or informants) were conducted by usually one, but occasionally two research psychologists in a quiet room. At the second assessment, occurring around the time of remission or stabilisation of symptoms (T2), the BPRS and SANS were rated by the research interviewer, along with a number of other instruments used in the design but not in the present study. Further assessment of the historical and developmental features of the patient's illness may also have taken place at this time given that patients' symptoms were likely to have stabilised sufficiently, with the patient possessing sufficient cognitive and behavioural organisation to cooperate with the task. Approximately six months following T2, the third assessment (T3) with the BPRS and SANS was undertaken, along with other instruments used

in the design but not in the present study. A further six months after that, at 12 months following T2, the fourth assessment (T4) took place, which again included the core psychopathology measures of the BPRS and SANS. The fifth and final long-term assessment with the BPRS and SANS occurred at an average 7.3 years after T2. The three mid assessments at initial recovery (T2), 6-month follow-up (T3) and 12-month follow-up (T4) constitute the 1-year short-term follow-up interval, conceptualised as the latent growth trajectory, which will be detailed in Statistical Methods (Chapter 5). As is typical of longitudinal psychopathology studies, the subject numbers assessed at each of the five time points were unbalanced and, despite efforts to collect data at the set times detailed above, the time interval between assessments was variable. Each of these five assessment points is described in detail below:

(i) Admission (T1)

The mean age of the 413 subjects at admission to the service was 21.8 years (SD=3.5). Service admission did not necessarily entail an admission to the inpatient unit, as individuals could be treated on an outpatient basis depending on the severity of their symptoms and whether they were at risk of self-harm. Treatment with antipsychotic medication was usually administered within a few days after service admission. The research assessment at initial admission was conducted as soon as possible following service admission (median=7 days). Of the study sample of 413 subjects, 389 (94.2%) received a research assessment at admission.

(ii) Initial recovery/stabilisation (T2)

This assessment was timed to take place around remission or stabilisation of the patient's positive and negative symptoms. Since the recovery process for individual patients is highly variable, with relatively short recovery intervals for some patients and extremely long recovery intervals for others (depending on the nature of their illness and the patient's response to administration of antipsychotic medication at admission), the timing of this assessment point was also highly variable. It is possible that on occasions the timing of this assessment might have been influenced by factors unrelated to the patient, for instance, availability of research staff, however this assessment can be broadly construed as representative of the point of recovery from the initial psychotic illness. Of the 413 subjects in the study sample, 394 (95.4%) received an assessment at initial recovery. The median length time from assessment at initial admission was 59 days (mean=66.8 days; SD=38.1; range 3-262 days). The mean age of individuals at this point was 22.1 years

(SD=3.5). This assessment is the reference point for subsequent assessments at 6-months (T3) and 1-year (T4), and importantly, marks the starting point of short-term follow-up interval, which encompasses the three assessments at initial recovery/stabilisation (T2), 6-months (T3) and 1-year follow-up (T4).

(iii) 6-month follow-up (T3)

This assessment was conducted six months subsequent to T2, though there was some variability around the timing of this assessment in practice. Of the 413 subjects in the study sample, 308 (74.6%) received an assessment at this point. The median assessment interval from T2 was 194 days (mean=197.4 days; SD=33.3; range 57-327 days). The mean age of subjects at this assessment was 22.6 years (SD=3.4). This assessment is the mid-point of the short-term follow-up interval.

(iv) 1-year follow-up (T4)

This assessment was conducted approximately one year following assessment at T2. Of the 413 subjects in the study sample, 295 (71.4%) received an assessment at this point. The median assessment interval from T2 was 380 days (mean=384.2 days; SD=40.8; range 281-532 days). The mean age of subjects at this assessment was 23.1 years (SD=3.5). This assessment marks the end-point of short-term follow-up interval.

(v) Long-term follow-up (T5)

The final long-term assessment was conducted between 5.6 years and 10.6 years following initial recovery (T2), with a mean interval of 7.3 years (SD=0.92; median=7.3 years). Of the 413 subjects in the study sample, 278 (67.3%) were interviewed at this point. The mean age of subjects at long-term follow-up was 29.4 years (SD=3.6).

4.4 Measures

4.4.1 Positive and Negative symptoms

The two scales described in this section were used to measure the severity of positive (psychotic) symptoms and negative symptoms. These scales are attached as Appendix I and Appendix II. At each of the five interviews from baseline to long-term follow-up, the severity of psychopathology was assessed using the 18-item or 24-item Brief Psychiatric Rating Scale

(BPRS) (Lukoff, Nuechterlein, & Ventura, 1986; P. D. McGorry, Goodwin, & Stuart, 1988; Overall & Gorham, 1962) and the Schedule for the Assessment of Negative Symptoms (SANS) (N. Andreasen, 1983).

4.4.1.1 Brief Psychiatric Rating Scale

The BPRS is an interviewer-rated instrument, and assesses severity of hallucinations, delusions, depression and anxiety experienced by the patient, in addition to rating observational psychopathology such as motor retardation, blunted affect, excitement and disorganised thought and speech. This scale is also used to monitor change in psychotic symptoms and is commonly used as a measure of the overall psychotic state.

The 24-item Brief Psychiatric Rating Scale (Lukoff et al., 1986) was expanded from the original scale (Overall & Gorham, 1962) used to assess the severity of psychiatric symptoms. Each of the 24 items was rated on a seven-point scale ranging from 1 (not present) to 7 (extremely severe). The18-item Brief Psychiatric Rating Scale (Nursing Modification) (BPRS-NM) (P. D. McGorry et al., 1988) is an adaptation of 24-item BPRS. It contains 18 items rated on a seven-point scale ranging from 0 (not present) to 6 (extreme), with a descriptive anchor for each point on the scale provided by the Glossary and Guidelines for Administration contained as part of The Royal Park Multidiagnostic Instrument for Psychosis (RPMIP) (P. D. McGorry, Copolov, et al., 1990; P. D. McGorry, Singh, et al., 1990). Each of the 18-item BPRS and the 24-item BPRS versions were used variously through the follow-up period, depending on the study design for each cohort. A psychotic symptom subscale (BPRS-PS) was derived from the 0-6 scaled BPRS, and included four items measuring conceptual disorganization, hallucinatory behavior, unusual thought content and suspiciousness (Harrigan et al., 2003). The same items from the 1-7 scaled BPRS version were calibrated to the 0-6 scale by applying a one-unit decrease to each item. Possible scores on the psychotic symptom subscale ranged from 0 to 24.

4.4.1.2 The Scale for the Assessment of Negative Symptoms

The Scale for the Assessment of Negative Symptoms (SANS) (N. Andreasen, 1983) measures the level of negative symptomatology, that is, deficiencies in 'normal' levels of emotionality, speech production, language, drive and energy. Five subscales relating to symptoms of affective flattening or blunting, alogia, avolition-apathy, ahendonia-asociality and attention

are measured in the SANS. Only the first four subscales are included in this analysis. The attention subscale is excluded, as it primarily taps into cognitive attributes (N. C. Andreasen et al., 2005).

Each of the four negative symptom subscales contains a varying number of items scored from 0 to 5, in addition to a global rating for each subscale. In this study, all non-global items were aggregated to form a total rating of negative psychopathology, with higher ratings corresponding to more severe levels of negative symptoms. The four negative symptoms were scaled to a common metric of 0 to 5 (achieved by dividing each subscale score by the number of items in the scale), where 0 = 'None'; 1 = 'Questionable'; 2 = 'Mild'; 3 = 'Moderate'; 4 = 'Marked'; 5 = 'Severe'. This was done to facilitate comparisons between the different negative symptom subscales, since there are different numbers of items in each subscale.

The SANS is designed to be rated by a trained interviewer and takes approximately 30 minutes to administer. The psychometric properties of this scale include excellent inter-rater reliability, with intraclass correlation coefficients ranging from 0.86 to 0.93 for the five subscale scores, and a coefficient of 0.92 for the total score. Internal consistency has been reported as acceptable to very good for each subscale, with Cronbach's alpha coefficients ranging from 0.63 to 0.84 (N. Andreasen, 1983).

4.4.2 Premorbid Adjustment Scale

The Premorbid Adjustment Scale (PAS) (Cannon-Spoor, Potkin, & Wyatt, 1982) is a rating scale that was developed to assess the level of achievement of developmental goals at several different intervals of a patient's life before the onset of schizophrenia. It is also commonly used to assess patients with other psychotic disorders. PAS ratings are based on histories derived from interviews with the patient and family members, as well as from patient hospital records. The four intervals assessed include Childhood (up to 11 years), Early Adolescence (12-15 years), Late Adolescence (16-18 years) and Adulthood (19 years and over). There is also a General subscale that is designed to measure a global highest level of functioning achieved before the onset of psychosis, in addition to characteristics and time span of the onset of illness and education.

Each subscale consists of a varying number of items, each one rated on a 7-point Likert-type scale ranging from 0 to 6, with 0 indicating the hypothetically healthiest end of the adjustment spectrum, and 6 representing the hypothetically least healthy end. The ratings for each subscale are summed and expressed as a total score divided by the highest possible score for that subscale, thus resulting in a proportion ranging from 0 to 1. To avoid potentially confounding pre-morbid functioning with the patient's prodromal phase of illness, the pre-morbid adjustment of the patient during the period immediately preceding the prodromal phase was used as an estimate of true pre-morbid functioning (Harrigan et al., 2003). Inter-rater reliability has been established as good for raters trained in the use of this scale, with intraclass reliability coefficients for items in the Early Adolescence subscale ranging from 0.76 to 0.99, with an overall coefficient of 0.91 (Cannon-Spoor et al., 1982), indicating excellent agreement. Extensive assessments of validity have also been undertaken, indicating reasonable discriminant and concurrent validity.

4.4.3 Diagnostic Instrument – Royal Park Multidiagnostic Instrument for Psychosis

The Royal Park Multidiagnostic Instrument for Psychosis (RP-MIP) (P. D. McGorry, Copolov, et al., 1990; P. D. McGorry, Singh, et al., 1990) was used to assess all patients upon service admission to EPPIC. This instrument features meticulous measurement of the illness duration components, including duration of untreated psychosis, and assessment of DSM-IV diagnosis according to carefully operationalised criteria. Multiple sources of information were obtained by interviewing patients and close relatives between T1 and T2, and this information was then merged to produce an accurate record of the onset, evolution and duration of the illness. Sociodemographic information was also assessed using the RP-MIP. The RP-MIP is not brief, although it is comprehensive and reliable. Inter-rater reliability has been previously established for several sub-sections of the RPMIP, and is reported later under Section 4.6.

Included in the RP-MIP are comprehensive ratings of clinical symptomatology, which permits diagnosis of psychotic disorders according to a range of diagnostic criteria, including Diagnostic and Statistical Manual of Mental Disorders Version III Revised (DSM-III-R) (Association, 1987) and DSM-IV (Association, 1994). The Diagnostic and Statistical Manual of Mental Disorders is the standard diagnostic classification systems of mental disorders, with multiaxial (or dimensional) systems of disorder. Included in these multiaxial systems are components focusing on clinical disorders such as schizophrenia and other psychotic

disorders, amongst others. The psychotic disorders in this thesis are assessed under Axis I: Clinical Syndromes. The purpose of the DSM classification system is to provide clear descriptions of diagnostic categories to enable clinicians and investigators to diagnose, study and treat people with mental disorders. Categorisation of mental disorders was made according to explicit diagnostic criteria and attempted to employ operational definitions of diagnostic categories that were mutually exclusive and exhaustive.

4.4.4 Age at Onset of Psychosis

Age at the onset of the first psychotic episode was defined as the age in years at the time of onset of the first sustained psychotic symptom of any type at threshold level. The RP-MIP was used to estimate the date of onset of psychosis.

4.4.5 Prodrome

The onset of prodrome was defined as the earliest deviation from the patient's premorbid personality, behaviour or level of functioning prior to the onset of psychotic symptoms. The duration of prodrome was the period of time in days between the onset of the prodrome and the onset of psychotic symptoms, both of which were estimated using the RP-MIP. Prodromal duration is not used in the analyses to be reported, but is described here since it is the immediate precursor to duration of untreated psychosis; the end of the prodrome marks the commencement of DUP.

4.5 Duration of Untreated Psychosis (DUP)

Onset of psychosis was defined as the emergence of the first sustained psychotic symptom of any type at threshold level, and was dated as precisely as possible to the nearest day, week or month using the RP-MIP. Duration of untreated psychosis (DUP) was defined as the number of days between the onset of psychosis and initiation of treatment, with the latter defined as the first recorded date of admission or acceptance into the service. A detailed review of DUP follows. This review: (i) outlines the importance of DUP as a potentially modifiable risk factor for outcome; (ii) considers the reasons for wide variability in DUP findings across different studies, and; (iii) explores the issues which threaten the accurate measurement of this construct.

4.5.1 DUP: Definition and Measurement

The course of schizophrenia and other psychotic disorders shows substantial individual variation, suggesting the possibility that something can be done to improve outcome (Wiersma, Nienhuis, Giel, & Slooff, 1998). However, most established predictors of outcome, such as gender, age of onset and premorbid adjustment, are fixed and are not able to be modified (Harrigan et al., 2003). Duration of untreated psychosis (DUP) is one exception because it is a potentially modifiable risk factor. This raises the possibility that outcome could be improved through early detection programs aimed at reducing DUP.

However, it is not sufficient to simply establish an association between DUP and outcome. DUP may be confounded to a greater or lesser extent by other predictors of outcome, such as pre-morbid adjustment, family psychiatric history, level of education, mode of onset and gender (Birchwood et al., 1998; Haas et al., 1998; T. K. Larsen et al., 2000; Loebel et al., 1992; Verdoux et al., 1998; Verdoux et al., 2001). If DUP is merely a proxy for other predictors of outcome, then establishing programs to reduce the duration of untreated psychosis would be of dubious value in improving outcome. On the other hand, if it can be established that prolonged DUP exerts a 'toxic' influence independently of other factors, and that delaying treatment adversely impacts patient outcome, then the growth of early intervention centres around the world will justify the focus of DUP as a 'best bet' for early intervention strategies (Harrigan et al., 2003).

There remains much debate around the nature of the association between DUP and outcome. The putative causal association between DUP and outcome is underpinned by much fuzziness and potential for error, particularly around the DUP construct. Although DUP has been shown to consistently predict outcome independently of potential confounding variables such as premorbid adjustment, some studies have failed to show an association between DUP and outcome (Barnes et al., 2000; Craig et al., 2000; B. C. Ho et al., 2000). Furthermore, there is wide variability in the estimates of DUP obtained by different studies (R. Norman & Malla, 2001; Perkins, Gu, Boteva, & Lieberman, 2005).

4.5.2 Variability in DUP findings – accounted for by what?

It has been noted (Keshavan & Schooler, 1992) that the wide variability of findings presented in the schizophrenia literature is commonly attributed to the presumed heterogeneity within this class of disorders, but this variability could equally be accounted for by the wide

discrepancies in the definitions and criteria used by different studies, ensuring that comparability between studies is difficult, if not impossible. This is almost certainly the case regarding DUP, with individual studies using different measurement criteria to define this critical concept. The lack of standardisation between studies is not the only issue in the measurement of DUP. Other issues which threaten the accurate measurement of DUP include the measurement error inevitably associated with retrospective assessment methodologies, sample bias, and the lack of structured and standardised assessment instruments for assessing onset of illness. Furthermore, many studies do not report reliability data for DUP, further compounding these problems. Although different studies tend to be reasonably consistent in their definition of DUP, the various components which constitute DUP are operationalised in highly diverse ways across different studies, thus potentially leading to widely varying estimates of DUP. Furthermore, dating the onset of psychosis reliably using retrospective methods poses its own challenges.

4.5.3 Operationalising the onset and offset of untreated psychosis

The majority of studies construe DUP as a continuous period of psychosis, which covers the time interval from the onset of psychosis until the initiation of treatment (R. Norman & Malla, 2001). This definition is usually quite consistent across studies, unlike the criteria used to operationalise the onset and offset of untreated psychosis, as shall be seen shortly.

However in reality, the course of untreated psychosis can be quite variable, with some people experiencing continual symptoms and others experiencing symptoms of a more intermittent nature (R. M. Norman, Townsend, & Malla, 2001). It is unknown whether it is the cumulative experience of active psychosis or simply the period of time since the onset of psychotic symptoms that is most detrimental to outcome. However, researchers in the relatively large-scale TIPS study conceded that cases presenting with an intermittent course of untreated symptoms were quite rare (Melle et al., 2004).

One can only hope that this is the case for the DUP literature, given the often difficult task of retrospectively establishing the onset of psychosis even for those for whom the period of psychosis is continuous, particularly those for whom DUP is very long (many years in some cases). The prospect of accurately rating multiple onset and offset dates of intermittent psychotic symptoms over a long and distant period of time could pose even greater challenges

than those faced at present. Of the few studies that have assessed the cumulative period of untreated psychosis (for example, (Melle et al., 2004; R. Norman & Malla, 2001)), none have described exactly how this was assessed, the difficulties experienced in accurately pinpointing multiple onset and offset dates, nor given information regarding the reliability and precision of such estimates.

Even if it can be assumed that DUP is usually limited to a single continuous episode, there are difficulties in operationalising the onset and endpoint of a psychotic episode. Identifying the onset and offset of untreated psychosis, which defines the DUP interval, is deceptively simple. However, there are a number of issues which make this more complex than might be initially thought:

4.5.3.1 Onset of psychosis – the starting point of DUP

The considerable lack of consistency in the definition of onset between studies has been noted (Keshavan & Schooler, 1992; R. Norman & Malla, 2001). These difficulties are probably largely due to the fact that no specific marker of emergent psychosis has yet been identified (Perkins et al., 2005). Some studies advocate the emergence of the first psychotic symptom, even if fleeting, as the beginning point of DUP (for example, (Perkins et al., 2005; Singh et al., 2005; Verdoux et al., 1998; Verdoux et al., 2001), whereas other studies specify that the psychotic symptom must be sustained for a defined period of time, for example, '…lasting throughout the day for several days or several times a week, not being limited to a few brief moments' (Addington et al., 2004; T. K. Larsen et al., 2000).

The use of severity indices in the definition of onset has also been advocated (Keshavan & Schooler, 1992), with the recommendation that the onset of a psychotic episode should be ascertained by a rating of at least 'moderate' on scales such as the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale. This contrasts with a number of earlier studies which sometimes blurred the distinction between prodromal and psychotic symptoms (for example (Beiser et al., 1993)). However there is often a fine and potentially arbitrary distinction to be made between judging whether an individual's behaviour or experience falls within the realm of psychosis or whether it is merely eccentric or unusual (R. Norman & Malla, 2001).

Studies also tend to be inconsistent in the types of symptoms used to define psychosis (R. Norman & Malla, 2001). Although hallucinations and delusions are commonly used to define psychosis, many studies also include thought disorder and disorganised, bizarre or catatonic behaviour (for example, (B. C. Ho et al., 2000)) in this definition. It is debatable whether patients presenting with these latter symptoms in the absence of positive symptoms such as hallucinations and delusions can be regarded as psychotic, therefore it can be argued that the presence of delusions and/or hallucinations is a minimum requirement in the operationalisation of the onset of psychosis.

4.5.3.2 Offset of psychosis – the DUP endpoint

Determining the endpoint of DUP is seemingly straightforward, however even this is more complicated than might be thought. The offset of untreated psychosis is commonly defined as the point at which antipsychotic medication is administered (R. Norman & Malla, 2001). However, it has been pointed out that the definition of onset of treatment is elusive, since the initial course of antipsychotic medication may be variable in length and it is uncertain whether there is a minimum duration of treatment that is critical in determining the prospects of recovery (Perkins et al., 2005).

The difficulty in defining what constitutes adequate treatment is highlighted by the considerable differences between studies in whether the endpoint of untreated psychosis is defined as the commencement of any level of antipsychotic medication or whether some more stringent criteria for adequacy has been met (T. Larsen et al., 1996; R. Norman & Malla, 2001) in terms of duration or dose. For instance, Larsen et. al. (T. K. Larsen et al., 2000) defined adequate treatment as '…an antipsychotic drug given in sufficient time and amount so that it would lead to clinical response in the average non-chronic schizophrenic patient (eg Haldol 5mg a day for 3 weeks)'. On the other hand, others have considered that up to 12 weeks of prior treatment with antipsychotics was within the limits of acceptability for determining eligibility for participation in their first-episode psychosis study (Loebel et al., 1992; D. Robinson et al., 1999; D. G. Robinson et al., 1999). The patient's adherence to their prescribed medication is usually not taken into account in applying the initiation of antipsychotic medication criteria, although is occasionally considered (Wunderink, Nienhuis, Sytema, & Wiersma, 2006).

Apart from the administration of antipsychotic medication as a common marker for the endpoint of DUP, there are a number of alternative definitions in use. These include admission to a psychiatric hospital (Bottlender et al., 2000; Craig et al., 2000; T. K. Larsen et al., 2000; Ucok, Polat, Genc, Cakir, & Turan, 2004; Verdoux et al., 1998), entry to treatment (Browne et al., 2000; P. D. McGorry, Copolov, et al., 1990), time until treatment response or the end of a defined period of time subsequent to administration of medication (for example, (Malla et al., 2002)), and time until the establishment of a definitive diagnosis (Chong, Mythily., Lum, Chan, & McGorry, 2005).

It would seem necessary to come up with a common definition of what constitutes adequate treatment, since this defines the endpoint of DUP. However, this begs a further question regarding whether it is sufficient to define treatment simply in terms of psychiatric hospitalisation or the administration of an antipsychotic. It could be that entry to treatment per se is sufficient as an endpoint to DUP, if consideration is given to defining a secondary malleable variable with some potential to impact on outcome after DUP as 'time until exposure to evidence-based treatment for first-episode psychosis' (P. D. McGorry, 2006). This variable would need to be carefully operationalised, but could include such components as (i) exposure and adherence to antipsychotic medication; (ii) exposure to psychosocial treatment and; (iii) tenure in care and other treatment variables. In fact, there are some who argue that if the patient does not receive psychosocial treatment then they have not received proper treatment, since the early implementation of psychosocial intervention aimed at improving self-esteem, social functioning and disease management could be an important factor in long-term outcome over and above the effects of medication administration which commonly defines the endpoint of DUP (de Haan, Linszen, Lenior, de Win, & Gorsira, 2003).

4.5.3.3 Treated psychosis – cause or consequence?

The period of *treated* psychosis, as distinct from the duration of untreated psychosis, is defined as the time interval from the initiation of treatment until the remission of psychotic symptoms. If prolonged DUP has an adverse effect on outcome, then it seems plausible that a long duration of treated psychosis is also likely to adversely impact patient outcome. This variable should perhaps be considered in studies assessing the relationship between DUP and outcome. However this is not entirely straightforward, since the time until the resolution of treated psychotic symptoms may also highly correlated with DUP, that is, it might well be a *consequence* of prolonged untreated psychosis, as much as being a predictor of outcome.

There is another important distinction to consider in the duration of treated psychosis, and that is the concept of early treatment resistance which should only be applied when a patient has definitely received potentially effective treatment but has failed to respond. This is a different scenario from the situation where a patient has failed to engage or adhere and has not received evidence-based care as yet. True treatment resistance could be viewed as an outcome variable for studying DUP and should not be confused with treated psychosis. Furthermore, it has been suggested that individuals who fail to be exposed to a genuine first pass at evidence-based care for FEP can be viewed as still 'clocking up' their DUP, albeit within rather than outside the health system.

4.5.4 The problems of retrospective assessment

Dating the onset of psychosis reliably is inevitably difficult since retrospective data must be relied on (Keshavan & Schooler, 1992; Maurer & Hafner, 1995). The onset of psychosis is often subtle and insidious (B. C. Ho et al., 2000) and the definition of the actual tipping point into psychosis is arbitrary. Furthermore, the more remote in time the event, the less accurate the history is likely to be. There is probably a relationship between DUP and the mode of onset, with acute onset linked to shorter DUP, and insidious onset associated with prolonged DUP. The crucial problem with the use of retrospective data relates to possible limitations in reliability due to recall bias (Maurer & Hafner, 1995). Maurer et.al. also found that as the temporal distance grows between an event and the interview, reliable timing is only made possible by a considerable reduction of the precision of measurement. They suggested that methods for the improvement in reliability via the reduction of sources of error should include:

- Specific measurement techniques such as the use of a standardised procedure
- The use of anchor events in the assessment
- The parallel collection of information from different sources
- The change from point estimation to interval assessment as a way of increasing the accuracy of onset identification, though at the cost of a reduction in precision.

Another issue compounding the retrospective recall of the onset of psychosis is the illness status of the individual when onset information is collected (Keshavan & Schooler, 1992; R. Norman & Malla, 2001). If the individual is floridly psychotic as well as cognitively impaired, the accuracy of recall may be adversely affected. For these reasons it is recommended that

information should be collected when patients are symptomatically stable to reduce this threat to the reliable dating of the onset of psychosis and furthermore, supplementing their report with collateral information from families (Keshavan & Schooler, 1992). Corroborative information from family members and other informants in relation to the onset, evolution and duration of symptomatology is essential to piece together the mosaic of the illness episode and to date its onset accurately. However it has been noted that observers' recall will be affected by a number of factors including their perceptiveness, possible denial, tolerance for eccentricity and the extent to which the onset is accompanied by bizarre symptoms (R. Norman & Malla, 2001).

4.5.5 Discrepancies between the accounts of patients and carers

There are other threats to the reliable dating of the onset of psychosis besides those posed by the use of retrospective data. For example, psychotic symptoms are subjectively experienced phenomena and not easily perceived by others (Browne et al., 2000), hence the private nature of these symptoms means that patients might date onset differently to relatives (R. Norman & Malla, 2001). This has been confirmed in a study which showed that psychotic symptoms were noticed by relatives 12 months later than first perceived by patients (Hafner, Maurer, Loffler, & Riecher-Rossler, 1993). The authors explained the difference as a consequence of the fact that psychotic symptoms, such as hallucinations, are experienced long before others can perceive them. In the light of findings such as these, it has been proposed that behavioural symptoms are best identified by the family, and that subjective symptoms such as hallucinations and delusions are more reliably reported by the patient (P. D. McGorry, Copolov, et al., 1990; P. D. McGorry, Singh, et al., 1990).

4.5.6 Sample bias

Most studies identify subjects at first hospitalisation. Thus, individuals with milder symptoms who do not require inpatient treatment may be excluded (Perkins et al., 2005). Clearly it is important to include in DUP studies those individuals whose symptoms qualify them as psychotic, but at a less acute level, so that the full spectrum of illness severity and its relationship to outcome can be examined. Related to this point is the fact that the majority of studies have narrow diagnostic inclusion criteria, thus excluding patients with affective psychoses. This is an issue because focusing only on schizophrenia-spectrum disorders limits

the generalisability of the findings to a subgroup of patients within the broader diagnostic spectrum of psychosis, although some might argue that the inclusion of affective psychosis is a self-fulfilling prophesy, since affective psychosis are known to be characterised by a shorter DUP and a more promising prognosis. Examples of the few studies which have included affective psychotic disorders in their assessment of the relationship between DUP and outcome include McGorry et al (1996), Craig et al (2000) and Harrigan et al (2003) (Craig et al., 2000; Harrigan et al., 2003; P. D. McGorry et al., 1996). Finally, another point to bear in mind is the thorny issue regarding the possible bias introduced by study refusal. Another study found that the DUP for subjects who refused to participate in study follow-up was significantly longer than for those subjects who agreed to follow-up (Friis et al., 2004). On the other hand, other research has found that the participant group (n=98; median DUP=96.5 days) was representative when compared to the group who failed to consent to any assessment (n=22; median DUP=68.0 days) on the critical DUP variable (Harrigan et al., 2003).

4.5.7 Failure to use standardised assessment instruments

It seems intuitive that DUP should be assessed directly by standardised interview with patients and relatives, but it would be convenient if a reasonable estimate of DUP could be obtained from clinical records. In an unpublished study, we assessed how reliably DUP could be estimated from patient file notes as compared with ratings derived from a 'gold-standard' interview with the patient and their family. The 'gold-standard' interview was based on the Royal Park Multidiagnostic Instrument for Psychosis (RP-MIP), which is a comprehensive semi-structured interview which features meticulous measurement of DUP and prodromal phases of illness according to carefully operationalised criteria. The RP-MIP has demonstrated very good to excellent inter-rater reliability for specific components, including a DSM-III-R diagnosis of schizophrenia (kappa = 0.92) and the onset and duration of symptoms (mean kappa = 0.79) (P. D. McGorry, Copolov, et al., 1990; P. D. McGorry, Singh, et al., 1990).

Multiple sources of information were obtained by interviewing 50 patients and close relatives and the information was then merged to produce an accurate record of the onset, evolution and duration of the illness. The onset of DUP was assessed as the date of the emergence of the first sustained psychotic symptom of any type at threshold level, and was dated as precisely as possible to the nearest day, week or month. The offset of psychosis was defined as initiation of treatment. An independent rater assessed the same variables using clinical file records, with

no other sources of information used. The DUP for two patients was unable to be ascertained from the file notes, leaving 48 subjects. DUP estimates derived from the clinical records were highly unreliable when compared with the 'gold-standard' DUP ratings from the RP-MIP (ICC = 0.22). There was perfect agreement on DUP for just three of the 48 cases, and only one-fifth of the sample (21%) was estimated to lie within 7 days either side of the gold-standard DUP. The clinical file method, over- or under-estimated DUP by more than 1 year for eight subjects (17%). Even when we changed from point estimation to interval assessment as a way of increasing the accuracy of onset identification, as per the suggestion made by Maurer and Hafner (Maurer & Hafner, 1995), the magnitude of error remained unsatisfactory, with a kappa rating (k = 0.39) of only fair (unpublished data). The magnitude of the discrepancies indicates that for the majority of cases, the file rating method fails to provide a reasonable estimate of DUP.

4.5.8 Conclusion of DUP measurement

A consequence of these inconsistent approaches in the operationalisation of onset and offset of psychosis is that the estimated DUP for a given individual with first-episode psychosis will almost certainly vary according to the operational criteria implemented by study team. This means that the measured DUP of any particular patient will depend on not only on the patient's intrinsic illness onset characteristics but will also be largely determined by extrinsic factors wholly defined by the operationalisation criteria chosen by the research study investigators. Hence the DUP of any given patient could be quite different depending on which the particular research study they happen to participate in. This is an important source of inter-centre unreliability which could be minimised by calibrating and standardising operational criteria relating to the onset and offset of psychosis. Despite all of this methodological variability, such as the information variance and criterion variance discussed above, the association between DUP and outcome still shines through this fuzziness. But it is still worthwhile trying to agree on conventions for operationalising the onset and offset of psychosis.

4.6 Inter-rater Reliability

Highly trained research psychologists assessed the EPPIC cohort, with some fluctuation in personnel occurring over this period during which ratings and assessments were carefully calibrated between incoming and outgoing raters to ensure satisfactory levels of reliability. Additionally, the RPMIP Glossary and Guidelines document provides a complete set of definitions and calibrations for rating symptom, historical and developmental aspects of the illness, which were strictly followed by the raters. Inter-rater reliability was previously established for a number of sub-sections of the RPMIP, including onset and duration of symptoms, which demonstrated very good reliability (kappa = 0.79), as did the diagnosis of schizophrenia (kappa = 0.92) (P. D. McGorry, Singh, et al., 1990).

At long-term follow-up, a small number (n=12) of inter-rater assessments on the BPRS, SANS and other measures were undertaken by three research interviewers who each assessed around 90% of the long-term follow-up cases. The raters were paired in all possible ways and each pair assessed the same number of participants. Excellent inter-rater reliability was established using a balanced incomplete block design (Fleiss J., 1986) for both the BPRS (ICC=0.97) and the SANS (ICC=0.91). Although serial inter-rater measurements were not carried out across the whole study period, inter-rater reliability over time was safeguarded by the comprehensive set of definitions for symptom ratings and for establishing the illness onset and duration of symptoms provided by the glossary and manual for the RPMIP, and monitored in the context of the extensive training provided for new raters and careful calibration and standardisation procedures.

4.7 Ethical Approval

The study received Human Research Ethics Committee approval. Written, informed consent was obtained from participants after a complete discussion of the study with the research interviewer, including a detailed explanation of the study aims and procedures. The study was conducted in accordance with the Declaration of Helsinki. Approval for the long-term follow-up was obtained from the Human Research and Ethics Committees of the North Western Mental Health Program, the Victorian Department of Human Services, the Australian Institute of Health and Welfare, and relevant area mental health services.

4.8 Intellectual Property

My use of the EPPIC data was approved by Professor Patrick McGorry, then Director of the Orygen Research Centre, The University of Melbourne and now Departmental Head of Orygen, The National Centre of Excellence in Youth Mental Health, The University of Melbourne. Professor McGorry gave written consent for free use of the dataset, publication of results and for this PhD thesis to be written. A copy of the letter of approval is attached as Appendix III.

4.9 Summary

This concludes the Method chapter which contained a description of the methodology of the study, its context and an overview of the sample and study design. The measures used in the study and their psychometric properties were described. A review was undertaken of duration of untreated psychosis (DUP), one of the few potentially modifiable risk factors for outcome. This was considered particularly important, given the wide variability in DUP findings across different studies. The review sought to consider the reasons for inter-centre unreliability, and explored the issues which threaten the accurate measurement of this construct. Inter-rater reliability aspects of the study were reported, with sections on Ethics approval and Intellectual Property concluding the chapter.

5 STATISTICAL METHODS

This chapter provides an account of the statistical methods used in this thesis. First, the meaning of the term 'trajectory' is defined, followed by a discussion of functional forms of change, and coding of time as it relates to linear and non-linear models. Coding of observed variables, and the desirability of centreing continuous predictors is then explained. Following on, details regarding model fitting and MLR estimator used for the initial unconditional model, and for the assessment of direct effects in subsequent conditional models, are contrasted with the use of a different method of inference for the detection of indirect effects, the bias-corrected bootstrap. Evaluation of model fit, and an overview of selected goodness of fit indices, is followed by a brief explanation of model modification via the use of modification indices. The chapter concludes with a comprehensive description of the logic behind the stepwise fitting of sequential models.

5.1 Conceptualisation of latent growth trajectory

In latent growth curve (LGC) models, the term 'trajectory' refers broadly to the shape, extent and pattern of change on a particular characteristic over time, established by repeated measurements or observations. Each individual's pattern of change on these observed measures (for instance, severity of psychotic symptoms) is described as their individual 'growth' trajectory. This trajectory can assume different functions, including simple linear increase or decline over time. The LGC approach hypothesises the existence of a continuous latent (unobserved) trajectory which governs these individual observed trajectories, and assumes that the pattern of change in the repeated observed measures provides indirect information about the underlying latent trajectories. Hence the analytic interest is not on the repeated observed variables per se, but on the unobserved latent trajectory factors driving the means, variances and covariances of the repeated observed variables (Bollen & Curran, 2006). The trajectories taken by the observed variables are central to LGC modelling. The word 'trajectory' also assumes a more specific meaning in LGC models. For instance, the basic linear trajectory model comprises two important latent growth factors that determine the shape of the growth. The first of these is the intercept, which represents the *true mean starting point* of the trajectory. The second factor is the slope, which represents the *true mean rate of change* over the time interval under observation.

The current investigation focuses on the latent growth psychopathology trajectory of 413 first-episode psychosis subjects over the 12-month interval following initial recovery. Observations underpinning this illness trajectory were collected on three occasions:

(i) initial recovery/stabilisation from the psychotic episode (T2);
(ii) 6-month follow-up (T3) and;
(iii) 1-year follow-up (T4).

This period is particularly relevant in a clinical sense, since the critical period for vulnerability to symptomatic deterioration, relapse and the development of disability is believed to occur during the early phase of psychosis, with relative stability subsequently (Birchwood et al., 1998). It is unclear what role, if any, is played by the psychopathology symptom trajectory in the first year post-recovery in the prediction of long-term outcome, whether (i) as a direct predictor, and/or; (ii) as a mediator of the effects of presenting features such as gender, age at onset of illness and DUP on long-term outcome. Furthermore, the degree to which the evolution of symptoms over the 1-year interval subsequent to initial recovery is impacted by presenting features of the participants is similarly uncertain. It is hoped that this research will assist in clarifying the nature of the role played by the short-term trajectory as a portent of long-term outcome, and also help identify whether there are particular presenting features which account for variability in symptom trajectories.

The basic linear trajectory model for the first-episode data contains two latent growth factors which determine the shape of the growth trajectory. The intercept is the first latent factor; it represents the mean starting point (T2) of the psychopathology trajectory. The slope is the second latent factor; it represents the mean rate of change in severity of psychopathology from the starting point (T2) across 6 month follow-up (T3) and 1-year follow-up (T4). In clinical terms, the intercept represents the average severity of symptoms at the point of recovery from the initial psychotic episode. The slope represents the average change in severity of psychopathology across the 1-year interval subsequent to the initial starting point. Thus these two latent factors; the mean starting point and the mean rate of change over the subsequent 1-year interval, comprise the short-term psychopathology trajectory estimate provided by the repeated observed symptom variables measured at T2, T3 and T4.

The latent growth factor model depicted in Figure 5.1 includes symptom measures observed on three occasions over a 1-year interval subsequent to initial recovery: T2 (the starting point of

the trajectory at initial recovery), T3, and T4; along with two latent growth factors. The observed variables are linked to the latent factors via a factor loading matrix. The linear latent curve model fixes these loadings to specific *a priori* values. In this model specification, the factor loadings relating the three repeated measures to the intercept factor have been set to 1.0, implying that the intercept factor equally influences all repeated measures across all assessment waves. Further detail is provided in section 5.3.1 regarding the time codings for the slope factor.

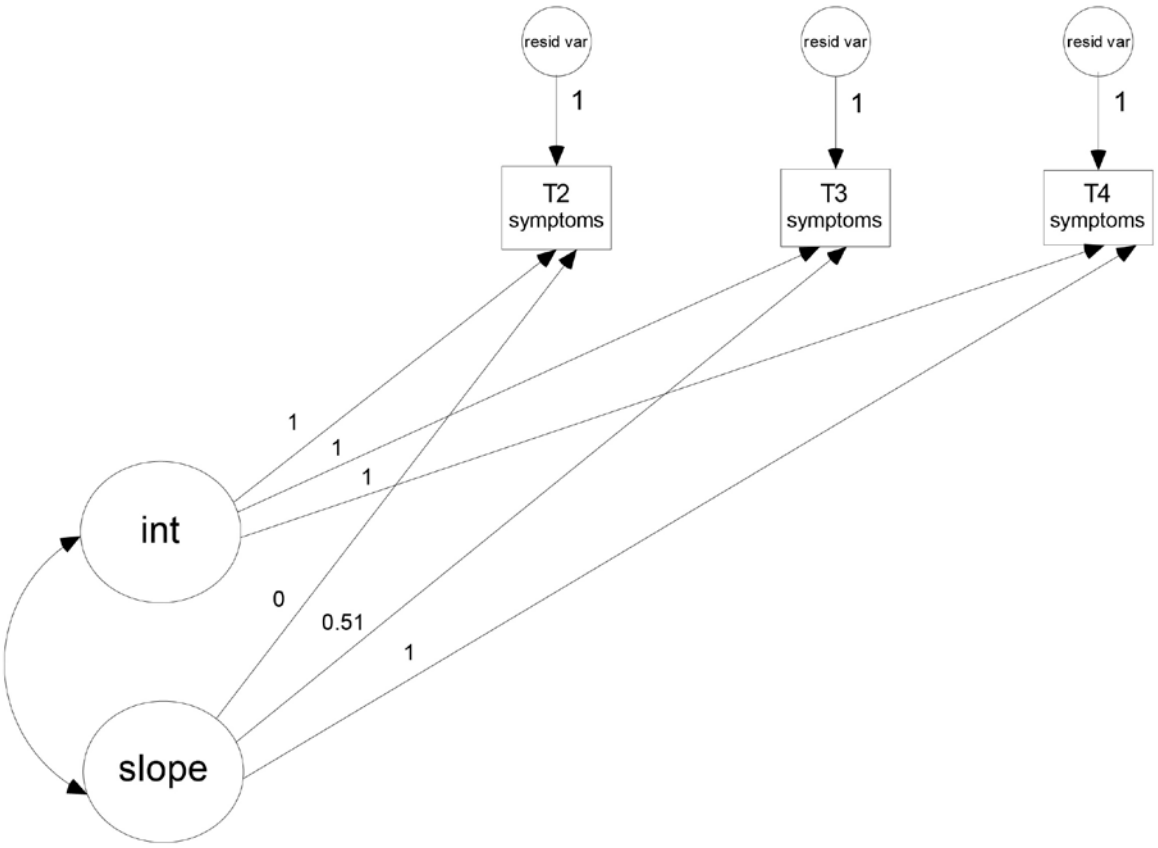


Figure 5.1. Unconditional linear latent trajectory model for symptoms measured at initial recovery, 6-month follow-up and 1-year follow-up.

5.2 Functional form of change over the short-term trajectory

To test whether the functional form of change is best described as linear or non-linear, two competing LGC models will be specified. Although a variety of approaches is available for modelling non-linear functions within the latent growth curve framework, for instance,

polynomials or piecewise methods, the additional parameters estimated in these models require a minimum number of waves of data to achieve model identification (where a unique solution exists for all of the model's parameters). In the case of the quadratic trajectory, a minimum of four waves of data is required, and for a cubic polynomial or a piecewise model, five waves of data is necessary (Bollen & Curran, 2006). Since there are only three waves of data underpinning the latent growth curve trajectories presented in the current study, it is not possible to implement polynomial or piecewise methods in modelling non-linearity. Instead, the 'freed-loading' approach proposed by Meredith and Tisak (Meredith & Tisak, 1984, 1990) will be implemented. This approach models non-linear trajectories by allowing one or more slope loadings in the latent curve model to be freely estimated. Further details regarding the implementation of this approach in this thesis are provided in section 1.3.2. The freed loading provides flexibility in fitting nonlinear forms and is a type of nonlinear 'spline' that best fits the data between any pair of time points (Bollen & Curran, 2006). Model identification for the freed-loading approach is less rigorous than for the polynomial or piecewise functions, and in the case of three waves of data, a non-linear model is exactly identified when one of the three slope loadings is estimated.

5.3 Time coding: linear and non-linear models

Consideration was given to treating time as a random variable in the latent growth curve analyses. This is a less restrictive approach as it allows the time intervals between assessments to vary for each individual, thus reflecting realities inherent in longitudinal follow-up research. However, treating time as random has three main disadvantages. Firstly, fit indices are not available for these models; secondly, a standardised solution — highly desirable for interpretation — is not possible and; thirdly, it is not possible to treat time as random for models where the linear trajectory is not a good fit. The latter point would potentially compromise the aim of trying to maintain the strategy for different symptom models as similar as possible. To assess the degree to which treating time as fixed or random influenced model parameters and any conclusions drawn, a comparative analysis was undertaken. A basic unconditional model was run with time specified as a random variable, with the resulting parameters compared with those derived from the model where time was fixed. Parameters and p-values from both models were comparable, and the conclusions drawn substantially similar. This suggested that there was no advantage in treating time as a random variable.

Consequently, it was decided to specify time as fixed, but to base it on the median for each interval as a proxy for actual intervals, as described below.

5.3.1 Linear model

A variety of codings for time were available for the slope factor. One possibility that was considered was to simply fix the time loadings to values of the wave of measure $\lambda_t = 0, 1, 2$, thus reflecting an equal spacing of time between the three assessments at T2, T3 and T4. Given that the assessments were notionally separated by 6-month increments, a one unit change in time would reflect a 6-month interval. An alternative coding for time is suggested by McArdle (McArdle, 1988) where the values of the first (λ_1) and last (λ_3) loadings are set to 0 and 1 respectively. In the case of the linear model, the intermediate loading λ_2, at 6-month follow-up, might be fixed at 0.50, with the values of $\lambda_t = 0, 0.50, 1$, reflecting equal 6-monthly increment between assessments. A further refinement of this coding might better accommodate the imprecise time intervals between assessments. For instance, the value of the fixed slope loading for the intermediate λ_2 might be determined by expressing the median time elapsed between initial recovery (T2) and 6-month follow-up (T3) as a proportion of the total median time between T2 and 1-year follow-up (T4). In the study data, the median time elapsed between T2 and T3 was 194 days, which, as a proportion of the median time elapsed from T2 to T4 of 380 days, was equivalent to 0.510, resulting in fixed values of $\lambda_t = 0, 0.510, 1$ for the linear model. Beginning the coding with zero allows the intercept factor to be defined as the starting point of the symptom trajectory (i.e., at initial recovery) (Bollen & Curran, 2006). In other words, by setting the first factor loading on the slope factor to zero, the intercept factor is defined as the starting point of the trajectory. These fixed values of λ_t can be seen in Figure 5.1.

The latent growth factor model depicted in Figure 5.1 includes symptom measures observed on three occasions over a 1-year interval subsequent to initial recovery: T2 (the starting point of the trajectory at initial recovery), T3, and T4; along with two latent growth factors. The observed variables are linked to the latent factors via a factor loading matrix. The linear latent curve model fixes these loadings to specific a priori values. In this model specification, the factor loadings relating the three repeated measures to the intercept factor have been set to 1.0, implying that the intercept factor equally influences all repeated measures across all assessment waves.

5.3.2 Non-linear model

A competing non-linear trajectory model was accommodated using the freed-loading approach proposed by Meredith and Tisak (Meredith & Tisak, 1984, 1990). As mentioned earlier, the freed loading provides flexibility in fitting nonlinear forms and is a type of nonlinear 'spline' that best fits the data between any pair of time points. In implementing this approach, a freed-loading non-linear latent curve model was estimated in which the first loading λ_1 (corresponding to initial recovery: T2) on the slope factor was fixed to 0, the second loading λ_2 (6-month follow-up: T3) was freely estimated, and the third loading λ_3 (1-year follow-up: T4) was fixed to 1, as per the recommendation by McArdle (McArdle, 1988). The estimated second loading λ_2 represents the proportion of change between the initial T2 to T3 time period, relative to the total change occurring from T2 to T4. For example, if the estimated value of the second loading was 0.70, this would reflect that 70% of the total observed change in symptom severity across the 1-year trajectory occurred between the first two assessments at T2 and T3. The fit statistics for this parameterisation are identical to those that would be obtained by freeing up either the first or third slope loadings. In practical terms, the difference between the linear and non-linear model is that the linear model fixes the intermediate loading λ_2, whereas the non-linear model allows this loading to be freely estimated.

Models are said to be 'nested' if one model contains all the terms of the other, and at least one additional term. The linear and non-linear models both contain the same terms except that the non-linear model contains an additional term comprising the slope loading at 6-month follow-up. Thus, the more restrictive linear model is nested within the more complex non-linear model. With nested models, the chi-square statistics of the linear and non-linear models can be compared to assess whether the more complex non-linear model provides a significantly better fit compared to the simpler linear model. However if the method of estimation is not maximum likelihood, the testing of nested models may be more complicated. This aspect will be covered in section 5.5.1 which discusses the type of estimator used for the analysis of direct effects.

5.4 Coding and Centreing of Observed Variables

5.4.1 Coding of observed variables

Negative symptoms

The four negative symptoms; Affective flattening, Alogia, Avolition and Anhedonia, were scaled to a common metric of 0 to 5 (achieved by dividing each subscale score by the number of items in the scale), where 0 = 'None'; 1 = 'Questionable'; 2 = 'Mild'; 3 = 'Moderate'; 4 = 'Marked'; 5 = 'Severe'. This was done to facilitate comparisons between the different negative symptom subscales, each of which contains a different number of items.

Gender

A dummy variable; 'male' was created, with male gender coded as 1, and female as 0. Thus, model coefficients for 'male' indicate the differential effect of being male (as opposed to being female) on the dependent variable(s), adjusting for other variables in the model.

DUP

Due to the very high positive skewness of DUP, it was necessary to transform this variable prior to analysis. DUP was cut into five pre-defined categories to facilitate clinical and statistical interpretability. These categories were as follows: 0 to 7 days; 8 to 28 days; 29 to 90 days, over 3 months up to 1 year; and over 1 year (Harrigan et al., 2003). The latter DUP category, $DUP_{1+\ year}$ was defined as the reference category against which other DUP categories were compared.

The rationale for selecting $DUP_{1+\ year}$ as the reference category was based on the premise that a range of short durations of untreated psychosis are more optimal, in a clinical and prognostic sense, than very long DUP. The opposing premise, that each additional duration category makes things worse, would, on the other hand, suggest the use of very short $DUP_{0\text{-}7\ days}$ as the reference category. In further deliberations, the decision to use $DUP_{1+\ year}$ as the reference category was aided by the DUP literature, which generally advocates getting people with psychosis into treatment before their DUP becomes *very long*, as opposed to simply getting people into treatment as soon as possible, which might suggest very short $DUP_{0\text{-}7\ days}$ as the reference. Selection of $DUP_{1+\ year}$ as the reference group will be useful in testing whether durations of, for instance, up to 90 days, are associated with better outcomes (either at T5 or T1) than DUP of more than one year. If very short $DUP_{0\text{-}7\ days}$ had been specified as the

reference, comparisons would be rather limited in that only very short durations would be compared with other categories. Thus the decision to use DUP $_{1+\ year}$ as the reference category for DUP analyses was defined by careful consideration of these arguments.

Pre-morbid functioning

The pre-morbid adjustment of the patient during the period immediately preceding the prodromal phase was used as an estimate of true premorbid functioning (Harrigan et al., 2003). The pre-morbid functioning score is on a continuum ranging from 0 to 1, with lower scores indicative of the healthiest end of the adjustment spectrum, and higher scores representing worse premorbid functioning.

5.4.2 Centreing of predictors

All continuous predictors were centred, comprising: age of onset of psychosis, admission (T1) psychopathology score, and pre-morbid functioning, to enable meaningful interpretation of the intercept and slope in conditional models (Models 2 to 4). Without centreing, the intercept and slope would be interpreted relative to a person with a score of 0 on each of these predictors, which is not conceptually meaningful. Each of the continuous predictors was centred by subtracting the sample mean from each individual's observed value, to facilitate interpretability. For instance, when T1 positive symptoms was centred on its sample mean, the model intercepts (the intercepts of the two latent growth variables and positive symptom outcome at long-term follow-up) represent estimated values for an individual with average levels of positive symptoms at admission, instead of basing the estimated intercept values on individuals with zero positive symptoms at admission, a scenario which is neither plausible or interpretable, especially given the usually florid nature of psychosis at intake.

A similar situation applies for negative symptoms. Centreing was carried out manually for each model (by subtracting the value of the estimated sample mean obtained for that model from the particular variable using the Mplus DEFINE command) as it centres precisely at zero, unlike the 'grandmean' centreing procedure, which does not precisely centre the variables at zero if there are missing data (for instance, pre-morbid functioning and T1 symptom score).

5.5 Model fitting

For each of the positive and negative symptom measures, a latent growth curve model was developed in four incremental stages in order to sequentially address the research questions (see Chapter 3). Each stage built on the preceding stage by incorporating additional observed variables and parameters, with each stage adding a particular set of research questions. Four main aspects were examined in the four-stage model for each symptom type:

(i) Characteristics of symptom trajectories for the overall group of 413 FEP subjects across the 12-month interval subsequent to initial recovery/stabilisation were described, and the degree of individual variability in trajectory estimates assessed (Model 1);

(ii) The utility of the short-term trajectory in predicting long-term outcome was investigated; firstly, when the effects of presenting attributes of the study participants were excluded (Model 2), secondly, when taking into account the effects of these features (Model 3), and thirdly, when the effects of baseline DSM-IV diagnosis were additionally accounted for (Model 4);

(iii) The extent to which the presenting features of the study participants impacted on (a) admission symptom levels, (b) change over the short-term trajectory and (c) long-term outcome were investigated (Model 3) and, similarly, the extent to which baseline DSM-IV diagnosis impacted these outcomes (Model 4);

(iv) Questions regarding whether effects of presenting attributes on long-term outcome were partly or fully mediated by the short-term trajectory were examined (Model 3); and, in Model 4, whether the effects of baseline DSM-IV diagnosis on long-term outcome were partly or fully mediated by the short-term trajectory.

5.5.1 Estimation of direct effects

For each symptom type, an initial model was developed as the framework for subsequent stages. This model fitted an unconditional growth curve to the symptom data at initial recovery (T2), 6-month follow-up (T3) and 1-year follow-up (T4), using the statistical package MPlus (L. K. Muthén & Muthén, 1998-2011). Historically, maximum likelihood (ML) has been used as the preferred method of estimation for such models, due to its attractive statistical properties in large samples, and the availability of a chi-square test of fit and family of accompanying goodness of fit indices. However, a main assumption underlying the use of ML

is that the scores on the observed variables are multivariately normally distributed, an untenable assumption for psychopathology data in general, and the positive and negative symptoms in the study dataset in particular.

Therefore, the type of estimator used for this fitting of the unconditional growth curve to the symptom data, and the analysis of direct effects in subsequent models, was maximum likelihood with robust standard errors (MLR). An advantage of MLR as compared with other estimation methods such as ML, is that it provides parameter estimates with standards errors and a chi-square statistic that are robust to non-normality. The MLR chi-square statistic is asymptotically equivalent to the Yuan-Bentler T2* test statistic (L. K. Muthén & Muthén, 1998-2011). MLR standard errors are computed using a sandwich estimator, a common tool used for variance estimation of parameter estimates. Sandwich estimators for standard errors are often useful particularly when model based estimators are very complex, computationally difficult and where robust alternatives are required.

Testing of nested models is more complicated than usual when using estimators such as MLR. For instance, assessing whether the more complex linear model provides a significantly better fit compared to the simpler linear model cannot be carried out using a simple chi-square difference test. This is because a difference between two chi-squares for nested models using this estimator is not distributed as chi-square (Satorra, 2000). The correct chi-square difference test statistic for models estimated with the MLR estimator is the Sattora-Bentler scaled chi-square difference test, which is described on the Mplus website http://www.statmodel.com/chidiff.shtml. The following pieces of information are required in order to calculate this test, and are extracted from the Statmodel web page:

1. Compute the difference test scaling correction cd, where do is the degrees of freedom in the nested model, co is the scaling correction factor for the nested model, d1 is the degrees of freedom in the comparison model, and c1 is the scaling correction factor for the comparison model. Be sure to use the correction factor given in the output for the Ho model.
2. cd = (do * co - d1*c1)/(do - d1)
3. Compute the Satorra-Bentler scaled chi-square difference test TRd as follows:
4. TRd = (To*co - T1*c1)/cd

Where To and T1 are the MLM, MLR, or WLSM chi-square values for the nested and comparison model, respectively. For MLM and MLR the products To*co and T1*c1 are the

same as the corresponding ML chi-square values.

This formula will be implemented where appropriate, when fitting the unconditional latent growth curve to the symptom data in the first stage of each model.

5.5.2 Estimation of indirect effects

The basis of inference for mediated effects in each model differs from the method of estimation used for the detection of direct effects for reasons explained in Statistical Mediation (Chapter 6). The presence of mediated effects in this study will be established using the bias-corrected bootstrap, which is recommended as the optimum method (MacKinnon, Lockwood, & Williams, 2004). Estimates of the mediated effect obtained from the bootstrap analysis will be based on the product of coefficients method (*ab*) which calculates the product of the *a* and *b* coefficients in Equations 6.2 and 6.3 in Mediation (Chapter 6), to produce the mediated (indirect) effect. The bias-corrected bootstrap procedure in software package MPlus (L. K. Muthén & Muthén, 1998-2011) will be used for the single and multiple mediator models, using 10,000 bootstrap draws. Bootstrapped standard errors and 95% confidence intervals (which are not necessarily symmetric around the point estimate of the (*ab*) mediated effect) are regarded as particularly appropriate in establishing whether the mediated effect is significantly different from zero, since these asymmetric intervals take non-normality of the mediation effect into account. Statistical significance will be determined by examining whether zero is included in the bias-corrected bootstrap confidence interval; if the interval does not encompass zero, then the result will be regarded as statistically significant.

5.5.3 Fit indices

A common approach in evaluating model fit is to test the underlying structure of a hypothesised model using an index that relates the goodness of fit of that model to the data. A good fitting model is one that is reasonably consistent with the data. Many indices have been proposed to evaluate the degree of fit, and to assess whether model fit can be improved by respecifying the model. Commonly used goodness of fit indices include the chi-square test statistic, the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA), and the Standardised Root Mean square Residual (SRMR). These fit indices will be used to evaluate model fit in this thesis, and are briefly described below:

Chi-square test: The chi-square test is a global omnibus test of the overall fit of the model to the data. As an absolute fit index, the chi-square does not use an alternative model as a base for comparison, but is derived from the fit of the observed and implied covariance matrices. The null hypothesis states that there is no difference between the study data (the sample covariance matrix of observed variables) and the covariance matrix reproduced by the model parameters. Small chi-square p-values < 0.05 indicate that the null hypothesis should be rejected, thus indicating the data and model do not fit well, whilst p-values ≤ 0.05 indicate that there is evidence to reject the assumption that the sample covariance matrix of observed variables equals the covariance matrix of model parameters. Thus, non-significant p-values are associated with better fitting models. Unfortunately, the chi-square test statistic is not always a reliable test of fit as it is influenced by sample size, which may result in model rejection with large enough N, and model retention with small enough N. Furthermore, it may result in model rejection with non-normal data. This is not a rationale to ignore chi-square, but preferably to supplement it with other goodness of fit indices.

RMSEA: This index is a 'badness of fit' index since a value of 0 indicates the best fit, whereas higher values indicate worse fit. The RMSEA index has several attractive properties. Firstly, it is a parsimony-adjusted index, as it incorporates a built-in adjustment for model complexity, and so favours simpler models. Secondly, it is a population-based measure that is relatively unaffected by sample size. Thirdly, this index has a known distribution therefore it is possible to have a confidence interval placed around it. The lower bound of the interval is a test of fit; if the lower bound of the confidence interval is below 0.05, then the chi-square test of close fit will not be rejected. The lower bound of the RMSEA confidence interval indicates the model fit at best, whereas the upper bound of the confidence interval indicates the model fit at worst. The following RMSEA cut points are used as guidelines to model assessment: 0.00 = exact fit; < 0.05 = close fit; 0.05 to 0.08 = moderate fit; 0.08 to 0.10 = mediocre fit; > 0.10 = poor fit.

CFI: Whereas the chi-square test and RMSEA index are measures of absolute fit, the CFI a comparative measure of fit bounded between 0 and 1. It is analogous to the R^2 found in multiple linear regression. Comparative indices such as the CFI assess the relative improvement in fit compared with a baseline model, such as the null model which assumes zero population covariances among the observed variables. CFI values range from 0 to 1, with CFI values of < 0.90 indicative of a close approximation, with preference for values > 0.95.

SRMR: The root mean square residual (RMSR) is a measure of the mean absolute value of the covariance residuals. Similar to the RMSEA index, this measure is a 'badness of fit' index since values closer to zero indicate the best fit, whilst higher values indicate poorer fit. Since the RMSR is computed with unstandardised variables, its range depends on the scales of the observed variables. The standardised root mean square residual (SRMR) is based on transforming both the sample covariance matrix and the predicted covariance matrix into correlation matrices. The SRMR is therefore a measure of the mean absolute correlation residual, being the overall difference between the observed and predicted correlations. It is known to be less biased by incorrect estimation methods than either the RMSEA or CFI. There is no generally agreed upon value, but values of approximately 0.07 to 0.08 indicate a reasonable fit, with preferences for values below 0.05. Since this is a sample-based measure, not a population-based measure, it is affected by sample size.

5.5.4 Model modification

Statistical models often do not fit well as first specified, or even after numerous attempts to improve the fit by introducing modification. This may be due to the estimation method being incorrect, but is more likely because the model is incorrectly specified. Modification indices (MI) give an indication of the most promising ways of changing the specification to improve model fit, by providing a measure of the expected improvement in the model chi-square from freeing up a fixed parameter. However, post hoc model modification must be used judiciously otherwise there is a risk of capitalising on chance sampling features in the dataset that will not be replicated in other samples (MacCallum, Roznowski, & Necowitz, 1992).

The optimal approach in using MIs to improve the fit of a model is to identify a large MI value which makes sense to free up, in both a conceptual and statistical sense. The corresponding parameter is then freed up and the model refitted. MI values are not independent of one another, so parameters should only be freed up one at a time. It may be necessary to inspect the MIs again, free up another meaningful parameter and re-fit the model. Each time a parameter is freed up to be estimated, the fit of the model is improved, and one degree of freedom is lost. Strictly speaking, post hoc modifications render the chi-square test statistic meaningless as a formal test of the hypothesis that the model fits exactly. However, it can arguably still be regarded as a goodness of fit test, as it is the goodness of fit chi-square value that would have been obtained had the resulting model been fitted *a priori*.

5.6 Model Fitting Logic

The latent growth curve models were developed in four incremental stages in order to address the defined research questions. Results from each of these stages are presented sequentially, as detailed below, with each of the two Results chapters partitioned into distinct sections, each corresponding to a particular stage of the model.

In the first and second stages, the 'core' working model for the T1-T5 data was developed. The first stage modelled the shape and rate of change in the symptom trajectory which was represented by the intercept and slope latent variables, and underpinned by the T2-T4 data. In this initial stage, the degree to which there is individual variability around the average symptom trajectory was also investigated. The second stage (Model 2) incorporated T1 symptoms as a predictor, and T5 symptoms, as an exogenous predicted outcome variable. Relationships between the intercept, slope, and T1 and T5 components were also specified.

Once this 'core' model was estimated, the third stage (Model 3) assessed the degree to which participants presenting features (e.g., gender, age at onset of psychosis, duration of untreated psychosis (DUP) and pre-morbid functioning) were able to differentiate short-term trajectories and long-term outcome, over and above the predictive capacity of the observed and latent variables in the stage two model. Importantly, this third model examined the direct and indirect effects of the predictors, for instance, whether the effects of T1 symptoms on T5 outcome were mediated by the short-term trajectory (T2-T4) or whether T1 symptoms directly accounted for the majority of what happened at T5. Similarly, the nature of the association between each of the presenting features and the short-term symptom trajectory and long-term outcome was investigated, to see whether the effects of these 'fixed' variables could be discounted as an explanation of the short-term trajectory and long-term outcome.

A fourth and final stage of the model included baseline DSM-IV diagnosis of the first psychotic episode. As mentioned in the research questions in Chapter 3, this predictor has the potential to differentiate symptom trajectories and final long-term outcome over and above the capacity of baseline presenting features. Although potentially an important predictor, there is some circularity in the inclusion of this variable. It is acknowledged that inclusion of DSM-IV diagnosis may be problematic, because its duration criteria for specific diagnoses are inherently linked with clinical predictors such as DUP, and symptom severity at admission

(T1). The effects of these predictors on short-term and long-term outcomes could therefore be expected to be attenuated as a result.

The research questions (previously presented in Chapter 3) embedded within each stage of model development follow. For the sake of completeness, all research questions are enumerated, but additional information is given only for those that involve additional modelling components or features.

Model 1: Growth Characteristics of Psychopathology over Short-Term Follow-up

RQ 1.1 What is the overall short-term trajectory for the entire sample?

RQ 1.2 What is the nature of variation of short-term trajectories between individuals?

The latent growth factor model depicted in Figure 5.1 (shown in Section 5.1) includes symptom measures observed on three occasions over a 1-year interval subsequent to initial recovery: T2 (the starting point of the trajectory at initial recovery), T3 (6 months post-T2), and T4 (12 months post-T2); along with two latent growth factors. The observed variables are linked to the latent factors via a factor loading matrix. The linear latent curve model fixes these loadings to specific a priori values. In this model specification, the factor loadings relating the three repeated measures to the intercept factor have been set to 1.0, implying that the intercept factor equally influences all repeated measures across all assessment waves.

The factor loadings relating the three repeated symptom measures to the slope factor have been set to $\lambda_t = 0, 0.510, 1$ for the linear model; the rationale for this time coding scheme is described in detail earlier in this chapter. To recap, the metric of loadings T2 (λ_1) and T4 (λ_3) are set to 0 and 1 respectively, thereby scaling the intermediate factor loading at 6-month follow-up relative to the amount of change occurring between T2 and T4. Beginning the coding with $\lambda_1 = 0$ allows the intercept factor to be defined as the starting point of the symptom trajectory (i.e., at initial recovery from the psychotic episode). The fixed loading of 0.510 for 6-month follow-up is determined by expressing the median time elapsed between T2 and T3 as a proportion of the total median follow-up time between T2 and T4. In this study sample, the median time elapsed between T2 and T3 is 194 days, which, as a proportion of the median time elapsed from T2 to T4 of 380 days, is equal to 0.510, as seen in the fixed intermediate slope loading in Figure 5.1. In the case of the non-linear model (not presented here), the second slope loading λ_2 would be freely estimated.

In this model, the intercept and slope in the unconditional model are correlated, because it is reasonable to expect that higher starting points in symptomatology will be associated with steeper decrements in symptoms over time. The residual variances of the observed variables are constrained to be equal, as a matter of parsimony.

Model 2: Symptoms at Admission and Long-Term Follow-up

Model 2 research questions

Measurements of symptoms made on two other occasions — admission (T1) and long-term follow-up (T5) — were added to the unconditional model established in Model 1. Severity of symptoms at admission, a time when participants are typically floridly psychotic, is specified as an exogenous covariate to the short-term growth trajectory. Severity of symptoms score at long-term follow-up (T5) is included as a distal outcome variable, and is predicted by symptoms at admission (T1) and by the two latent growth trajectory factors, the intercept and slope. The covariance between the disturbance terms of the intercept and slope was initially constrained to zero (unless otherwise indicated), since correlated disturbance terms might imply the presence of another common factor. A path diagram representing the direct effects in this model is presented in Figure 5.2.

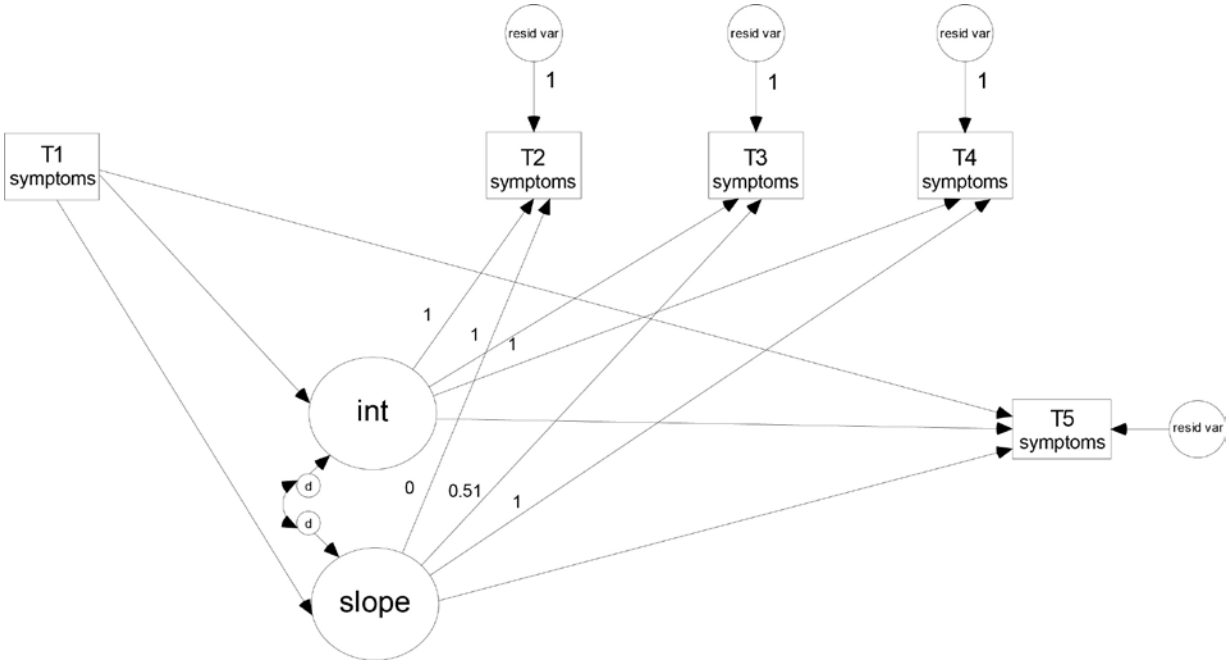


Figure 5.2. Conditional linear latent trajectory model for severity of symptoms, incorporating symptoms at admission (T1) as a covariate and long-term symptoms (T5) as an outcome variable.

Direct effects

RQ 2.1 Does symptom severity at admission directly predict the short-term growth trajectory?

RQ 2.2 Does symptom severity at admission directly predict long-term outcome?

RQ 2.3 Does the short-term trajectory directly predict long-term symptom severity?

The magnitude and direction of these direct effects will be presented in a table as regression coefficients (with standard errors and probability values) linking severity levels at initial admission, each of the intercept and slope latent growth factors, and observed long-term symptoms.

Indirect effects

RQ 2.4 Is the effect of severity of symptoms at admission on long-term symptom levels mediated in full or in part by the latent trajectory variables?

Model 3: Effects of Participants' Presenting Features on Short and Long-term Follow-up

The preceding conditional model will be further developed by integrating four exogenous baseline predictors of the following outcome measures: (i) symptom levels at admission; (ii) the short-term trajectory, and; (iii) long-term outcome. These predictors are: gender, age at onset of psychosis, duration of untreated psychosis (DUP), and pre-morbid functioning. A path diagram representing the direct effects in this model is presented in Figure 5.3

These new variables are exogenous and are not predicted by any variable in the model. All paths in the preceding conditional model 2 are retained. Long-term symptom levels are now also being predicted by gender, age at onset, DUP and pre-morbid functioning. Symptom levels at admission has become an endogenous variable, and is predicted by gender, age at onset, DUP, and pre-morbid functioning. The short-term growth trajectory is predicted by gender, age at onset, DUP, and pre-morbid functioning. The residual variances of the observed symptom variables comprising the short-term trajectory are again being constrained to be equal, as a matter of parsimony. The covariance between the disturbance terms of the intercept and slope is constrained to zero unless otherwise indicated.

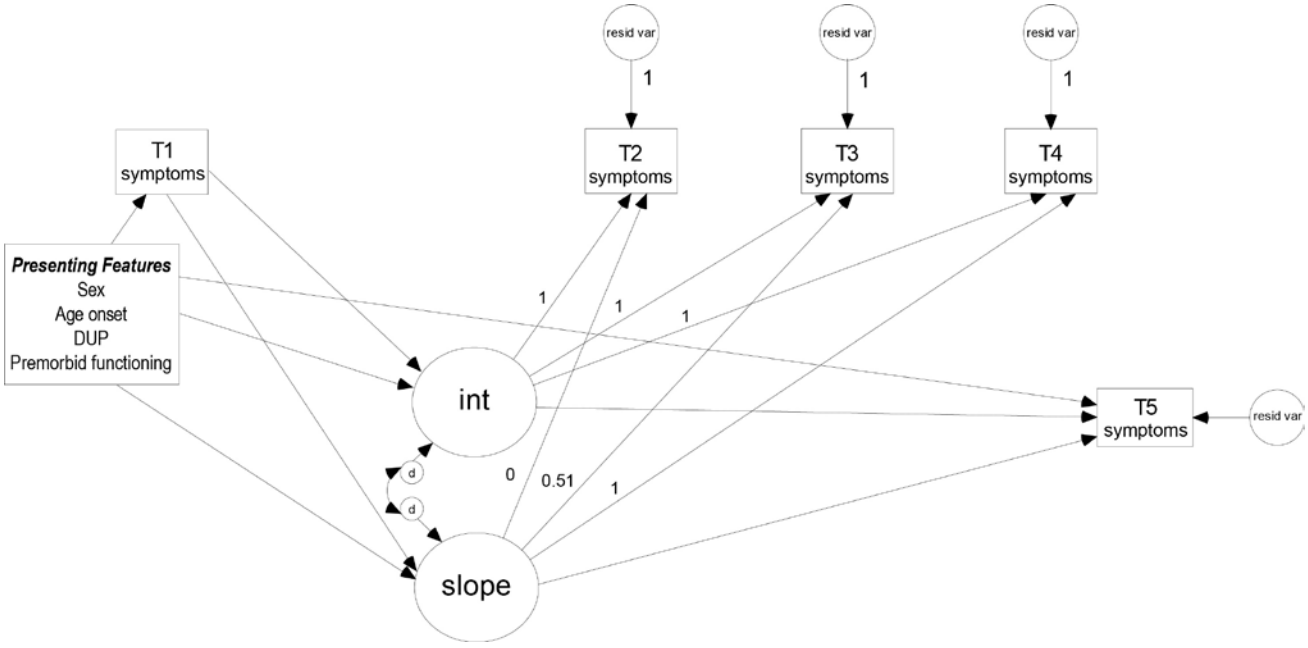


Figure 5.3. Conditional linear latent trajectory model for severity of symptoms, incorporating effects of gender, age at onset of psychosis, DUP and pre-morbid functioning as predictors of symptom severity at admission, short-term trajectory and long-term outcome.

Model 3 research questions

The main question addressed by this model is whether the effects of the participants' presenting features on distal symptom severity levels (T5) are mediated either fully or partly, or not at all, by the intercept and slope latent trajectory variables which represent the short-term trajectory in the 1-year interval subsequent to initial recovery (T2), and/or mediated by symptom levels at admission (T1). This question is of particular interest given that research has suggested that these presenting features are significantly associated with both short-term and long-term outcome even after the effects of known confounders are taken into account (Addington et al., 2004; Harris et al., 2005; T. K. Larsen et al., 2000; Marshall et al., 2005). If some form of mediation is found, then it would imply that the particular characteristic transmits its effect on long-term outcome solely, or partly, through the short-term change that has occurred after initial recovery, and/or by the severity of symptoms at admission. In addition to these indirect effects, which are presented in RQ 3.4 and RQ 3.5, there are three research questions of interest concerning direct effects for this model, specifically:

Direct effects

RQ 3.1 Do the four presenting features (gender, age of onset, DUP or pre-morbid functioning) directly predict symptom levels at admission?

RQ 3.2 Is there a direct effect of any presenting feature on the latent growth factors?

RQ 3.3 Do the four presenting features directly predict long-term outcome?

Indirect effects

RQ 3.4 Are the effects of gender, age of onset, DUP and pre-morbid functioning on the short-term symptom trajectories mediated in full or in part by level of symptoms at admission?

RQ 3.5 Are the effects of gender, age of onset, DUP and pre-morbid functioning on long-term symptom levels mediated in full or in part by either the latent trajectory variables or by symptom levels at admission?

The magnitude and direction of these and other effects in this model will be tabled as raw regression coefficients linking gender, age at onset of psychosis, DUP, pre-morbid functioning, admission symptom levels, the latent growth factors and the observed long-term symptoms measure.

Model 4: Effect of DSM-IV Baseline Diagnosis on Short-term and Long-term Outcome

The final model includes one further refinement of the preceding conditional model, achieved by including DSM-IV diagnosis of the first episode of psychosis as a predictor of symptom levels at initial admission, of the short-term trajectory, and of long-term outcome. Diagnosis comprised six broad categories:

(i) Schizophrenia (reference category);
(ii) Schizophreniform;
(iii) Schizoaffective disorder;
(iv) Bipolar psychotic disorder;
(v) Depressive Psychosis;

(vi) Other psychotic disorders (comprising psychotic disorder NOS, delusional disorder, brief psychotic disorder).

A path diagram representing the direct effects in this model is presented in Figure 5.4. Diagnosis is exogenous to admission symptoms, the short-term latent trajectory variables, and long-term outcome, all of which are predicted by diagnosis. All variables and paths in the preceding conditional model 3 are retained in this model 4 specification. The residual variances of the observed symptom variables comprising the short-term trajectory are again constrained to be equal, as a matter of parsimony. The covariance between the disturbance terms of the intercept and slope is constrained to zero unless otherwise indicated.

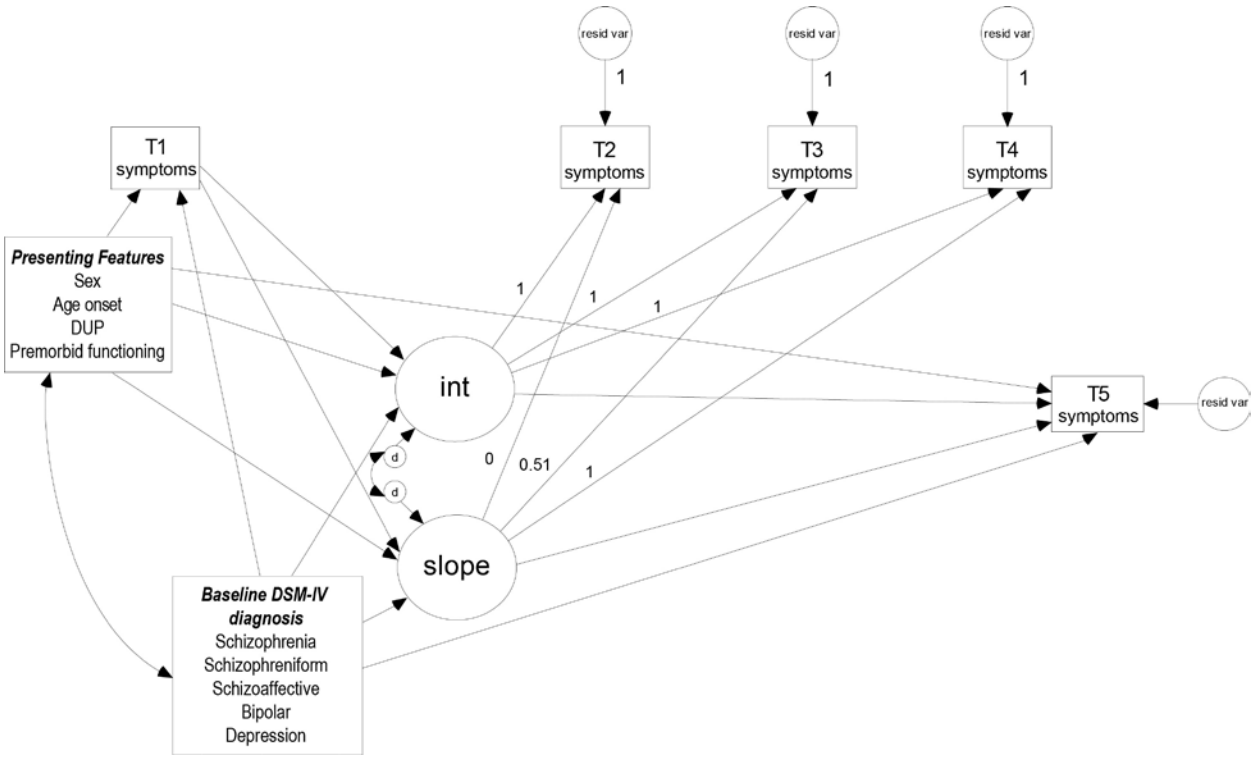


Figure 5.4. Conditional linear latent trajectory model for severity of symptoms, incorporating effects of baseline DSM-IV diagnosis as a predictor of symptom severity at admission, short-term and long-term outcome.

5.6.1 Model 4 research questions

The principal question addressed by this model is whether the effect of DSM-IV diagnosis on distal symptom severity levels (T5) is mediated either fully or partly, or not at all, by the intercept and slope latent trajectory variables which represent the short-term change that occurs in the 1-year interval subsequent to initial recovery, and/or mediated by symptom levels at admission (T1). If some form of mediation is found, then it would imply that the diagnosis transmits its effect on long-term outcome solely, or partly, through the short-term change that has occurred after initial recovery, and/or by the severity of symptoms at admission. In addition to these indirect effects, which are presented in RQ 4.4 and RQ 4.5, there are three research questions of interest concerning direct effects for this model, specifically:

Direct effects

RQ 4.1 Does baseline diagnosis directly predict symptom levels at admission?

RQ 4.2 Is there a direct effect of diagnosis on the latent growth factors?

RQ 4.3 Does baseline DSM-IV psychotic diagnosis directly predict long-term outcome?

Indirect effects

RQ 4.10 Are the effects of baseline psychotic diagnosis on the short-term symptom trajectories mediated in full or in part by level of symptoms at admission?

RQ 4.11 Are the effects of baseline diagnosis on long-term symptom levels mediated in full or in part by either the latent trajectory variables or by symptom levels at admission?

The magnitude and direction of these and other effects in this model will be tabled as raw regression coefficients linking DSM-IV diagnosis, gender, age at onset of psychosis, DUP, pre-morbid functioning, initial admission symptom levels, the latent growth factors and the observed long-term symptoms measure.

6 MEDIATION

Several research questions in this thesis address the general hypothesis that the effects of independent variables (for instance, duration of untreated psychosis) on dependent variables such as long-term outcome may be mediated by other variables. The concept of mediation is simple– that a third variable (the mediating variable) is part of a causal 'chain' in the effect of one variable to another; the mediator 'transmits' an effect (MacKinnon, 2008). Possible mediators in this study include severity of symptoms at admission, and the short-term trajectory (STT), represented by the latent intercept and slope variables. These mediational pathways are of particular interest because they may help explain the process or mechanism by which hypothesized predictor variables impact long-term symptomatic outcome.
This aspect of the research requires consideration of how to best evaluate whether mediation is occurring. The next section contains a brief overview of the mediation model for a single mediator and the regression equations which underpin it, followed by a description of the most widely used method of assessing mediation and its limitations, concluding with a recommended approach to establishing the presence of mediation.

6.1 The Single Mediator Model

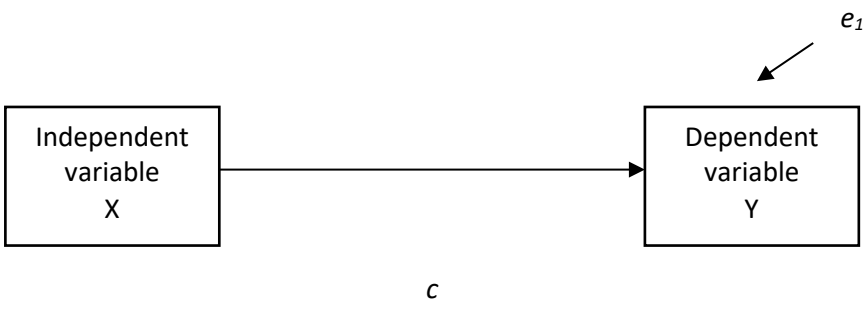
The three commonly used approaches to statistical mediation analysis, namely; (i) causal steps (Baron & Kenny, 1986; Judd & Kenny, 1981a, 1981b); (ii) difference in coefficients and (iii) product of coefficients (MacKinnon, 2004) , all use information from three regression equations:

$$Y = i_1 + cX + e_1 \qquad 6.1$$

$$Y = i_2 + c'X + bM + e_2 \qquad 6.2$$

$$M = i_3 + aX + e_3 \qquad 6.3$$

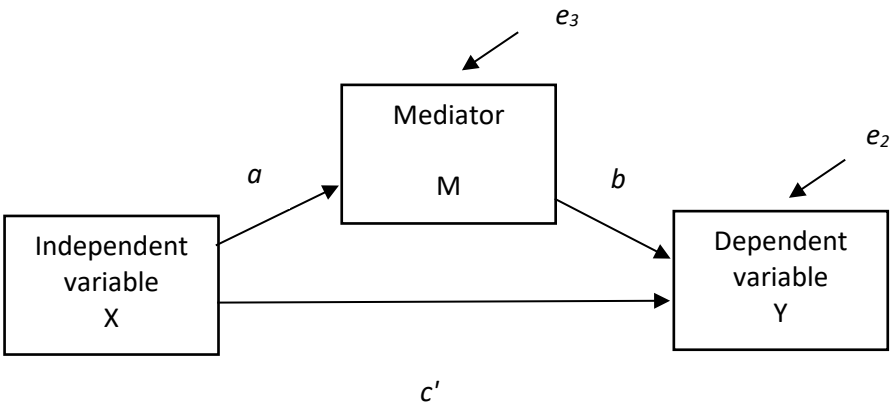
Depicted in Figure 6.1 is equation 6.1, which represents the simplest model of the relationship between one variable and another. Figure 6.1 is an example of a total effects model, where the relationship of X to Y is represented without consideration of the effects of other variables. The arrow in the diagram indicates that X (the independent variable) predicts Y (the dependent variable); this path is represented by the symbol c. The coefficient e_1 represents variation in Y that is not accounted for by X. The symbol i_1 is the intercept.



$$Y = i_1 + cX + e_1$$

Figure 6.1. Path diagram and equation for X → Y regression model

The mediation model depicted in Figure 6.2 adds a third variable to the X to Y relationship. This model depicts equations 6.2 and 6.3. In Figure 6.2, the independent variable (X) is related to the mediating variable (M), which is correspondingly related to the dependent variable (Y). There is also a relationship of X to Y that is not mediated by M; this is the *direct effect* of X on Y, denoted by the symbol c'. This c' coefficient adjusts for the presence of the mediator (M), and is a partial regression effect. The path between the X and M variable is denoted by the symbol a, and the path between M and Y is denoted by b, a partial effect which adjusts for the effect of the independent variable X on Y. The coefficient e_2 represents variation in Y that is not accounted for by its relationship with X and M, and e_3 represents variation in M that is not accounted for by X. The intercepts i_2 and i_3 are not used to compute mediation effects, however they are included in the equations for completeness.



$$Y = i_2 + c'X + bM + e_2$$
$$M = i_3 + aX + e_3$$

Figure 6.2. Path diagram and equations for the mediation model

6.1.1 Causal Steps Approach to Mediation

Of the three main approaches to statistical mediation analysis, the most widely used method is the causal steps approach advocated by Baron and Kenny (Baron & Kenny, 1986), and Judd & Kenny (Judd & Kenny, 1981b). This approach is based on testing hypotheses consistent with mediation, and consists of a series of significance tests of the a, b, c and c' regression coefficients detailed above. Four steps are involved in the causal steps approach:

Step 1: The independent variable (X) must significantly predict the dependent variable (Y) in equation 6.1 (i.e. path ***c*** in Figure 6.1). The main purpose of this test is to show that there is an effect to mediate, therefore if this path is non-significant, the mediational analysis stops.

Step 2: The independent variable (X) must significantly predict the mediator (M) in equation 6.3 (i.e. path a in Figure 6.2);

Step 3: The mediator must significantly predict the dependent variable (Y) when the independent variable (X) is also accounted for in equation 6.2 (i.e. path b in Figure 6.2). If the mediator is unrelated to the dependent variable (Y), then it makes sense that the effect of the independent variable on the mediator cannot be transmitted to the dependent variable.

Step 4: The direct effect of the independent variable (X) on the dependent variable (Y) must be non-significant (i.e. path c' in Figure 6.2), when taking into account the mediator (M). This step is required by (Judd & Kenny, 1981b) to fulfil the requirement for mediation, but not by (Baron & Kenny, 1986), whose approach allows for partial mediation, where the c coefficient (i.e., the total effect, relating the independent variable to the dependent variable) is statistically larger in absolute value than the c'coefficient (i.e., the direct effect, relating the independent variable to the dependent variable whilst accounting for effect of the mediator). This partial mediation permits the c' coefficient to be significant, and is likely to be more realistic, since complete mediation is an unlikely scenario in psychiatric research domains such as this, where symptoms and behaviour are likely to have a variety of causes (Judd & Kenny, 1981a).

Most analysts assert that only steps 2 and 3 in the causal steps approach are essential to establish the presence of mediation (Kenny, 2009). Thus this approach stipulates that the X to M relation (path a), and the M to Y relation (path b) are each statistically significant in order to meet the requirement for mediation. Shrout and Bolger (Shrout & Bolger, 2002) recommend that step 1 should not be applied where the total effect between X and Y (i.e., path c) is, *a priori*, expected to be small. This is likely to occur where the outcome (Y) is very distal to both the independent variable (X) and the mediator (M).

Furthermore, the test described in step 1 is regarded as controversial because it is possible for the relation between the independent variable (X) and dependent variable (Y) (i.e., the total effect, as represented by c in equation 6.1) to be non-significant, yet for substantial mediation to exist (MacKinnon, 2008). This may occur because the statistical power for the test of the mediated effect is greater than the statistical power of the test for the overall relation of X on Y in some situations. This phenomenon is known as inconsistent mediation and occurs where at least one mediated effect has a different sign to other mediated or direct effects in the model.

Inconsistent mediation is more common in multiple mediator models where mediated effects have different signs (MacKinnon, Fairchild, & Fritz, 2007). An example of inconsistent mediation in a multiple mediation model is given by Salthouse (Salthouse, 1984) where there is a non-significant relation between age on typing proficiency, because of two opposing mediational processes. In this example, age (X) increases reaction time (M_1), which has a

negative effect on typing proficiency (Y), whilst age (X) also increases cognitive skills (M_2), which improves typing proficiency (Y). In this case, the overall relation between age and typing proficiency is non-significant because of opposing mediational processes.

MacKinnon (MacKinnon, 2008) points out that the additional conditions imposed by steps 1 and 4 may be important in some situations. For instance, if the researcher is only interested in direct and mediated effects of the same sign, then step 1, which requires a significant effect of X on Y, is important. Furthermore, the interpretation of the mediated effect is also clearer if there is evidence for total mediation, as per step 4 in Judd and Kenny's (Judd & Kenny, 1981b) approach.

6.1.2 Other approaches to statistical mediation

There are two other approaches to statistical mediation. They rely on information derived from equations 6.1 to 6.3, are the 'difference in coefficients' method and the 'product of coefficients' method (MacKinnon, 2004). The 'difference in coefficients' method calculates the size of the mediated effect of X on Y (also known as the indirect effect) by calculating the difference between the total effect (c) and the indirect effect (c') in equations 6.1 and 6.2, that is ($c - c'$). Conceptually, this corresponds to the reduction in the independent variable effect on the dependent variable when adjusted for the mediator.

The 'product of coefficients' method (ab), on the other hand, calculates the product of the a and b coefficients in equations 6.2 and 6.3 to produce the mediated (indirect) effect. The rationale behind the ab method is that mediation depends on the extent to which the independent variable affects the mediator (coefficient a) and the extent to which the mediator affects the dependent variable (coefficient b).

Both the (ab) and ($c - c'$) mediational measures have been demonstrated to be algebraically equivalent for normal theory least squares and maximum likelihood estimation of the three mediation regression equations (MacKinnon, Warsi, & Dwyer, 1995). The two are only approximately equal for logistic regression, survival analysis and multilevel models due to different standardization across mediation regression equations (MacKinnon, 2008). For such models, it has been suggested that it is inadvisable to directly compute the total effect (c) from step 1; rather, the total effect should be inferred from ($c' + ab$) (Kenny, 2009)

6.1.3 Standard Error of the Mediated Effect

As described above, both the (ab) and ($c - c'$) values provide an estimate of the indirect (mediated) effect. The most commonly used method of testing the statistical significance of an indirect effect is to divide the estimate of the indirect effect by its standard error and compare the resulting z statistic with a critical value from the standard normal distribution (MacKinnon et al., 2004). Several alternative formulas for the standard error of (ab) and ($c - c'$) are available to test statistical significance and to construct confidence intervals for these estimates (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Standard errors based on (ab) are referred to as product of coefficient standard errors, and standard errors based on ($c - c'$) are referred to as difference in coefficients standard errors.

A commonly reported standard error of the mediated effect is the asymptotic formula for the (ab) product derived by Sobel (Sobel, 1982) using the multivariate delta method based on a first order Taylor series approximation. This method is probably the least biased of several formulas which compute the standard error of the mediated effect (MacKinnon & Dwyer, 1993; MacKinnon et al., 2002; MacKinnon et al., 1995), however evidence will be presented below that demonstrates that confidence limits based on these values do not perform well. The formula for Sobel's standard error is presented in equation 6.4:

$$\sigma_{ab\ first} = \sqrt{a^2\sigma_b^2 + b^2\sigma_a^2} \qquad 6.4$$

In this formula, σ_a^2 represents the squared standard error of coefficient a, and σ_b^2 represents the squared standard error of coefficient b. To test for significance, the value of the ab product is divided by the standard error of the product presented in equation 6.4; if the absolute value of the ratio exceeds 1.96, then the mediated effect is regarded as significantly different from zero at the 0.05 level of significance.

Because ab is algebraically equivalent to ($c - c'$), this standard error can also be used to calculate significance and symmetric confidence intervals for ($c - c'$) (MacKinnon, 2008). The standard error formula of ($c - c'$) usually gives very similar results to equation 6.4, however equation 6.4 is easier to compute and can be generalised to more complicated models. Equation 6.4 is the formula used in any covariance structure programs such as MPlus (L. K.

Muthén & Muthén, 1998-2011) (see p.613) and LISREL (Joreskog & Sorbom, 1993) to compute standard error estimates for mediated effects.

Symmetric confidence limits for the mediated effect can be calculated using equation 6.5:

$$ab \pm z_{1-\omega/2} * \sigma_{ab} \qquad 6.5.$$

where $z_{1-\omega/2}$ is the value of the z statistic on the standard normal distribution for a given level of confidence (e.g., 1.96 for 95% confidence intervals, assuming a large sample size) (MacKinnon et al., 2004). The increasing movement towards the use of confidence intervals has been attributed to a number of factors: firstly, it compels researchers to consider the magnitude of the effect, along with its statistical significance; secondly, the confidence interval carries a valid interpretation regarding probability; and thirdly, a wide confidence interval conveys the inherent inaccuracy in the value of the effect, suggesting that it may not easily be replicated (Krantz, 1999).

6.1.4 Significance Testing in Mediation: Issues and Solutions

As described above, one method of testing for statistical significance of the mediated effect (i.e. the ab product) is to divide the estimate of the mediated effect by its standard error and compare the value to tabled values of the normal distribution. A second method of determining whether a mediated effect is significantly different from zero is to assess whether zero is included in the confidence interval; if so, then the effect is regarded as non-significant. A third variant is to jointly assess whether the a coefficient is statistically significant (i.e. step 2 in the causal steps approach), and whether the b coefficient is statistically significant (i.e. step 3 in the causal steps approach), though this method does not yield confidence intervals, nor does it provide a test of the ab product.

In results obtained from a simulation study by MacKinnon, Lockwood, et. al. (MacKinnon et al., 2002), it was discovered that their evaluation of 14 tests for mediation yielded considerable differences in Type 1 error rates and statistical power. In particular, the requirement in step 1 of the widely used Baron & Kenny causal steps approach (that a significant relation between X and Y exists) severely reduced power to detect mediation, especially where mediation was complete (i.e., the direct effect, c', was zero). Lower power was also observed for those

mediational tests based on dividing an estimator of the mediational effect (for instance, $c - c'$ and/or ab) by the corresponding standard error, such as the formula shown in equation 6.4.

The main reason identified was that the ratio of the estimate to its standard error often failed to follow a normal distribution, hence these methods of assessing statistical significance were frequently inaccurate. Furthermore, confidence intervals based on the normal distribution for the mediated effect were often incorrect, with the discovery made by earlier simulation studies that intervals tended to lie to the left of the true value for positive mediated effects (for example, where the a and b coefficients were both positive or both negative), and to the right for negative mediated effects (where either of the a and b coefficients was positive and the other negative) (MacKinnon et al., 1995; Stone & Sobel, 1990).

The most important conditions for mediation identified by MacKinnon, Lockwood et. al. (MacKinnon et al., 2002) in their simulation study were that: (i) the a coefficient in step 2 and (ii) the b coefficient from step 3 are each statistically significant, i.e., the third variant of significance testing described above. This approach was found to offer the most power and most accurate Type I error rates compared with other tests of mediation. However, as noted earlier, there is no parameter estimate or standard error of the mediated effect directly available with this method, which means that effect sizes and confidence intervals cannot be readily calculated. Therefore, the authors of this study suggested using other tests that are close to the joint significance test in accuracy, such as asymmetric confidence intervals. Unlike symmetric confidence intervals, the lower and upper bounds of asymmetric confidence intervals are not equidistant from the point estimate of the mediated effect.

A later simulation study (MacKinnon et al., 2004) demonstrated that asymmetric confidence intervals based on the (i) distribution of the ab product or (ii) bootstrap resampling estimation (each of which has fewer distributional assumptions) were more accurate than traditional mediation analysis, since the mediated effect does not always follow a normal distribution. However, the study found that confidence intervals based on the distribution of the product were still imbalanced. Two potential explanations were offered. Firstly, there was the possibility that the appropriate comparison distribution is the product of two t distributions rather than two normal distributions, and that the distribution of the product of two variables with t distributions may be more complex than the distribution of the product of two normal variables. Secondly, it was suggested that the discrepancy might be due to a

combination of sampling variability of the a and b estimates, and the different shape of the distribution of the product for each different combination of a and b (MacKinnon et al., 2004).

The study authors recommended resampling as the optimal method of analysis if raw data are available, with one caveat: not all resampling methods represent an improvement over distribution of product methods, and hence caution is required in selecting an appropriate method. Resampling methods are discussed in detail below, along with a recommendation regarding the optimum resampling procedure. Alternatively, if the researcher does not have access to the raw data for analysis, thus ruling out the use of resampling methods, then single sample tests that use the distribution of the ab product to create confidence intervals and test the significance of the results were recommended as the best methods.

6.1.5 Bootstrap Sampling

Resampling methods are generally regarded as the technique of choice when assumptions underlying statistical methods fail to be met. An advantage of resampling methods such as bootstrapping in testing mediated effects is that they generally have more accurate Type I error rates and more statistical power than single sample methods based on the normal distribution (MacKinnon, 2008). The bootstrap method consists of randomly sampling, with replacement, from N observations in an original sample, so that a new sample of N observations is obtained and a mediated effect estimated, and then this procedure is repeated many times. For example, in a bootstrap analysis of a mediated effect with an original sample of N=250, a new sample of N=250 is generated, with replacement from the original sample, and a mediated effect is estimated for this new sample. Since sampling is with replacement, it is possible for a particular observation to be represented multiple times in this and any given bootstrap sample. A second sample of N=250 is then generated from the original sample (again with replacement), and a mediated effect is estimated for this second sample. This process is repeated, with at least 1000 replications usually required to compute confidence intervals (Efron & Tibshirani, 1993).

The mediated effect obtained from each of the 1000 replications forms a distribution of mediated effect estimates, from which standard errors and 95% confidence intervals for the mediated effect are obtained. The simplest form of bootstrapping is the percentile bootstrap where the 95% confidence interval is obtained by finding the values of the mediated effect at

the 2.5th and 97.5th percentile in the distribution of mediated effects. Bootstrapped confidence intervals take non-normality of the mediation effect into account, hence are not necessarily symmetric around the point estimate of the mediated effect (L. K. Muthén & Muthén, 1998-2011) (p.613). The bias-corrected bootstrap corrects for bias in the central tendency of the estimate and is more complex than the percentile bootstrap described above. It consists of adjusting each bootstrap sample for potential bias in the estimate of the mediated effect; the difference between the observed sample mediated effect and the average mediated effect in the bootstrap distribution is used to correct the percentiles in the bootstrapped distribution (MacKinnon, 2008).

The performance of six resampling methods was evaluated by MacKinnon et al. (MacKinnon et al., 2004) in response to the identification of non-normal distribution of indirect effects by earlier research (MacKinnon et al., 2002). More accurate confidence limits were obtained using resampling methods, as compared with methods based on an assumed normal distribution. Of the six resampling methods, which included the jacknife, percentile bootstrap, bias-corrected bootstrap, bootstrap-*t*, bootstrap-*Q* and Monte Carlo, the bias-corrected bootstrap was identified as the best overall. The bias-corrected bootstrap also had Type 1 error rates close to the nominal level, together with more power than the other methods (MacKinnon et al., 2004). It was also suggested as being appropriate in adjusting for severely non-normal data. The bias-corrected bootstrap is recommended as the method of choice in the analysis of indirect effects.

6.1.6 Assumptions of Mediation

There are several assumptions underlying mediation analysis. MacKinnon, Fairchild & Fritz (MacKinnon et al., 2007) identified the following assumptions for tests of mediation:

(i) independence of the residuals in equations 6.2 and 6.3, and also independence of the mediator (M) and the residual in equation 6.2 (McDonald, 1997; Merrill, 1994);

(ii) no interaction between the independent variable (X) and the mediator (M) in equation 6.3; this issue is further addressed in the following Section 6.1.7 'Other third-variable effects';

(iii) no misspecification of causal order (e.g., Y-> M-> X as opposed to X-> M -> Y) ;

(iv) no misspecification of causal direction (e.g., the existence of reciprocal causation between the mediator (M) and the dependent variable (Y));

(v) no misspecification due to the omission of variables that cause variables in the mediation analysis, and;

(vi) no misspecification due to imperfect measurement.

MacKinnon et. al. (MacKinnon et al., 2007) highlight the difficulty in testing these assumptions, and point out that they may in fact be untestable in most situations, so that absolute proof of mediation is impossible. Selected points will now be elaborated. Regarding point (iii), misspecification of causal order, this is usually difficult to defend if the study design is cross-sectional, since the temporal precedence of the variables is unclear due simultaneous measurement. One of the benefits of longitudinal designs noted by MacKinnon and colleagues (MacKinnon et al., 2007) is that these designs allow particular aspects of mediation models to be examined that are not possible in cross-sectional designs, including whether there is evidence for one of the important conditions of causality, temporal precedence. Point (v) refers to the assumption that no variables that affect the mediation model are omitted, since the omitted variables may account for a mediated effect. Such omitted variables may include unmeasured moderators and mediators. MacKinnon (MacKinnon, 2008) suggests that the best a researcher can do is to measure and include in the model as many of these variables as possible, in addition to considering the possible effects of unmeasured, omitted variables, and hope that these omitted effects exert only random or small effects on the mediation process.

Point (vi) relates to measurement error and its potential to invalidate observed relationships between variables, underlining the importance of data with high reliability. This can be a particularly difficult issue in mediation analysis, since measurement error in the independent variable (X) leads to attenuated effects between X and the mediator (M) (i.e., the a path), and error in the mediator leads to attenuated effects between the mediator (M) and the dependent variable (Y) (i.e., the b path), thus the a and b coefficients are reduced as reliability of the measures decreases (Hoyle & Kenny, 1999). Crucially, as unreliability in the mediator increases, the c' path (i.e., the direct effect of X on Y, adjusted for the mediator M) is overestimated and the b path is underestimated, thereby inflating the size of the direct effect and reducing the size of the mediated effect. An advantage of latent variable models is that they improve reliability, thus the use of latent variables to measure mediators improves the accuracy of mediated effect measurement (MacKinnon, 2008).

A further assumption of mediation analysis is identified by MacKinnon (MacKinnon, 2008); that the observed mediation relationship represents the true underlying relationship among the variables. There are a number of ways that the relationships between X, M and Y may not be what they appear to be. This leads into the next section which deals with third-variable effects that are distinct from mediated effects.

6.1.7 Other Types of Third-Variable Effects

It is important to recognise that there are other possible interpretations apart from the 'mediated variable' effect, when considering the effect of a third variable on the relationship between an independent variable (X) and dependent variable (Y). Three types of other third-variable effects include confounder, covariate and moderator effects. The way in which a mediated effect differs from these other third-variable effects hinges on the defining characteristic of the mediator, which explains and identifies the causal process underlying the relationship between two other variables, such that the independent variable is hypothesised to *cause* the mediating variable, which in turn is hypothesised to *cause* the dependent variable (MacKinnon, 2004). It is contended that in many instances, it may not be possible to completely distinguish between mediation and other third-variable effects, with additional supporting information (such as theory) required in order to build a case for mediation (MacKinnon, 2008). These three-types of other third-variable effects are briefly described in turn:

Confounder effects

A confounder is a variable that changes the observed relationship between X and Y not because it is in a causal sequence relating X to Y, but because it is related to both these variables (MacKinnon, 2004). This is distinct from mediation, which explains the effect because the independent variable (X) causes the mediating variable, in turn affecting the dependent variable (Y). Whilst the conceptual distinction between confounder and mediator effects is clear, Mackinnon points out that it can be difficult to differentiate between both types of effects with actual data. The underlying causal sequence is the important aspect of the mediating variable.

Covariate effects

A second possibility is that along with the independent variable (X), the third variable is another predictor of Y, such that both it (the third variable) and X, predict Y. In this situation, the third variable will improve the prediction of Y since it accounts for additional variability in Y, but if the third variable is only minimally related to X, as is typically the case, then the analysis will not change the relationship between X and Y. These types of third variables are known as covariates (MacKinnon, 2008). The main way in which a confounder differs from a covariate is that the former is related to X and Y in such a way that taking the confounder into account changes the relationship between X and Y.

Moderator effects

Like confounder effects, moderator third-variable effects do not transmit the effect of X on Y, and are similarly not part of a causal sequence relating X to Y. Rather, the effect of X on Y in moderator effects varies according to different levels of the moderator, such as in interaction effects. Therefore, in this type of third-variable effect, the form of the relationship between the independent variable and dependent variable is changed, similar to confounder effects. Mediators are considered more interesting than moderators, because they address the mechanisms involved in an effect; moderators on the other hand simply provide information on when effects are present (MacKinnon, 2008).

Moderated mediation

Mediation effects may differ for different subgroups defined by variables within the mediation model or outside it (MacKinnon et al., 2007). One of the assumptions underlying mediation analysis is that there is no interaction between the independent variable (X) and the mediator (M), such as that observed with moderator third-variable effects. However, a statistically significant X×M interaction will not negate mediation findings but may provide additional information about a mediated effect (MacKinnon, 2008). However, analysis of mediation effects is complicated when the effects of a mediator is moderated by another variable (Tein, Sandler, MacKinnon, & Wolchik, 2004).

Mediation models that include moderators have a number of limitations. For example, obtaining sufficient power to detect interaction effects usually requires very large sample sizes or effect sizes (Aiken & West, 1991). Furthermore, heterogeneous variances across different levels of the moderator may impact on the accuracy of mediation results, and assumptions

regarding causal relationships are more complex. For instance, some effects may be present only at particular values of the moderator. Additionally, the presence of measurement error can seriously distort effects of moderators. Moderators measured on a continuous scale introduce additional complexities due to the large number of values in the moderator. Models that combine mediators and moderators are inherently complex, and render interpretation difficult. It may not be practical to test for moderation in complicated mediation models. Detection of moderated mediation is beyond the scope of this thesis, with the focus on analysis of simple mediation effects.

6.1.8 Multiple Mediators

Since symptoms and behaviours are likely to have a variety of causes, each of which may have a different mechanism of action, multiple mediator models are more likely to provide a comprehensive assessment of mediational effects and to offer a more realistic approach. The modelling in this thesis incorporates and tests for the presence of multiple mediators, including severity of symptoms at admission, and the latent intercept and slope variables which represent the short-term symptom trajectory. The analysis of multiple mediators is a straightforward extension of the single mediator model described above. The causal steps approach has substantial shortcomings with respect to the multiple mediator model, primarily because more than one mediated effect is present, with specific mediated effects through each mediator, and a total mediated effect comprising all of the mediated effects (MacKinnon, 2008).

6.2 Testing of mediation research questions

The presence of mediated effects in this study will be established using the bias-corrected bootstrap, which is recommended as the optimum method (MacKinnon et al, 2004). Estimates of the mediated effect obtained from the bootstrap analysis will be based on the 'product of coefficients' method (ab), which calculates the product of the a and b coefficients in equations 6.2 and 6.3 to produce the mediated (indirect) effect. As indicated previously, the rationale behind the ab product of coefficients method is that mediation depends on the extent to which the independent variable (X) affects the mediator (M), (represented by coefficient a) and the extent to which the mediator (M) affects the dependent variable (Y) (represented by coefficient b).

The bias-corrected bootstrap procedure in software package MPlus (L. K. Muthén & Muthén, 1998-2011) will be implemented for the single and multiple mediator models, using 10,000 bootstrap draws. Bootstrapped standard errors and 95% confidence intervals (which are not necessarily symmetric around the point estimate of the *ab* mediated effect) are particularly appropriate in establishing whether the mediated effect is significantly different from zero, since these asymmetric intervals take non-normality of the mediation effect into account. Statistical significance will be determined by examining whether zero is included in the bias-corrected bootstrap confidence interval; if the interval does not encompass zero, then the result will be regarded as statistically significant.

6.2.1 Logic Behind Mediation Research Questions: An Example

There are four possible scenarios regarding the presence of mediated effects in the latent growth trajectory models presented in this thesis: (i) full mediation; (ii) partial mediation; (iii) inconsistent mediation (for models with more than one mediating variable); and (iv) no mediation. The logic behind these four possible outcomes is demonstrated using a practical example from the second of the latent growth models, Model 2, which was presented in Chapter 5 (Statistical Methods).

One of the research questions in this model concerns whether the effect of symptoms at initial admission (X) on distal long-term symptom levels (Y) is mediated either fully or partly, or not at all, by the short-term symptom trajectory over the 1-year interval subsequent to the initial recovery/stabilisation point of the first psychotic episode, with the STT being represented by the intercept and slope latent trajectory variables (M_1 and M_2). If some form of mediation were to be found, it would imply that symptom severity at admission transmits its effect on long-term outcome solely, or partly, through the short-term change in symptoms following initial recovery. These mediational aspects are of interest because they may help explain the mechanism by which hypothesized predictor variables impact long-term psychopathology levels.

The following overview of the mediator model provides a contextual explanation of the building blocks underpinning this research question. To further this objective, a visual depiction of the mediator model is shown in Figure 6.3. It includes two mediators that come

between the independent variable; admission symptoms, and the dependent variable; long-term outcome.

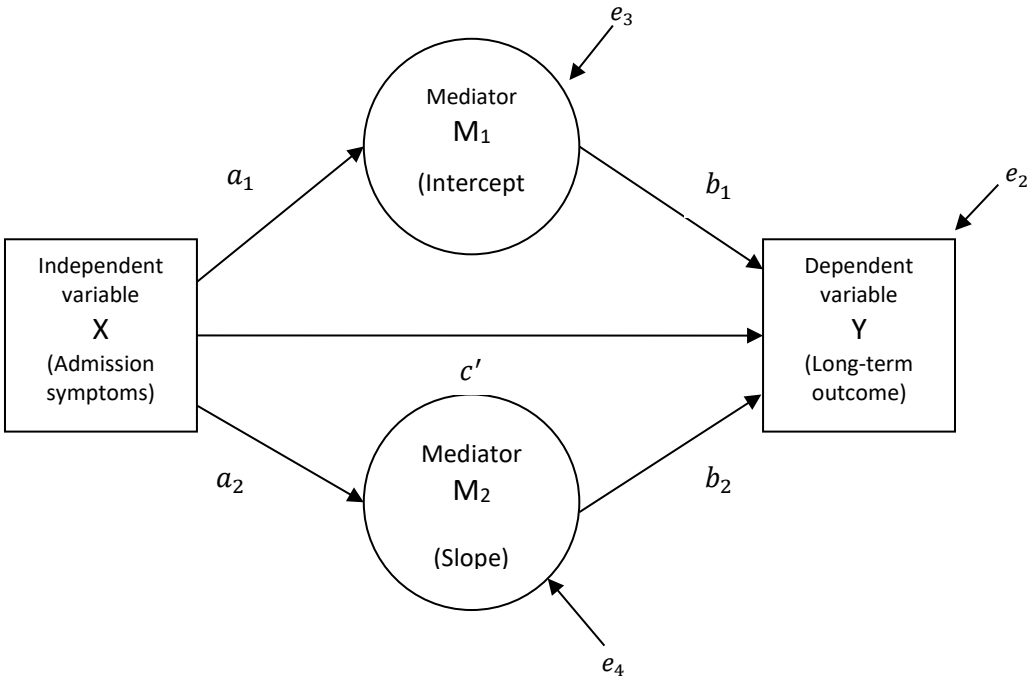


Figure 6.3. Path diagram and equations for the two mediator model.

Four regression equations are used to assess mediation in this two-mediator model:

$$Y = i_1 + cX + e_1 \qquad 6.6$$

$$Y = i_2 + c'X + b_1M_1 + b_2M_2 + e_2 \qquad 6.7$$

$$M_1 = i_3 + a_1X + e_3 \qquad 6.8$$

$$M_2 = i_4 + a_2X + e_4 \qquad 6.9$$

where:

Y is the dependent variable; long-term outcome;

X is the independent variable; admission symptoms;
M_1 is the first mediator; intercept latent variable (i.e., starting point of the short-term symptom trajectory);

M_2 is the second mediator; slope latent variable (i.e., rate of change in the short-term trajectory);

c is the parameter relating the independent variable (initial admission symptoms) and the dependent variable (long-term outcome) in the first equation;

c' is the parameter relating the independent variable (admission symptoms) to the dependent variable (long-term outcome), adjusted for mediators M_1 and M_2 (intercept and slope latent variables);

b_1 is the parameter relating the first mediator (i.e., intercept latent variable) to the dependent variable (long-term outcome) adjusted for the independent variable (admission symptoms) and second mediator M_2 (slope latent variable);

b_2 is the parameter relating the second mediator (slope latent variable) to the dependent variable (long-term outcome) adjusted for the independent variable (admission symptoms) and first mediator M_1 (intercept latent variable);

a_1 is the parameter relating the independent variable (admission symptoms) to the first mediating variable M_1 (intercept latent variable);

a_2 is the parameter relating the independent variable (admission symptoms) to the second mediating variable M_2 (slope latent variable);

e_1, e_2, e_3, and e_4 represent error variability and the intercepts are i_1, i_2 i_3 and i_4

The overall relationship between the independent variable (X) and dependent variable (Y) is termed the *total effect*, and is represented by the parameter c, which corresponds to the change in Y linked to a one unit change in X. The addition of the two mediating variables will potentially provide further information about the mechanisms by which this change occurs. The product of the a_1 and b_1 parameters, a_1b_1, and the product of the a_2 and b_2 parameters, a_2b_2, are the two mediated effects in the model. The relationship of X to Y that is not mediated by M_1 or M_2 is the *direct effect* c', which adjusts for the two mediators and is a partial regression effect. The *total mediated* effect, a_1b_1 plus a_2b_2, is equivalent to the difference between the total effect c and the direct effect c', hence a_1b_1 plus $a_2b_2 = c - c'$. As such, the total mediated effect, a_1b_1 plus a_2b_2, is equal to the difference between the c and c' coefficients, where c is the total effect of X on Y, hence $c = c' + a_1b_1 + a_2b_2$. The total effect c can thus be decomposed into a direct effect c', and two mediated effects a_1b_1 plus a_2b_2.

There are four possible outcomes in the analysis of the mediated effects represented in Figure 6.3 and equations 6.6 to 6.9. Each outcome is defined by a set of conditions:

1. *Full mediation*: this implies that the severity of an individual's symptoms at admission transmits its effect on long-term outcome solely through the short-term change (as represented by the intercept and slope latent variables) that has occurred after initial recovery, and requires:

(iii) Absence of a direct relationship between admission symptoms (X) and long-term outcome (Y) when the mediators (M_1, M_2) are accounted for, and;

(iv) Statistical significance of either or both mediated effects (a_1b_1 and a_2b_2 products) obtained from the bias-corrected bootstrap analysis. Statistical significance will be determined by examining whether zero is included in the bias-corrected bootstrap 95% confidence interval; if the interval does not encompass zero, then the result will be regarded as statistically significant.

2. *Partial mediation*: indicates that severity of symptoms at admission transmits its effect on long-term outcome both directly, and indirectly. The indirect effect is manifested via the impact of admission symptom severity on the short-term trajectory, which in turn transmits the effects on to long-term symptom levels. Partial mediation requires:
   (i) Presence of a direct relationship between initial admission (X) and long-term outcome (Y) whilst accounting for the mediators (M_1, M_2), and;

   (ii) Statistical significance of either or both mediated effects (a_1b_1 and a_2b_2 products) obtained from the bias-corrected bootstrap analysis. Statistical significance of the mediated effects is defined above.

3. *Inconsistent mediation*: when opposing mediational processes occur, at least one mediated effect has a different sign to other mediated or direct effects in the model. Inconsistent mediation processes such as these can result in an overall non-significant relation of the X to Y variable. For instance, if level of admission symptoms (X) positively predicts symptom status at initial recovery (the intercept, M_1), which positively predicts long-term symptom levels (Y), but at the same time, level of admission symptoms (X) negatively predicts the rate of short-term change (i.e., the slope, M_2) that occurs over the 1-year interval subsequent to initial recovery, which then positively predicts long-term symptom levels (Y), then inconsistent mediation is said to occur. In this scenario, the overall relation between level of initial symptoms (X) and long-term symptom levels (Y) may not differ significantly from zero because of these opposing mediational processes.

4. The fourth possibility is *no mediation*. Absence of mediation will be established if both mediated effects (a_1b_1 and a_2b_2 products) obtained from the bias-corrected bootstrap analysis are non-significant. Non-significance is deemed to be met if the 95% confidence intervals obtained from the bias-corrected bootstrap analysis include zero.

The expressions of inconsistent mediation and mediational absence detailed in points 3 and 4 have different implications. If absence of mediation is due to the products of coefficients being non-significant, then the possibility that any effects of X on Y are transmitted via mediating processes can be ruled out. If, however, the evidence points to inconsistent mediational processes, as detailed in point 3, then this would be of interest since the apparent overall zero relation between X and Y is a consequence of these inconsistent effects cancelling each other out.

It should be noted that the product of coefficients method (ab) used in this analysis, which is recommended as the optimum method to establish the presence of mediated effects, differs from the joint significance test employed in the causal steps approach outlined earlier in this chapter. The joint significance test requires that both steps 2 and 3 in the causal steps approach outlined earlier in this chapter must be significant for there to be mediation, thus stipulating that the X to M relation (coefficient a), and the M to Y relation (coefficient b) are each statistically significant in order to meet the requirement for mediation. It is thus possible for the product of the a and b coefficients to be statistically significant (based on bootstrapped standard errors and 95% confidence intervals, which are not necessarily symmetric around the point estimate of the ab mediated effect), and for the joint significance method to be non-significant, and vice versa. As previous research has demonstrated, bootstrapped standard errors and 95% confidence intervals are particularly appropriate in establishing whether the mediated effect is significantly different from zero, since these asymmetric intervals take non-normality of the mediation effect into account.

6.3 Summary of Mediation

Resampling methods are a useful option for models with mediated effects. There is a substantial body of evidence that resampling techniques have greater power and more accurate Type I error rates than single sample methods which assume a normal distribution, an assumption that does not usually hold for mediated effects. Bootstrapped confidence intervals accommodate non-normality of the mediation effect, hence are not necessarily symmetric around the estimate of the mediated effect. The bias-corrected bootstrap has advantages over other forms of resampling, including greater accuracy and statistical power. It is recommended as the method of choice in the analysis of mediated effects.

7 SAMPLE DESCRIPTION

7.1 Study Sample

The study sample consisted of 413 young people consecutively admitted to the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, Australia, between January 1993 and September 1997, who consented to assessment over the course of their first psychotic episode and to follow-up assessment over the 12 months after their illness recovery or stabilisation. Long-term follow-up assessments were subsequently conducted between 5.6 years and 10.6 years following illness remission/stabilisation (T2), with a mean interval of 7.3 years (SD=0.92; median=7.3 years). Figure 7.1 below depicts the study assessment design.

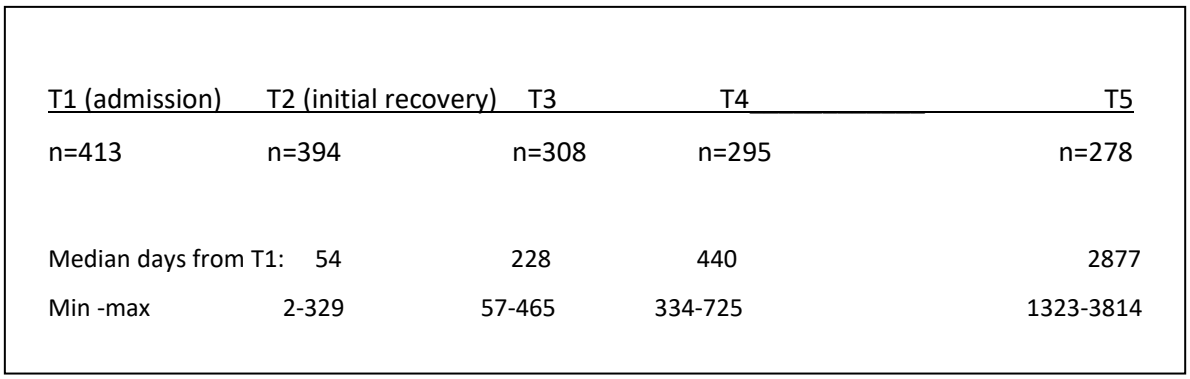


Figure 7.1. Study assessment design, with sample size at each time point, and median days from service admission (T1).

Table 7-1 displays the demographic, illness and clinical characteristics of study participants at baseline. Study participants were predominantly male (n=301; 72.9%), unmarried (n=350; 84.7%), with a mean age of 21.8 years (SD=3.5) at service entry (T1). The mean age at which psychotic symptoms onset was 21.3 years (SD=3.5). Duration of untreated psychosis was highly positively skewed, with a mean of 184.2 days (SD=346.5), and a median of 60.0 days. As for categorical DUP, 16.9% of participants experienced very short duration of untreated psychosis (0-7 days), whilst 12.3% experienced very long duration (over 1 year). The remainder were approximately evenly divided between the intermediate groupings: 21.5% (8-29 days); 21.1% (30-90 days); and 28.1% (3 months-1 year).

The majority of participants were assigned a diagnosis of schizophrenia or schizophreniform disorder (59.1%); the next largest group was affective psychosis (25.7%), followed by

schizoaffective disorder (10.2%), and then other psychotic disorders (5.1%, comprising delusional, psychotic disorder NOS, and brief reactive psychosis). The mean highest average daily dose of neuroleptic medication administered during the initial episode was 281.8 (SD=266.2) in CPZ equivalents, with a median of 200mg.

Table 7-1. Baseline demographic, illness and clinical features of the 413 study participants

Baseline characteristics	Means (SDs) or percentages (n)
Demographics:	
Age at service entry, years:	21.8 (3.5)
Age at onset of psychotic symptoms, years:	21.3 (3.5)
Gender:	
% male	72.9 (301)
Marital status, % never married	84.7 (350)
Education, % post-secondary	30.1 (124)
Work status, %:	
Employed at some level	58.6 (242)
Student	24.5 (101)
Unemployed/Home duties	16.9 (70)
Living alone, %	7.7 (32)
Australian-born, %	81.4 (336)
Illness and Clinical features:	
DSM-IV Diagnosis, %:	
schizophrenia/Schizophreniform	59.1 (244)
affective (Bipolar/Depressive)	25.7 (106)
sSchizoaffective	10.2 (42)
delusional/NOS/brief reactive psychosis	5.1 (21)
Duration of untreated psychosis (DUP; categorical), %	
0-7 days	16.9 (70)
8-29 days	21.5 (89)
30-90 days	21.1 (87)
3 months-1 year	28.1 (116)
Over 1 year	12.3 (51)
Duration of untreated psychosis (DUP) in days:	184.2 (346.5)
Median	60.0
Duration of prodromal symptoms in days[a]:	470.0 (573.3)
Median	245.0
Highest average daily dose of antipsychotics, CPZ equivalence	281.8 (266.2)
Median	200.0
Pre-morbid functioning	0.31 (0.19)
Previous self-harm, %	23.0 (94)
Family history of psychiatric illness, %	60.0 (245)
Illicit drug use, %	
None	24.0 (99)
Occasional/moderate use	36.1 (149)
Problem use/severe problem evident	40.0 (165)
Alcohol use, %	
None	18.9 (78)
Occasional/moderate use	65.4 (270)
Problem use/severe problem evident	15.7 (65)

Baseline characteristics	Means (SDs) or percentages (n)
***Psychopathology at admission (T1)*:**	
BPRS Total score	29.4 (9.4)
BPRS Positive symptom subscale	10.9 (3.7)
SANS	24.2 (14.9)
***Psychopathology at initial recovery (T2)*:**	
BPRS Total score	15.0 (8.6)
BPRS Positive symptom subscale	3.9 (3.7)
Median	3.0
SANS	20.5 (15.0)
Median	18.0
BDI depression severity	8.5 (7.3)
	6.0

[a] Only for the 333 study participants who experienced a prodromal phase

7.2 Positive symptoms

7.2.1 Overall change over time

Table 7-2 presents the observed means, standard deviations and medians of positive symptoms measured at T1 to T5. The positive symptom severity scores range from 0 (no symptoms) to 24 (extremely severe).

Table 7-2. Positive symptoms observed mean (SD) and median scores at T1 (service admission), T2 (initial recovery/stabilisation), T3 (6 months), T4 (12 months) and T5 (7.3 years on average).

Positive Symptoms	T1	T2	T3	T4	T5
mean	10.9	3.9	3.2	3.5	3.6
(SD)	(3.7)	(3.7)	(3.8)	(3.5)	(4.2)
median	11.0	3.0	2.0	2.0	2.0

Figure 7.2 below displays the observed means for positive symptoms at T1-T4. The final assessment point, T5, is not displayed here, as the average interval of 7.3 years is too distal from the preceding time points to allow change in short-term symptoms to be clearly represented. It is important to note that these are only averages, with no indication of the degree of individual variability around the mean values. The substantial drop in severity of

positive symptoms between T1 and T2 is largely due to the administration of antipsychotic medication soon after service admission.

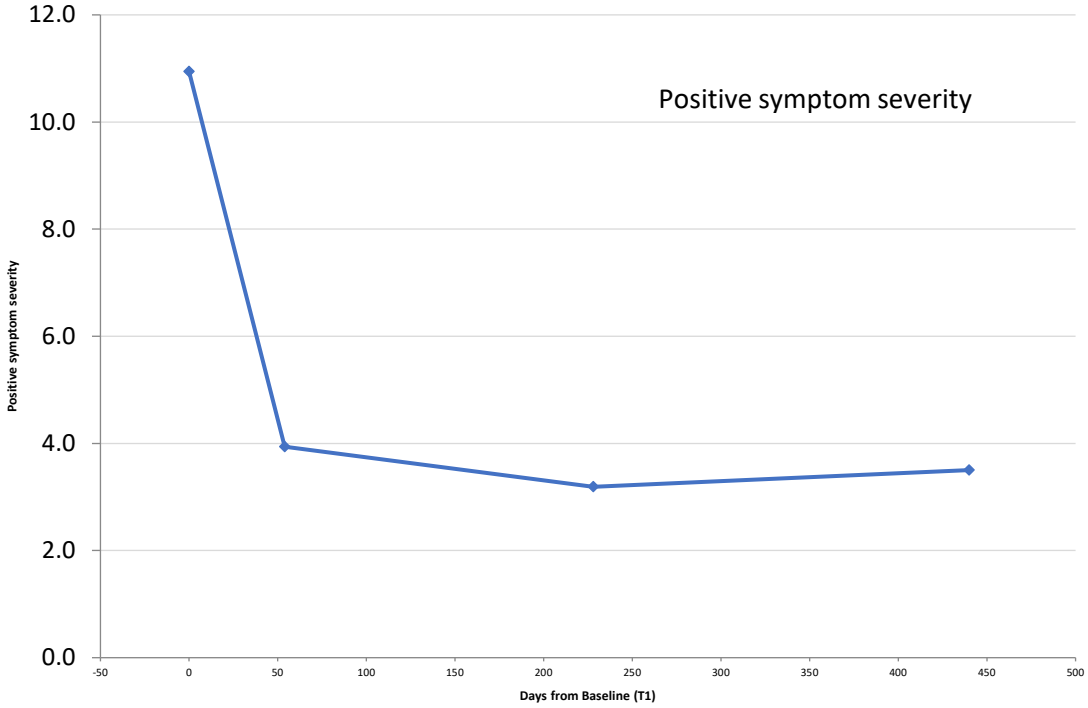


Figure 7.2. Observed means for positive symptoms from T1 (admission) to T4 (12-month follow-up).

7.2.2 Patterns of individual variability over time in positive symptoms

7.2.2.1 T1-T5 trajectories of change

Figure 7.3 displays the individual positive symptom trajectories from T1 to T5 for the 413 study participants. Note how the short-term change between the first assessment point at 0 years (T1: service entry) and approximately 2 years (T4: 12 months after T2 initial recovery/stabilisation) is distorted due to the scale of the x-axis, which extends to up to 10 years. Figure 7.4 and Figure 7.5 will zoom in to show the detail in the short-term change trajectories.

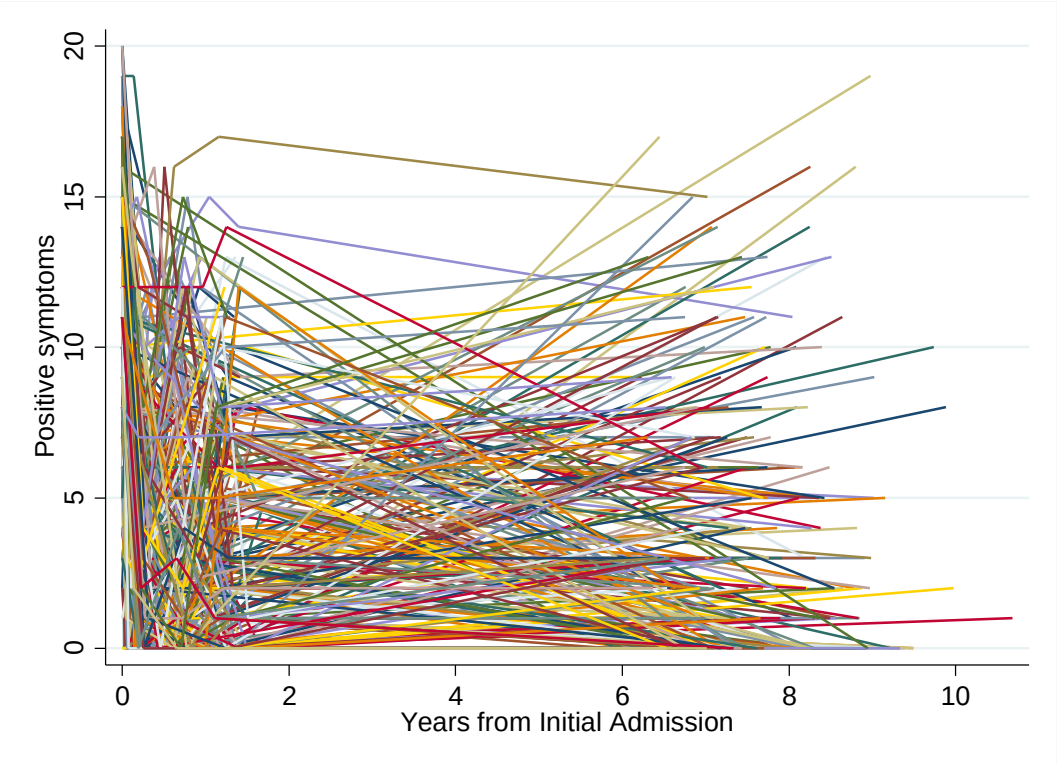


Figure 7.3. Positive symptom trajectories from T1 to T5

7.2.2.2 T1-T4 trajectories of change

Figure 7.4 depicts the individual variability inherent in the evolution of positive symptoms over the short-term follow-up interval across service admission (T1), initial recovery/stabilisation (T2), 6-month follow-up (T3), and 12-month follow-up (T4), presented by baseline DSM-IV diagnosis. Presenting the symptom trajectories by categories such as diagnosis is simply a method of separating out the trajectories and displaying the individual detail more clearly. Inspection of the graph reveals that higher levels of positive symptom severity are apparent at service admission (T1) for the majority of participants, with a general tendency (though not always) towards symptom reduction thereafter.

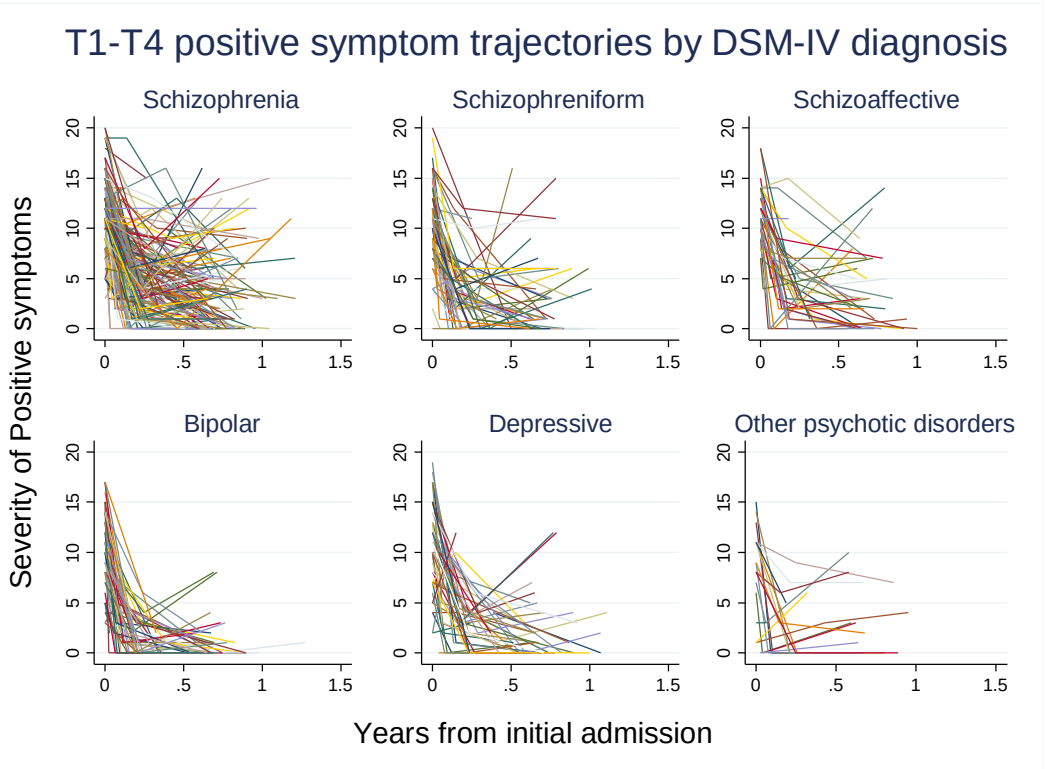


Figure 7.4. Positive symptom trajectories from T1 (admission) to T4 (12-month follow-up).

7.2.2.3 T2-T4 trajectories of change

Figure 7.5 displays the individual short-term trajectories which underlie the T2-T4 latent growth curves used in the LGC models in this thesis. These short-term positive symptom trajectories are presented by baseline DSM-IV diagnostic category in order to display individual detail in symptom change.

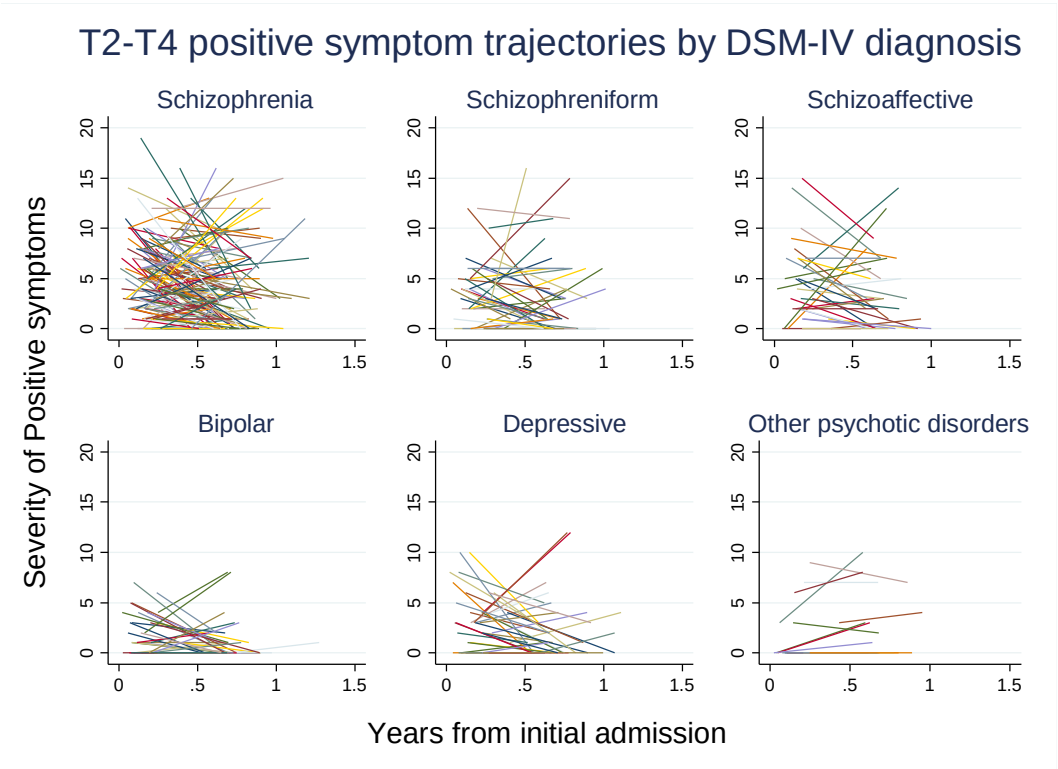


Figure 7.5. Positive symptom trajectories based on assessments at T2 (initial recovery/stabilisation), T3 (6-month follow-up) and T4 (12-month follow-up).

7.3 Negative symptoms

7.3.1 Overall change over time

Table 7-3 presents the observed means for the four SANS subscales, each of which was scaled to a common metric of 0 to 5, where 0 = 'None'; 1 = 'Questionable'; 2 = 'Mild'; 3 = 'Moderate'; 4 = 'Marked'; 5 = 'Severe'. This was done to facilitate comparisons between the four negative symptom subscales, which each contain a different number of items.

Table 7-3. Individual negative symptoms: observed mean (SD) and median scores at T1 (admission), T2 (initial recovery/stabilisation), T3 (6 months), T4 (12 months) and T5 (7.3 years on average).

Symptom measure	T1	T2	T3	T4	T5
Affective flattening:					
mean	0.98	0.90	0.74	0.68	0.57
(SD)	(0.88)	(0.90)	(0.85)	(0.83)	(0.76)
Median	0.86	0.71	0.43	0.29	0.29
Alogia:					
mean	1.0	0.61	0.51	0.53	0.43
(SD)	(0.91)	(0.72)	(0.67)	(0.75)	(0.59)
median	0.75	0.50	0.25	0.25	0.12
Avolition:					
mean	1.23	1.09	1.18	1.12	1.41
(SD)	(1.03)	(0.97)	(1.11)	(1.14)	(1.31)
median	1.00	1.00	1.00	1.00	1.33
Anhedonia:					
mean	1.64	1.60	1.53	1.52	1.99
(SD)	(1.18)	(1.18)	(1.18)	(1.23)	(1.48)
median	1.50	1.50	1.50	1.25	2.00

Figure 7.6 below displays the observed means for the four SANS subscales at T1-T4.

The final assessment point, T5, is not displayed here, as the average interval of 7.3 years is too distal from the preceding time points to allow change in symptoms to be clearly presented. As mentioned previously, it is important to note that these are only averages, with no indication of the degree of individual variability around the mean values.

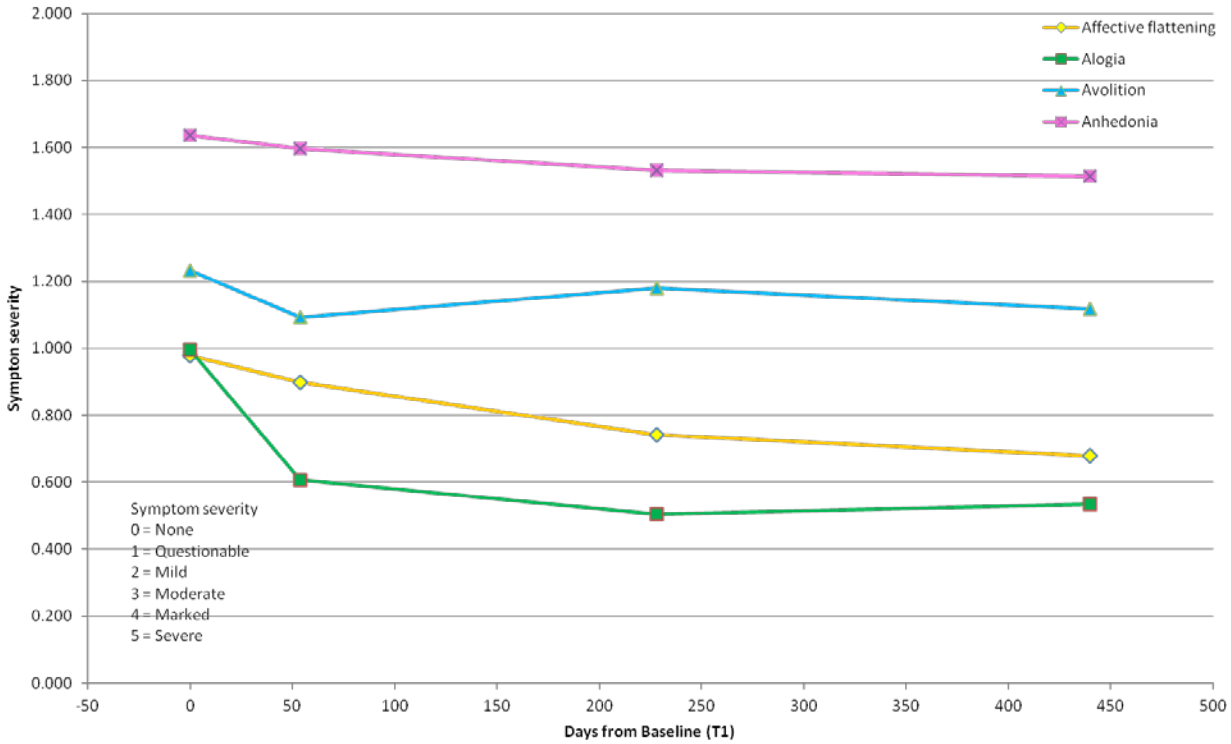


Figure 7.6. Observed means for the four type of negative symptoms from T1 (service admission) to T4 (12-month follow-up).

7.3.2 Patterns of individual variability over time in negative symptoms

7.3.2.1 T1-T5 trajectories of change

Figure 7.7 and Figure 7.8 display the individual negative symptom trajectories from T1 to T5 for the 413 study participants. Similar to positive symptoms, the short-term change between the initial assessment point at 0 years and 2 years (T1-T4) is compressed due to the extended scale of the x-axis. The detail in the short-term change trajectories will be presented in Figures 7.9 to 7.12.

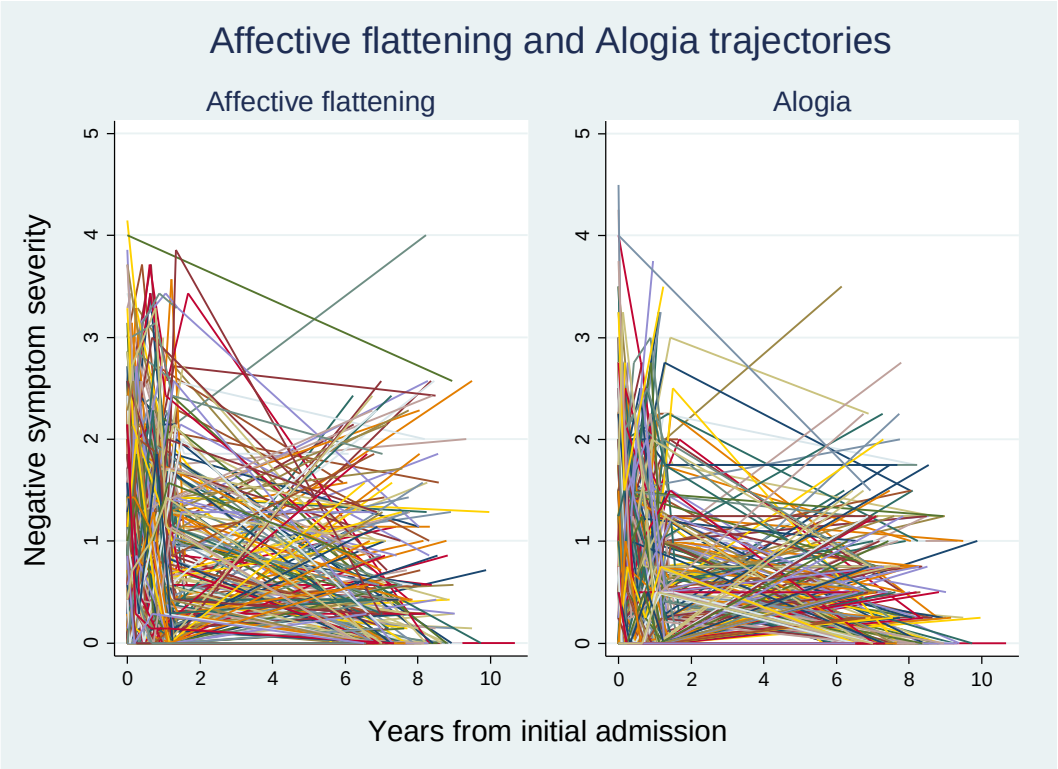


Figure 7.7. Affective flattening and alogia symptom trajectories from T1 to T5

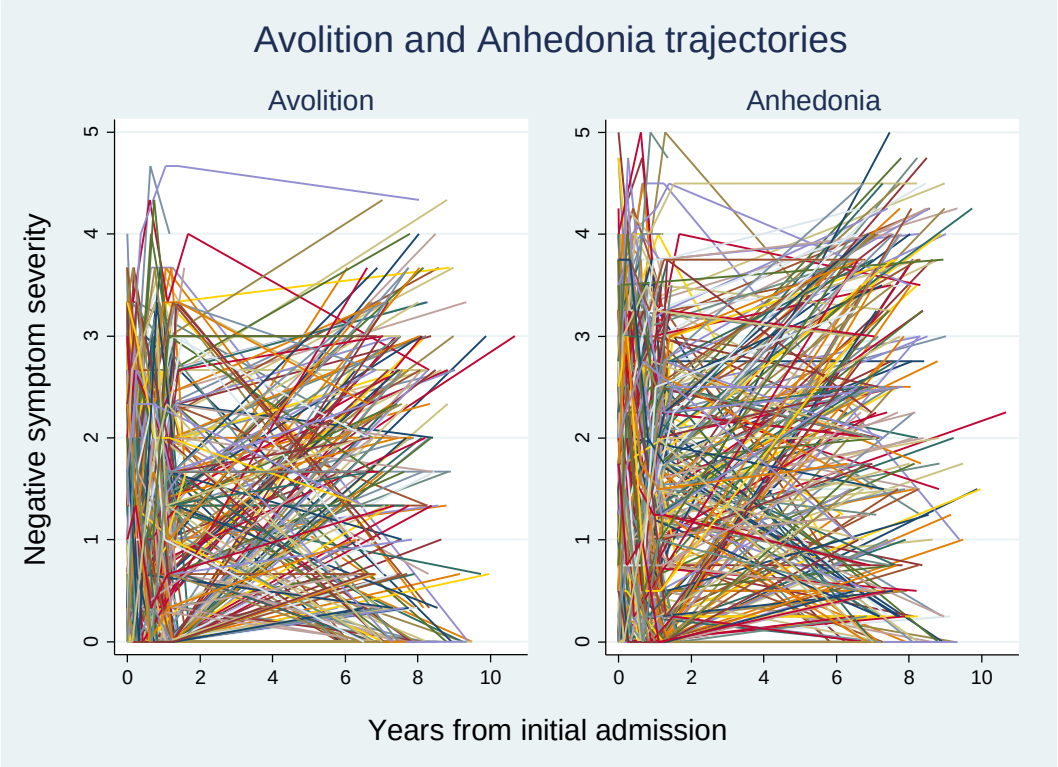


Figure 7.8. Avolition and anhedonia symptom trajectories from T1 to T5

7.3.2.2 T1-T4 trajectories of change

Figure 7.9, Figure 7.10, Figure 7.11, and Figure 7.12 depict the individual variability inherent in the evolution of negative symptoms over the short-term follow-up interval across service admission (T1), initial recovery/stabilisation (T2), 6-month follow-up (T3), and 12-month follow-up (T4), presented by baseline DSM-IV diagnosis. Presenting the symptom trajectories by diagnostic categories separates the trajectories and displays individual detail more clearly. Visual inspection of these graphs indicates that anhedonia appears to have patterns of greater severity compared with the other three negative symptoms.

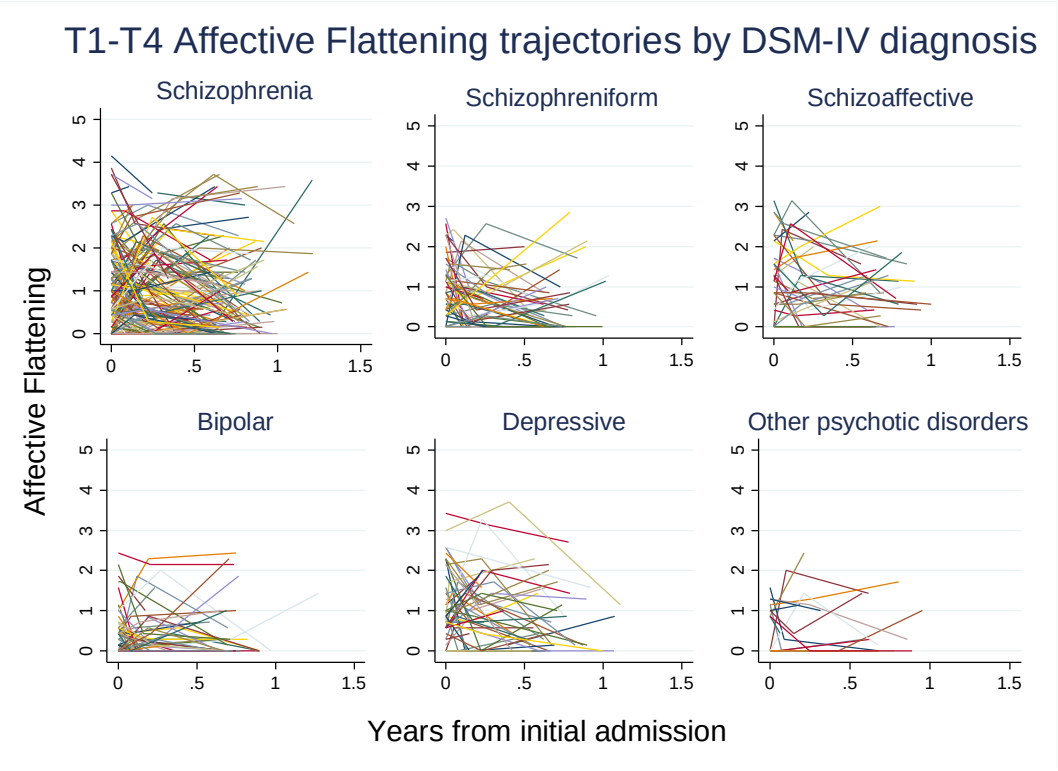


Figure 7.9. Affective flattening trajectories from T1 (admission) to T4 (12-month follow-up).

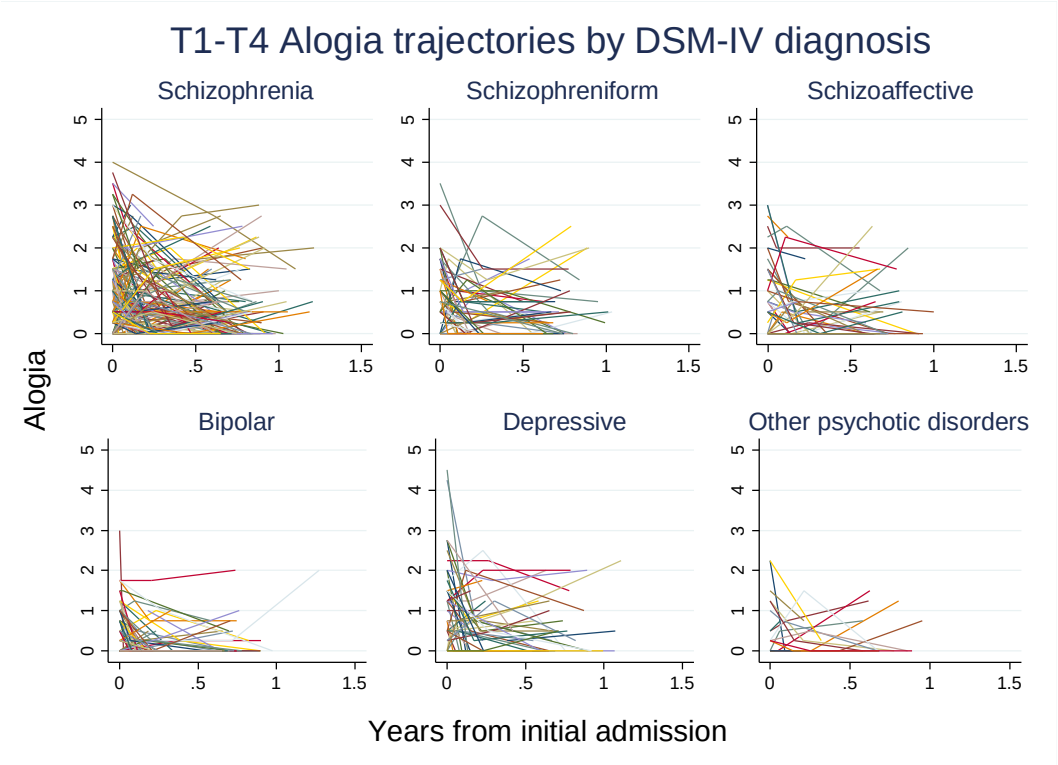


Figure 7.10. Alogia trajectories from T1 (admission) to T4 (12-month follow-up).

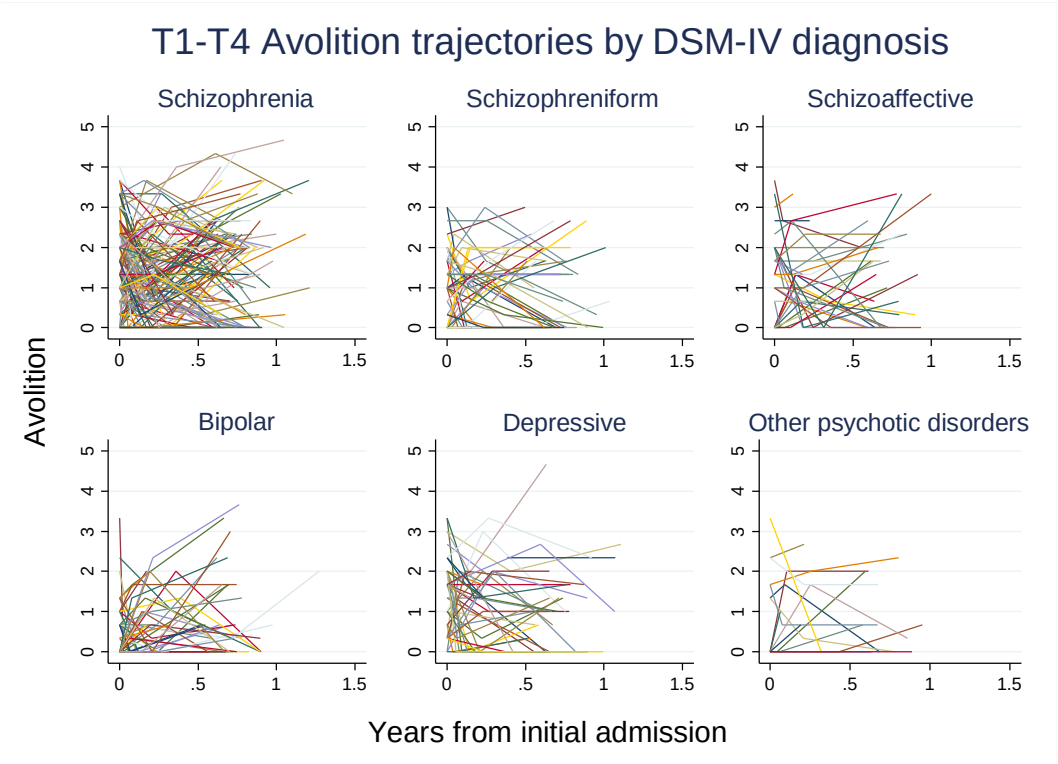


Figure 7.11. Avolition trajectories from T1 (admission) to T4 (12-month follow-up).

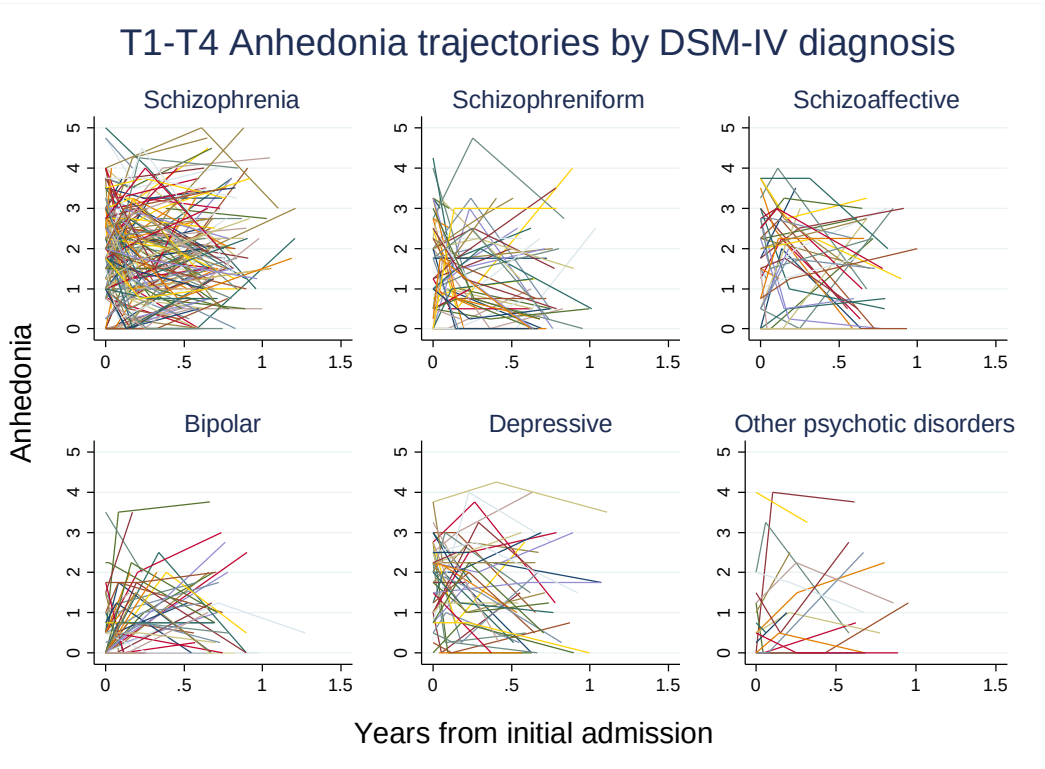


Figure 7.12. Anhedonia trajectories from T1 (admission) to T4 (12-month follow-up).

Figure 7.13, Figure 7.14, Figure 7.15, and Figure 7.16 display the individual short-term trajectories which underlie the T2-T4 latent growth curves used in the LGC models in this thesis. Similar to figures 7.9 to 7.12, these short-term negative symptom trajectories are presented by baseline DSM-IV diagnostic category to display more detail.

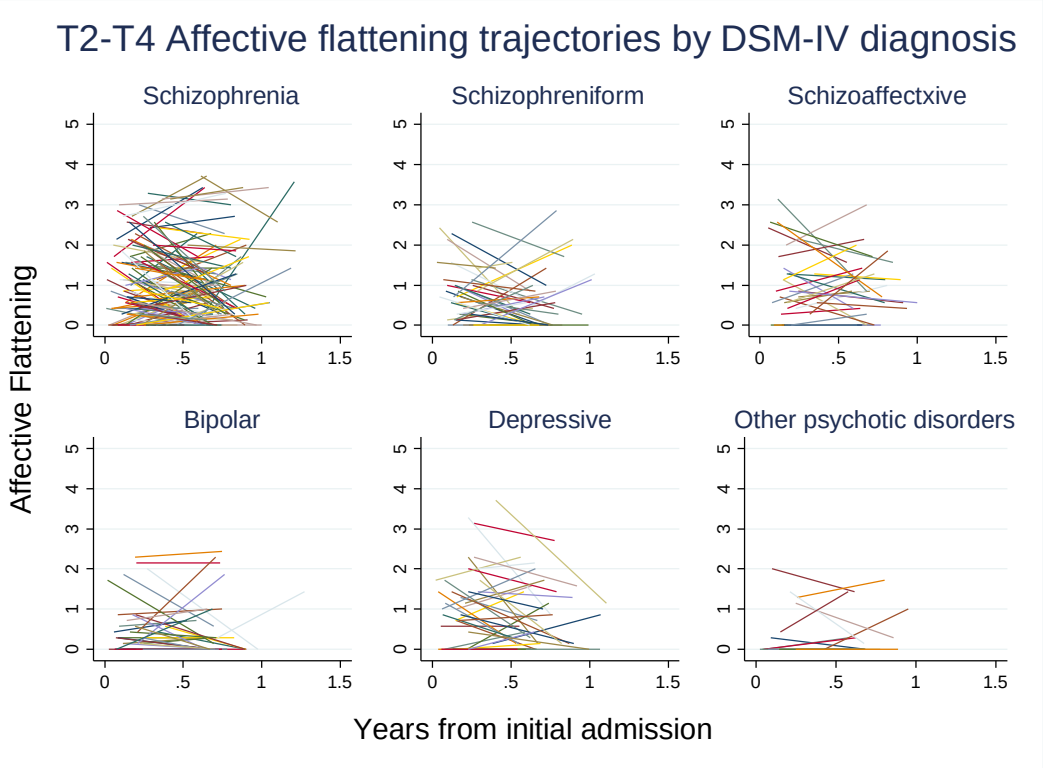


Figure 7.13. Affective flattening trajectories from T2 (initial recovery/stabilisation) to T4 (12-month follow-up).

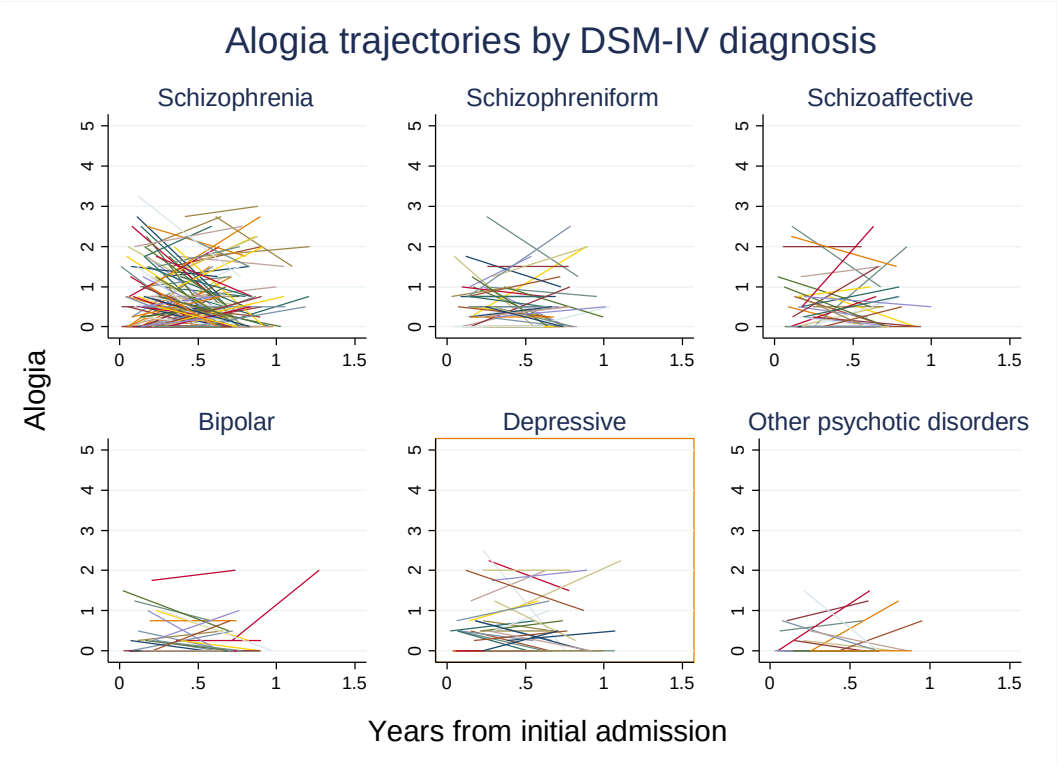


Figure 7.14. Alogia trajectories from T2 (initial recovery/stabilisation) to T4 (12-month follow-up).

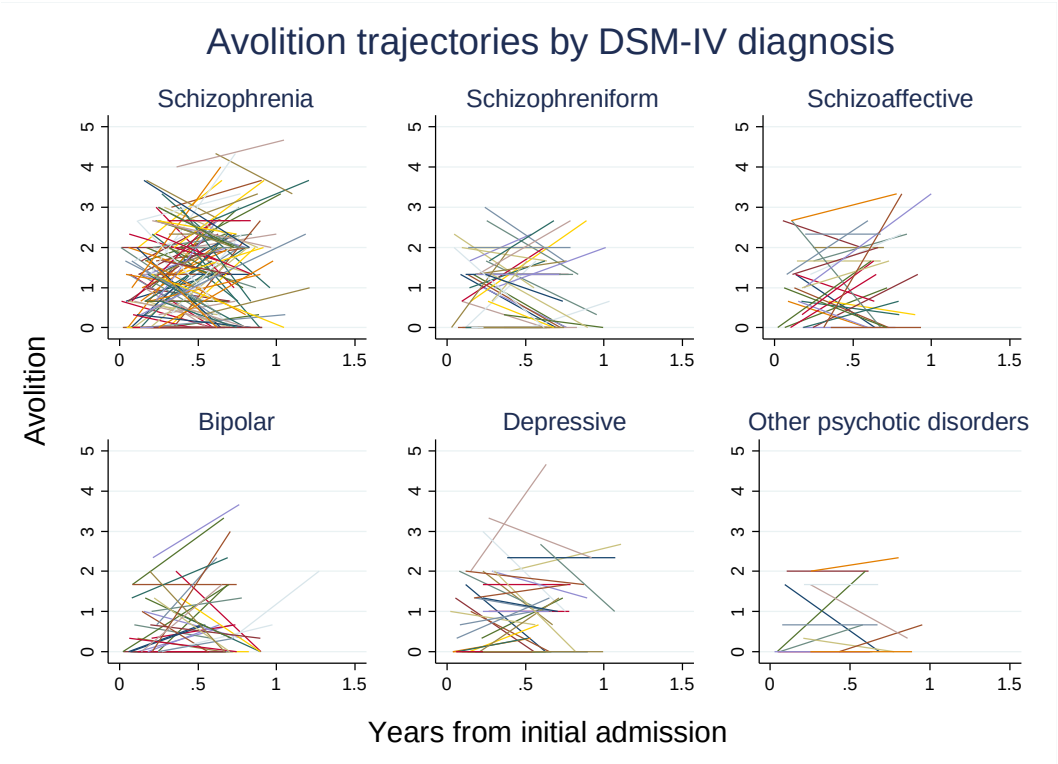


Figure 7.15. Avolition trajectories from T2 (initial recovery/stabilisation) to T4 (12-month follow-up).

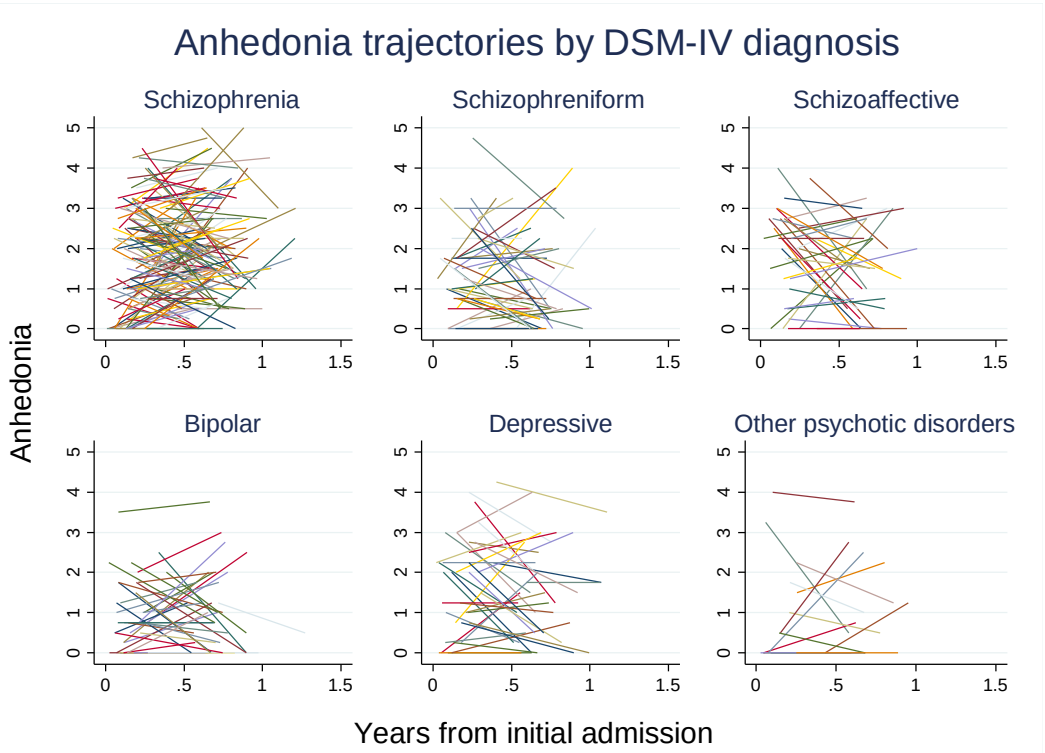


Figure 7.16. Anhedonia trajectories from T2 (initial recovery/stabilisation) to T4 (12-month follow-up).

Examination of these graphs reveals that anhedonia appears to have patterns of greater severity compared with the other three negative symptoms.

7.4 Missing data mechanisms

Missing data are a widespread problem in scientific research, with most data analysis techniques ill-equipped to accommodate this issue until relatively recently. Older and well-entrenched techniques for dealing with missing data such as listwise deletion (also known as complete case analysis) are implemented by default in many statistical software programs. Another technique, pairwise deletion, uses different sets of sample units to produce different parameters. Each of these methods comes with its own set of problems, however they are both liable to produce biased parameter estimates, depending on the reason that the data are missing in the first place – the missing data mechanism.

In longitudinal research, participants may be present for some waves of data collection and missing for others. It is not uncommon for participants to be absent for a particular assessment and then to reappear for later assessments (Schafer & Graham, 2002). Indeed, this is precisely the situation for the present study. Because repeated measurements on an individual tend to be correlated, procedures that use all available data for each participant are recommended, since missing data can be partially recovered from earlier or later waves. Maximum likelihood (ML) modelling of longitudinal data is suggested as a highly efficient way of using all available data. Of course, even sophisticated techniques such as ML rest on a number of crucial assumptions. The reasons why the data are missing in the first place are one such assumption. Missing data mechanisms are concerned with the extent to which the missing data depend on observed and unobserved data values. It is important to distinguish between different missing data mechanisms, because different methods used to deal with missing data may be based, either implicitly or explicitly, on the assumption of a particular missing data mechanism.

There are three types of missing data mechanisms. At one end of the spectrum is the missing completely at random (MCAR) mechanism. In this scenario, missing data are unrelated to the values of the variable of interest, or to the values of any other variables in the dataset. In other words, the observed data are essentially a random sample of the full dataset. Under MCAR, listwise and pairwise deletion of cases with missing data will produce unbiased estimates (although these methods of dealing with the missing data may not be efficient, and result in reduced statistical power).

At the other end of the spectrum is the missing not at random (MNAR) mechanism. In this scenario, the probability of missingness is systematically related to the hypothetical data values that are missing. For instance, study participants with extremely severe psychotic symptomatology and poor functioning at the time when the long-term follow-up is conducted might be less likely to be contactable by research staff due to the severity of their illness, and are therefore much less likely to be assessed. In this case the data are not MNAR. This type of missing data is also known as non-ignorable missing data.

Another missing data mechanism located in between the MCAR and MNAR extremes is the missing at random (MAR) mechanism, where missingness is unrelated to the variable of interest, but may be related to other variables in the dataset. In this scenario, the data can be considered MAR if the missingness does not depend on the value of the missing data point after controlling for another variable. To the extent that missingness is correlated with other variables in the analysis, the data are said to be MAR.

7.4.1 Missing data

Participants were classified as missing a particular assessment if both the BPRS positive symptom subscale AND all SANS subscales at that particular time point were absent. Twenty-four (5.8%) of the study sample of 413 participants missed the T1 assessment, whilst 19 (4.6%) missed the T2 assessment. No participant missed both T1 and T2 assessments. At T3, 105 (25.4%) of the study sample missed the assessment, 118 (28.6%) missed the T4 assessment and 135 (32.7%) missed being assessed at T5. The matrix below displays the number of participants at each time point and between each pair of assessment points:

	T1	T2	T3	T4	T5
T1	**389**				
T2	370	**394**			
T3	286	308	**308**		
T4	273	295	268	**295**	
T5	262	263	210	211	**278**

Of the study sample of 413 participants, 43.1% were assessed at all five time points, 28.6% were assessed on four occasions, 17.7% on three occasions, 9.4% on two occasions and 1.2% were

assessed at only one time point. All participants had complete data on the baseline demographic and clinical predictors used in the latent growth curve (LGC) models (age at onset of psychosis, gender, pre-morbid functioning, DUP, DSM-IV psychotic diagnosis), with the exception of pre-morbid functioning, where data were missing for 99 individuals. Much of this missingness (55.0%) was accounted for by subtle planned variations in instrument batteries between some of the EPPIC studies comprising the overall study sample, as mentioned previously (refer Section 4.1 in Method chapter 4); 54 participants who were part of a particular study cohort did not receive assessments on pre-morbid functioning or on the items comprising the avolition subscale of the SANS measure of negative symptoms. These data are likely to fulfil the requirements of being MCAR, because their missingness was planned.

Patterns of missing data, and missing data mechanisms in this dataset were assessed using two approaches. Firstly, Little's missing completely at random (MCAR) test was carried out on each of the five datasets (one for each of the four SANS and BPRS measures) used for the latent growth curve models, to assess the degree to which the data were likely to meet the MCAR mechanism. Secondly, prediction of missingness at each of the five assessment points was undertaken using binary logistic regression, with a range of baseline sociodemographic, clinical and psychopathology variables used to predict the presence or absence of a particular assessment. Exact logistic regression was carried out using LogXact version 8.0.0 for the analysis of categorical data containing an observed zero value.

Little's MCAR test indicated that there was little evidence to suggest that missing data in four of the five datasets deviated from the MCAR assumption, since all four probability values exceeded the critical value of .05. Each of these test results are displayed below in Table 7-4. However, there was some evidence to suggest that the missing data mechanism for the dataset underpinning the anhedonia LGC models did not meet MCAR assumptions.

Table 7-4. Little's MCAR test for each of the datasets used in the latent growth curve models.

	LGC dataset variables	Little's MCAR test result
Positive symptoms	T1-T5 positive symptoms + baseline predictors*	χ^2= 108.0; df=106; p=0.428
Affective flattening	T1-T5 affective flattening + baseline predictors*	χ^2=111.7; df=102; p=0.240
Alogia	T1-T5 alogia + baseline predictors*	χ^2=113.6; df=99; p=0.149
Avolition	T1-T5 avolition + baseline predictors*	χ^2=111.4; df=97; p=0.151
Anhedonia	T1-T5 anhedonia + baseline predictors*	χ^2=128.2; df=99; p=0.026

*Baseline predictors include: age at onset of psychosis, gender, DUP, pre-morbid functioning, DSM-IV diagnosis.

The five tables below (Table 7-5 to Table 7-9) present the results of the logistic regression analyses for each respective T1-T5 follow-up assessment. It should be noted that since only a small number of participants missed assessments at T1 (n=24) and T2 (n=19), these analyses were relatively underpowered to detect any but large effects. Prediction of missingness at subsequent time points was relatively well-powered, given the robust numbers of participants who missed assessments (T3: n=105; T4: n=118; T5: n=135). The results of these analyses are summarised below.

At T1, two statistically significant predictor of missingness (n=24) were identified: alcohol use and illicit substance use. Participants who used alcohol occasionally/moderately prior to baseline were more than four times as likely to receive a T1 assessment (95% CI (1.96, 11.41)) compared with non-users, whilst participants with problem/severe problem alcohol use were more than five times as likely to receive a T1 assessment (95% CI (1.23, 26.61) compared with non-users. Participants with problem/severe problem use of illicit drugs prior to baseline were more than six times as likely (95% CI (1.8, 24.8)) to receive a T1 assessment compared with participants who did not use. Note the width of these 95% confidence intervals around each of the three ORs, indicating the uncertainty inherent in these estimates, due largely to the small number of cases missing the T1 assessment (n=24).

Five significant predictors of missingness (n=19) at T2 were identified: participants were more likely to receive a T2 assessment if they (i) were older at admission; (ii) older at the onset of their psychotic symptoms; (iii) possessed a post secondary education qualification; (iv) were

rated with longer duration of prodromal symptoms, and (v) were on higher average doses of antipsychotics at baseline. Similar to the T1 results, 95% confidence intervals around the estimates also indicated the extent of uncertainty in these estimates, due to a large extent to the small number of cases missing the T2 assessment (n=19).

At T3, only one statistically significant predictor of missingness (n=131) was identified. Participants who were assessed at T3 had higher levels of depressive symptoms at remission/stabilisation point (T2). The magnitude of difference could be regarded as clinically trivial (mean difference = 1.6 points; median difference = 1.5 points), and represented a small effect size in Cohen's terminology (*d*=0.22). At T4, marital status was the only predictor of missing assessments (n=118), with single participants almost twice as likely to receive a T4 assessment compared with partnered participants.

At T5, two predictors of missing assessments (n=135) were identified: (i) participants who lived alone at baseline were approximately half as likely to receive a T5 assessment compared with participants living with others; (ii) participants assessed at T5 had higher levels of depressive symptoms at initial recovery/stabilisation (T2) than those who did not receive a T5 assessment, though mean and median differences were small (mean difference = 1.3 BDI severity points; median difference = 2.5 BDI severity points).

In summary, participants with missing assessments were broadly comparable to participants with non-missing data at the five assessment points across a range of sociodemographic, diagnostic, illness duration and psychopathology variables collected at baseline and illness stabilisation. Although some minor differences were identified, inspection of data presented in Tables 7-5 to 7-9 reveals that these differences represent relatively trivial and clinically unimportant effects. For instance, the finding that those participants with more severe depressive symptoms at initial recovery were more likely to receive an assessment at T3 and T5 than participants with less severe symptoms is of limited practical significance given the modest magnitude of these effects. Differences on other characteristics between missing and non-missing groups at other time points were also relatively minor. For instance, participants who were single at baseline were more likely to receive an assessment at T4, whilst participants living alone at baseline were approximately half as likely to be assessed at T5. In considering the magnitude of such effects, coupled with the absence of a consistent pattern of missingness over the five assessment points, there is no compelling evidence that participants

who missed any particular assessments were consistently or markedly different from those participants who received assessments. Hence it may be concluded that the available data across the five assessment points are not compromised by missingness and that the sample is representative.

Table 7-5. Means (SDs) or percentages (n), for baseline demographic and clinical predictors of presence/absence of T1 assessment

Baseline characteristics	Missing T1 assessment n=24	Received T1 Assessment n=389	OR	p-value*
Demographics:				
Age at service entry, years:	21.5 (3.4)	21.8 (3.5)	1.03	0.652
Age at onset of psychotic symptoms, years:	20.7 (3.2)	21.3 (3.5)	1.06	0.348
Gender:				
% male	58.3 (14)	73.8 (287)	2.01	0.104
Education, % post-secondary	20.8 (5)	30.7 (119)	1.68	0.313
Work status, %:				
Employed at some level [a]	45.8 (11)	59.4 (231)	-	-
Student	25.0 (6)	24.4 (95)	0.75	0.588
Unemployed/Home duties	29.2 (7)	16.2 (63)	0.43	0.093
Living alone, %	4.2 (1)	8.0 (31)	1.99	0.507
Australian-born, %	91.7 (22)	80.7 (314)	0.38	0.198
Clinical features:				
DSM-IV Diagnosis, %:				
schizophrenia/schizophreniform [a]	70.8 (17)	58.4 (227)	-	-
affective (bipolar/depressive)	16.7 (4)	26.2 (102)	1.91	0.255
schizoaffective	4.2 (1)	10.5 (41)	3.07	0.282
delusional/NOS/brief reactive psychosis [b]	8.3 (2)	4.9 (19)	0.71	0.664
Previous self-harm, %	8.3(2)	24.0 (92)	3.47	0.097
Family history of psychiatric illness	66.7 (16)	59.6 (229)	0.74	0.496
Illicit drug use, %				
None [a]	44.0 (11)	28.6 (156)	-	-
Occasional/moderate use	40.0 (10)	38.5 (210)	1.74	0.227
Problem use/severe problem evident	16.0 (4)	32.8 (179)	6.75	**0.004**
Alcohol use, %				
None [a]	45.8 (11)	22.6 (88)	-	-
Occasional/moderate use	41.7 (10)	35.7 (139)	4.73	**0.001**
Problem use/severe problem evident	12.5 (3)	41.6 (162)	5.73	**0.026**
Duration of untreated psychosis (DUP) in days [c]	335.3 (687.6)	174.9 (313.0)	0.72	0.266
median	61.0	60.0		
Duration of prodromal symptoms in days [c, d]	199.7 (157.6)	482.8 (582.6)	2.33	0.069
median	122.0	253.5		

Baseline characteristics	Missing T1 assessment n=24	Received T1 Assessment n=389	OR	p-value*
	(n=15)	(n=318)		
Highest average daily dose of antipsychotics, CPZ equivalence [c]	283.1 (175.0)	281.7 (271.1)	0.98	0.598
Median	250.0	200.0		
Pre-morbid functioning	0.25 (0.21)	0.31 (0.18)	6.47	0.150
	(n=22)	(n=292)		

* Based on univariate logistic regression analyses

† Exact logistic regression p-value

[a] Reference category against which the other categories are compared

[b] 'Other' diagnostic category includes delusional disorder, psychotic disorder not otherwise specified, and brief psychotic disorder

[c] Log-transformed due to extreme positive skewness however untransformed data are presented here

[d] Only for those participants who experienced a prodromal phase

Table 7-6. Means (SDs) or percentages (n), for baseline demographic and clinical predictors of presence/absence of T2 assessment

Baseline characteristics	Missing T2 assessment n=19	Received T2 Assessment n=394	OR	p-value*
Demographics:				
Age at service entry, years:	19.9 (3.5)	21.9 (3.5)	1.20	**0.017**
Age at onset of psychotic symptoms, years:	19.4 (3.5)	21.4 (3.6)	1.20	**0.017**
Gender:				
% male	84.2 (16)	72.3 (285)	0.49	0.265
Education, % post-secondary	5.3 (1)	31.3 (123)	8.21	**0.042**
Work status, %:				
Employed at some level [a]	78.9 (15)	57.6 (227)	-	-
Student	21.1 (4)	24.6 (97)	1.60	0.413
Unemployed/Home duties	0 (0)	17.8 (70)	-	†
Living alone, %	5.3 (1)	7.9 (31)	1.54	0.681
Australian-born, %	84.2 (16)	81.2 (320)	0.81	0.744
Clinical features:				
DSM-IV Diagnosis, %:				
Schizophrenia/Schizophreniform [a]	68.4 (13	58.6 (231)	-	-
Affective (Bipolar/Depressive)	10.5 (2)	26.4 (104)	2.93	0.162
Schizoaffective	10.5 (2)	10.2 (40)	1.13	0.879
Delusional/NOS/Brief reactive psychosis [b]	10.5 (2)	4.8 (19)	0.53	0.432
Previous self-harm, %	26.3 (5)	22.9 (89)	0.83	0.729
Family history of psychiatric illness, %	52.6 (10)	60.4 (235)	1.37	0.501
Illicit drug use, %				
None [a]	15.8 (3)	24.4 (96)	-	-
Occasional/moderate use	57.9 (11)	35.0 (138)	0.39	0.159
Problem use/severe problem evident	26.3 (5)	40.6 (160)	1.00	1.000
Alcohol use, %				
None [a]	15.8 (3)	19.0 (75)	-	-
Occasional/moderate use	78.9 (15)	64.7 (255)	0.68	0.550
Problem use/severe problem evident	5.3 (1)	5.3 (64)	2.56	0.421
Duration of untreated psychosis (DUP) in days [c]:	199.3 (327.4)	183.5 (347.8)	0.77	0.431
median	88.0	59.0		
Duration of prodromal symptoms in days [c, d]:	212.9 (260.7)	483.9 (582.4)	3.24	**0.008**
median	92.0	266.0		

Baseline characteristics	Missing T2 assessment n=19	Received T2 Assessment n=394	OR	p-value*
	(n=17)	(n=316)		
Highest average daily dose of antipsychotics, CPZ equivalence [e]	147.4 (82.4)	288.4 (270.4)	1.11	**0.015**
Median	100.0	200.0		
Psychopathology at admission (T1):				
BPRS Total score	27.6 (7.4)	29.5 (9.5)	1.02	0.392
	(n=19)	(n=368)		
BPRS Positive symptom subscale	10.4 (3.2)	11.0 (3.7)	1.04	0.492
	(n=19)	(n=367)		

* Based on univariate logistic regression analyses

† Exact logistic regression p-value

[a] Reference category against which the other categories are compared

[b] 'Other' diagnostic category includes delusional disorder, psychotic disorder not otherwise specified and brief psychotic disorder

[c] Log-transformed due to extreme positive skewness but untransformed data are presented here

[d] Only for those participants who experienced a prodromal phase

[e] A square-root transformation was applied due to moderate positive skewness but untransformed data are presented here

Table 7-7. Means (SDs) or percentages (n), for baseline demographic and clinical predictors of presence/absence of T3 assessment

Baseline characteristics	Missing T3 assessment n=105	Received T3 Assessment n=308	OR	p-value*
Demographics:				
Age at service entry, years:	21.8 (3.7)	21.8 (3.4)	1.00	0.953
Age at onset of psychotic symptoms, years:	21.4 (3.6)	21.3 (3.4)	0.99	0.789
Gender:				
% male	75.2 (79)	72.1 (222)	0.85	0.530
Marital status, % never married	81.9 (86)	85.7 (264)	1.33	0.350
Education, % post-secondary	23.1 (24)	32.5 (100)	1.60	0.073
Work status, %:				
Employed at some level [a]	61.9 (65)	57.5 (177)	-	-
Student	21.0 (22)	25.6 (79)	1.32	0.325
Unemployed/Home duties	17.1 (18)	16.9 (52)	1.06	0.849
Living alone, %	9.5 (10)	7.1 (22)	0.73	0.432
Australian-born, %	81.9 (86)	81.2 (250)	0.95	0.867
Clinical features:				
DSM-IV Diagnosis, %:				
Schizophrenia/Schizophreniform [a]	60.0 (63)	58.8 (181)	-	-
Affective (Bipolar/Depressive)	26.7 (28)	25.3 (78)	0.97	0.907
Schizoaffective	7.6 (8)	11.0 (34)	1.48	0.350
Delusional/NOS/Brief reactive psychosis [b]	5.7 (6)	4.9 (15)	0.87	0.783
Previous self-harm, %	22.1 (23)	23.4 (71)	1.07	0.796
Family history of psychiatric illness, %	53.4 (55)	62.3 (190)	1.44	0.112
Family history of suicide, %	6.9 (7)	4.3 (13)	0.60	0.294
Illicit drug use, %				
None [a]	23.8 (25)	24.0 (74)	-	-
Occasional/moderate use	32.4 (34)	37.3 (115)	1.14	0.659
Problem use/severe problem evident	43.8 (46)	38.6 (119)	0.87	0.641
Alcohol use, %				
None [a]	19.0 (20)	18.8 (58)	-	-
Occasional/moderate use	65.7 (69)	65.3 (201)	1.00	0.988
Problem use/severe problem evident	15.2 (16)	15.9 (49)	1.06	0.888
Duration of untreated psychosis (DUP) in days [c]	157.5 (259.3)	193.5 (371.5)	0.99	0.973
median	61.0	60.0		

Baseline characteristics		Missing T3 assessment n=105	Received T3 Assessment n=308	OR	p-value*
Duration of prodromal symptoms in days [c, d]		449.0 (576.2)	477.6 (573.2)	1.14	0.560
median		243.5	245.0		
		(n=88)	(n=245)		
Highest average daily dose of antipsychotics, CPZ equivalence [e]		306.4 (283.1)	273.5 (260.2)	0.98	0.166
	Median	250.0	200.0		
Pre-morbid functioning		0.32 (0.19)	0.30 (0.19)	0.61	0.500
		(n=63)	(n=251)		
Psychopathology at admission (T1):					
BPRS Total score		30.2 (9.0)	29.2 (9.5)	0.99	0.349
		(n=102)	(n=285)		
BPRS Positive symptom subscale		11.1 (3.9)	10.9 (3.6)	0.98	0.539
		(n=101)	(n=285)		
SANS [e]		27.2 (16.9)	23.2 (14.1)	0.87	0.089
		(n=79)	(n=256)		
Psychopathology at initial recovery (T2):					
BPRS Total score [e]		15.7 (9.4)	14.8 (8.3)	0.91	0.370
	Median	14.0	14.0		
		(n=86)	(n=308)		
BPRS Positive symptom subscale [e]		3.8 (4.0)	4.0 (3.6)	1.01	0.413
	Median	3.0	3.0		
		(n=86)	(n=308)		
SANS [e]		20.6 (15.7)	20.5 (14.9)	1.02	0.763
	Median	18.0	18.0		
		(n=81)	(n=278)		
Beck Depression Inventory [e]		7.2 (7.2)	8.8 (7.3)	1.20	**0.044**
	Median	5.5	7.0		
		(n=76)	(n=392)		

* Based on univariate logistic regression analyses

[a] Reference category against which the other categories are compared

[b] 'Other' diagnostic category includes delusional disorder, psychotic disorder not otherwise specified, and brief psychotic disorder

[c] Log-transformed due to extreme positive skewness but untransformed data are presented here

[d] Only for those participants who experienced a prodromal phase

[e] A square-root transformation was applied due to moderate positive skewness but untransformed data are presented here

Table 7-8. Means (SDs) or percentages (n), for baseline demographic and clinical predictors of presence/absence of T4 assessment

Baseline characteristics	Missing T4 assessment n=118	Received T4 Assessment n=295	OR	p-value*
Demographics:				
Age at service entry, years:	21.9 (3.5)	21.8 (3.5)	0.99	0.655
Age at onset of psychotic symptoms, years:	21.8 (3.7)	21.4 (3.6)	0.98	0.486
Gender:				
% male	73.7 (87)	72.5 (214)	0.94	0.806
Marital status, % never married	78.0 (92)	87.5 (258)	1.97	**0.017**
Education, % post-secondary	27.4 (32)	31.2 (92)	1.20	0.444
Work status, %:				
Employed at some level [a]	63.6 (75)	56.6 (167)	-	-
Student	22.0 (26)	25.4 (75)	1.29	0.332
Unemployed/Home duties	14.4 (17)	18.0 (53)	1.40	0.280
Living alone, %	9.3 (11)	7.1 (21)	0.75	0.451
Australian-born, %	79.7 (94)	82.0 (242)	1.17	0.576
Clinical features:				
DSM-IV Diagnosis, %:				
Schizophrenia/Schizophreniform [a]	57.6 (68)	59.7 (176)	-	-
Affective (Bipolar/Depressive)	26.3 (31)	25.4 (75)	0.93	0.793
Schizoaffective	11.0 (13)	9.8 (29)	0.86	0.682
Delusional/NOS/Brief reactive psychosis [b]	5.1 (6)	5.1 (15)	0.97	0.945
Previous self-harm, %	27.6 (32)	21.2 (62)	0.71	0.170
Family history of psychiatric illness, %	55.7 (64)	61.8 (181)	1.29	0.256
Family history of suicide, %	5.3 (6)	4.8 (14)	0.90	0.836
Illicit drug use, %				
None [a]	25.4 (30)	23.4 (697)	-	-
Occasional/moderate use	33.1 (39)	37.3 (110)	1.23	0.478
Problem use/severe problem evident	41.5 (49)	39.3 (116)	1.03	0.917
Alcohol use, %				
None [a]	15.3 (18)	20.3 (60)	-	-
Occasional/moderate use	70.3 (83)	63.4 (187)	0.68	0.191
Problem use/severe problem evident	14.4 (17)	16.3 (48)	0.85	0.670
Duration of untreated psychosis (DUP) in days [c]	155.0 (247.6)	195.5 (378.6)	1.07	0.639
median	55.5	61.0		

Baseline characteristics		Missing T4 assessment n=118	Received T4 Assessment n=295	OR	p-value*
Duration of prodromal symptoms in days [c, d]		456.2 (597.2)	475.5 (564.7)	1.13	0.579
median		233.5	273.0		
		(n=94)	(n=239)		
Highest average daily dose of antipsychotics, CPZ equivalence [e]		264.8 (258.8)	288.4 (269.1)	1.01	0.382
	Median	200.0	200.0		
Pre-morbid functioning		0.32 (0.18)	0.30 (0.19)	0.524	0.363
		(n=71)	(n=243)		
Psychopathology at admission (T1):					
BPRS Total score		30.2 (9.3)	29.1 (9.4)	0.99	0.281
		n=116	n=271		
BPRS Positive symptom subscale		10.9 (3.9)	10.9 (3.6)	1.00	0.989
		n=115	n=271		
SANS [e]		24.1 (15.7)	24.2 (14.7)	1.00	0.956
		n=88	n=247		
Psychopathology at initial recovery (T2):					
BPRS Total score [e]		15.1 (9.5)	15.0 (8.2)	1.01	0.917
	Median	13.0	14.0		
		n=99	n=295		
BPRS Positive symptom subscale [e]		3.7 (3.7)	4.0 (3.7)	1.08	0.452
	Median	3.0	3.0		
		n=99	n=295		
SANS [e]		19.2 (14.7)	21.0 (15.2)	1.07	0.291
	Median	16.0	19.0		
		n=90	n=269		
Beck Depression Inventory [e]		7.6 (7.5)	8.8 (7.2)	1.18	0.067
	Median	5.0	7.0		
		n=87	n=255		

* Based on univariate logistic regression analyses

[a] Reference category against which the other categories are compared

[b] 'Other' diagnostic category includes delusional disorder, psychotic disorder not otherwise specified, and brief psychotic disorder

[c] Log-transformed due to extreme positive skewness but untransformed data are presented here

[d] Only for those participants who experienced a prodromal phase

[e] A square-root transformation was applied due to moderate positive skewness but untransformed data are presented here

Table 7-9. Means (SDs) or percentages (n), for baseline demographic and clinical predictors of presence/absence of T5 assessment

Baseline characteristics	Missing T5 assessment n=135	Received T5 Assessment n=278	OR	p-value*
Demographics:				
Age at service entry, years:	21.8 (3.6)	21.8 (3.4)	1.00	0.940
Age at onset of psychotic symptoms, years:	21.3 (3.6)	21.3 (3.4)	1.00	0.899
Gender:				
% male	80.0 (108)	69.4 (193)	0.57	0.024
Marital status, % never married	84.4 (114)	84.9 (236)	1.03	0.906
Education, % post-secondary	26.7 (36)	31.8 (88)	1.28	0.290
Work status, %:				
Employed at some level [a]	60.7 (82	57.6 (160)	-	-
Student	23.0 (31)	25.2 (70)	1.16	0.567
Unemployed/Home duties	16.3 (22)	17.3 (48)	1.12	0.701
Living alone, %	11.9 (16)	5.8 (16)	0.45	**0.033**
Australian-born, %	77.0 (104)	83.5 (232)	1.50	0.118
Clinical features:				
DSM-IV Diagnosis, %:				
Schizophrenia/Schizophreniform [a]	59.3 (80)	59.0 (164)	-	-
Affective (Bipolar/Depressive)	27.4 (37)	24.8 (69)	0.91	0.699
Schizoaffective	9.6 (13)	10.4 (29)	1.09	0.815
Delusional/NOS/Brief reactive psychosis [b]	3.7 (5)	5.8 (16)	1.56	0.401
Previous self-harm, %	22.0 (29)	23.6 (65)	1.09	0.723
Family history of psychiatric illness, %	58.6 (78)	60.7 (167)	1.09	0.688
Family history of suicide, %	5.3 (7)	4.8 (13)	0.90	0.820
Illicit drug use, %				
None [a]	19.3 (26)	26.3 (73)	-	-
Occasional/moderate use	39.3 (53)	34.5 (96)	0.64	0.125
Problem use/severe problem evident	41.5 (56)	39.2 (109)	0.69	0.193
Alcohol use, %				
None [a]	18.5 (25)	19.1 (53)	-	-
Occasional/moderate use	64.4 (87)	65.8 (183)	0.99	0.977
Problem use/severe problem evident	17.0 (23)	15.1(42)	0.86	0.674
Duration of untreated psychosis (DUP) in days [c]:	175.1 (303.0)	188.7 (366.2)	0.97	0.814
median	61.0	59.5		

Baseline characteristics		Missing T5 assessment n=135	Received T5 Assessment n=278	OR	p-value*
Duration of prodromal symptoms in days [c, d]:		452.3 (594.5)	478.9 (563.5)	1.20	0.376
median		233.0	281.0		
		n=111	n=222		
Highest average daily dose of antipsychotics, CPZ equivalence [e]		293.6 (264.2)	276.1 (267.4)	0.99	0.447
	Median	225.0	200.0		
Pre-morbid functioning		0.33 (0.20)	0.30 (0.18)	0.46	0.237
		n=94	n=220		
Psychopathology at admission (T1):					
BPRS Total score		29.9 (9.6)	29.2 (9.3)	0.99	0.478
		n=127	n=260		
BPRS Positive symptom subscale		10.8 (3.6)	11.0 (3.7)	1.01	0.662
		n=126	n=260		
SANS [e]		25.1 (15.7)	23.7 (14.6)	0.96	0.570
		n=110	n=225		
Psychopathology at stabilisation (T2):					
BPRS Total score [e]		15.6 (9.2)	14.7 (8.2)	0.92	0.418
	Median	14.0	14.0		
		n=131	n=263		
BPRS Positive symptom subscale [e]		3.9 (3.6)	4.0 (3.7)	1.01	0.881
	Median	3.0	3.0		
		n=131	n=263		
SANS [e]		21.3 (15.3)	20.1 (14.9)	0.97	0.610
	Median	19.0	17.0		
		n=118	n=241		
Beck Depression Inventory [e]		7.6 (7.3)	8.9 (7.3)	1.18	**0.040**
	Median	5.5	8.0		
		n=112	n=230		

* Based on univariate logistic regression analyses

[a] Reference category against which the other categories are compared

[b] 'Other' diagnostic category includes delusional disorder, psychotic disorder not otherwise specified, and brief psychotic disorder

[c] Log-transformed due to extreme positive skewness but untransformed data are presented here

[d] Only for those participants who experienced a prodromal phase

[e] A square-root transformation was applied due to moderate positive skewness but untransformed data are presented here

8 POSITIVE SYMPTOMS

This chapter reports an investigation of characteristics and predictors of the short-term positive symptom trajectory and long-term (7.3 year) outcome in the sample. The nature of the effects of these predictors on short-term and long-term outcome is also identified. The chapter is partitioned in four sections: the unconditional model presented in Section 8.1 demonstrates that the average short-term trajectory measured on up to three occasions over the 1-year interval subsequent to initial recovery from the first psychotic episode is non-linear. Section 8.2 focuses on the prediction of short-term symptom trajectories (STTs) and long-term outcomes by severity of positive symptoms at admission. Section 8.3 examines the nature of the effects of four presenting features of participants on short-term and long-term symptoms; age at onset of psychosis, gender, duration of untreated psychotic symptoms (DUP) and pre-morbid functioning. Section 8.4 introduces baseline DSM-IV psychotic diagnosis as a predictor of short-term and long-term positive symptom outcomes. A summary of the findings is provided at the end of the chapter in Section 8.5 (Ctrl + click on hyperlink to go directly to summary).

8.1 Model 1: Growth Characteristics of Positive Symptoms over Short-Term Follow-up

A base model was developed as the framework for subsequent stages. This model fitted an unconditional growth curve to the positive symptoms data at initial recovery from the psychotic episode, 6-month follow-up, and 1-year follow-up. The MLR estimator was used for this and subsequent models. (A detailed description of MLR is provided in Statistical Methods, Chapter 5). Two questions are addressed within the unconditional model framework: the first relates to the characteristics of the short-term psychopathology growth trajectory for the overall group, whilst the second question relates to the degree to which there is individual variability in psychopathology trajectory estimates across individuals. These questions are detailed in sections 8.1.1 and 8.1.2.

The basic linear trajectory model includes measures observed on three occasions: positive symptom scores at initial recovery (T2), 6-month follow-up (T3) and 1-year follow-up (T4), and two latent growth factors. The latent growth factors and observed variables are presented

in Figure 8.1 below. The first factor represents the intercept component of the trajectory and the second factor represents the slope component. As described in chapter 5, the value of the fixed slope loading λ_2 for the intermediate assessment at 6-month follow-up was determined by expressing the median time elapsed between the initial recovery point and 6-month follow-up as a proportion of the total median time between initial recovery point and 1-year follow-up. In this case, the median time elapsed between initial recovery and 6-month follow-up is 194 days, which, as a proportion of the median time elapsed from initial recovery to 1-year follow-up of 380 days, is equal to 0.510, resulting in fixed values of λ_t = 0, 0.510 and 1 for the linear model.

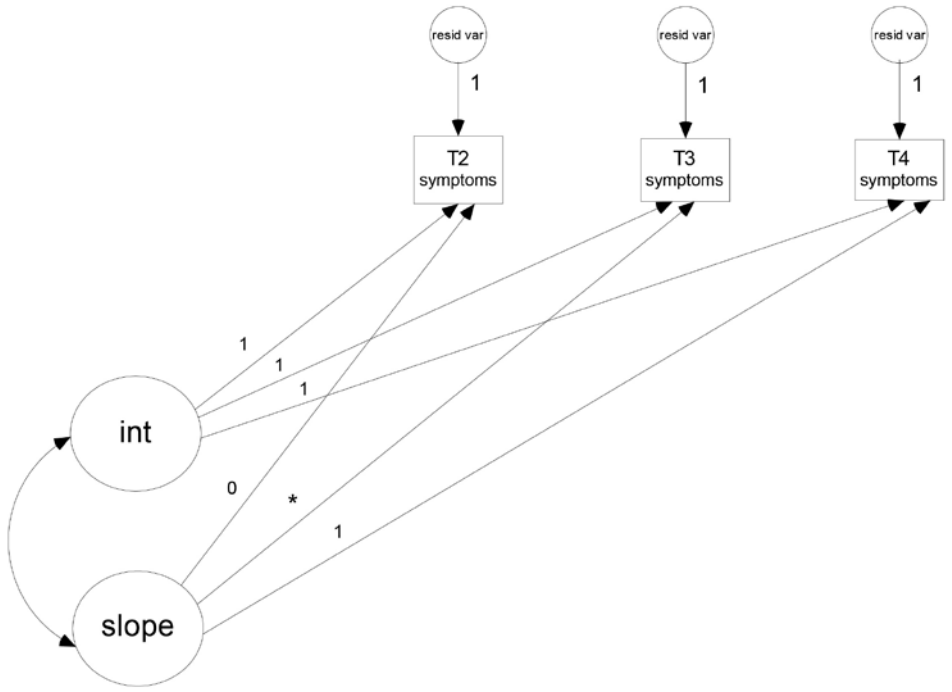


Figure 8.1. Unconditional non-linear latent trajectory model for positive symptoms measured at initial recovery; 6-month follow-up and 1-year follow-up.

8.1.1 What is the overall short-term positive symptom trajectory for the sample?

What is the mean trajectory of the severity of positive symptoms assessed across initial recovery, 6-month follow-up and 1-year follow-up? Specifically, this question aims to identify:

a) the average initial level of severity at the starting point (T2) of the trajectory;

b) whether the average symptom severity changes significantly over the 1-year interval subsequent to the starting point, and if so;

c) whether the change over time can be best described as linear or non-linear.

This set of questions relates to the characteristics of the growth trajectory for the overall group. Question 8.1.1(iii) is concerned with describing the shape of symptom change over the 1-year interval subsequent to initial recovery. A linear model was fitted initially, however, judged by multiple indices, the fit was poor (χ^2 = 14.076, df=3, p=0.0028; CFI = 0.888; RMSEA = 0.097; SRMR = 0.083). These results suggest that an unconditional linear latent curve model is inadequate in describing the shape of the symptom trajectory.

A non-linear trajectory was accommodated using the freed loading approach proposed by Meredith and Tisak (Meredith & Tisak, 1984, 1990). As detailed in Chapter 5, the freed loading provides flexibility in fitting nonlinear forms and is a type of nonlinear spline that best fits the data between any pair of time points. In implementing this approach, a non-linear latent curve model was estimated in which the first loading (corresponding to initial recovery) on the slope factor was fixed to 0; the second loading (corresponding to 6-month follow-up) was freely estimated; and the third loading (corresponding to 1-year follow-up) was fixed to 1, as recommended by McArdle (McArdle, 1988). The estimated second loading represents the proportion of change between the initial time period at initial recovery and 6-month follow-up, relative to the total change occurring from initial recovery to 1-year follow-up. For example, if the estimated value of the second loading was 0.70, this would reflect that 70% of the total observed change in symptom severity across the 1-year interval occurred between the first two assessments at the initial recovery point and 6-month follow-up. In practical terms, the difference between the linear and non-linear model is that the linear model fixes the loading of the slope for the middle point at 6-month follow-up, whereas the non-linear model allows this loading to be freely estimated.

Since these models are nested, the chi-square statistics of the linear and non-linear models were compared to assess whether the more complex non-linear model provides a significantly better fit compared to the simpler linear model using a likelihood ratio test. The non-linear model achieved a significantly better fit compared to the linear model (χ^2 =4.801 df=2, p=0.0907; CFI = 0.972; RMSEA = 0.060 (95% CI < 0.001, 0.130); SRMR = 0.046), with an improvement in the chi-square goodness of fit of 7.609 (df=1; p< 0.010) using the chi-square difference test for the Satorra-Bentler scaled chi-square (Satorra, 2000; Satorra & Bentler, 1999). The freed factor loading for the intermediate slope factor at 6-month follow-up was equal to 1.024 (SE=0.182; p< 0.001). This reflects that the change that had occurred in the first

six months subsequent to initial recovery was approximately two percent greater than the change that occurred in the 12 months subsequent to initial recovery. Hence, the rate of change between initial recovery and 6-month follow-up was more rapid than the change between initial recovery and 1-year follow-up.

The MLR estimate of the mean intercept of the non-linear trajectory was 3.941 (SE=0.183; 95% CI (3.581, 4.300); p< 0.001), reflecting that, on average, patients scored approximately 4 out of a possible total score of 24 on the positive symptoms subscale at the point of initial recovery of their initial psychotic episode. This estimate corresponds to an average rating of 'Very mild' on the positive symptoms subscale at initial recovery. The estimate of the mean slope of the trajectory was -0.585 (SE=0.210; 95% CI (-0.997, -0.172); p=0.005), reflecting that the average rate of change in positive symptoms between initial recovery and 1-year follow-up was equal to 0.585 points. This rate of change was significantly different from zero.

8.1.2 What is the nature of variation of short-term trajectories between individuals?

Is there significant variability of individual trajectories from the overall population mean trajectory? This question aims to identify whether this unconditional model is able to capture the individual variability in trajectory estimates, specifically:

a) initial levels of symptom severity at the starting point (i.e., intercept latent factor);
b) the rate of change in symptom severity over the 1-year interval subsequent to starting point (i.e., slope latent factor).

Model fitting provided estimates of the variance of the intercepts (7.178; SE=1.503; 95% CI (4.233, 10.123); p< 0.001) and the variance of the slopes (4.206; SE=2.282; 95% CI (-0.266, 8.678); p=0.065). The statistical significance of the intercept variance implied that there is significant individual variability of the intercept around its mean value, however the variability of the individual slopes around its mean value was not captured by the model, since this estimate narrowly failed to attain statistical significance. The significant covariance between the intercept and slope (r = -0.387; SE=0.164; p = 0.018) implies that individuals with higher initial scores at initial recovery show greater decline in severity over time. Finally, the residual variance estimate (6.308; p< 0.001), constrained to be equal for the observed variables, was significantly different from zero, indicating that there remains unexplained variability in the repeated measures above and beyond that explained by the growth factors.

8.1.3 Model 1 Summary

These results provide answers to two questions of interest. Firstly, the starting point of positive symptoms score at initial recovery (T2) has been identified, as has the average rate of change over the three assessment points (T2, T3, T4) across the entire sample of first-episode psychosis patients. Each of these was significantly different from zero. The shape of this change conforms optimally to a non-linear trajectory. Secondly, there is evidence to suggest that there was substantial variability in individual initial starting values at initial recovery, but that there was no significant individual variability around the mean slope. In other words, patients vary significantly in their initial symptom levels at the starting point of positive symptoms but not in their rates of change in the 1-year interval subsequently.

A third, yet unanswered question relates to the possibility of incorporating variables which might account for the characteristics of patients who experience higher severity of positive symptoms at the point of initial recovery, and those for whom the severity of symptoms decreased more rapidly over the 1-year interval subsequent to initial recovery. This question, amongst others, will be investigated using results obtained from the next three models, which were developed in incremental stages. The next stage, Model 2, builds on the first stage, the unconditional model, by incorporating two additional observed variables: (i) level of positive symptoms at admission (T1) and (ii) level of positive symptoms at long-term follow-up (T5). This model will include parameters which correspond to the next set of sequential research questions.

8.2 Model 2: Positive Symptoms at Admission and Long-Term Follow-up

Measurements of positive symptoms made on two other occasions—at admission to the service (T1) and at long-term follow-up (T5) —were incorporated into the unconditional non-linear model from Section 8.1. A path diagram of this model is presented in Figure 8.2; the paths represent the specification of the conditional non-linear model, and are formalised as research questions in sections 8.2.2.1 to 8.2.2.3.

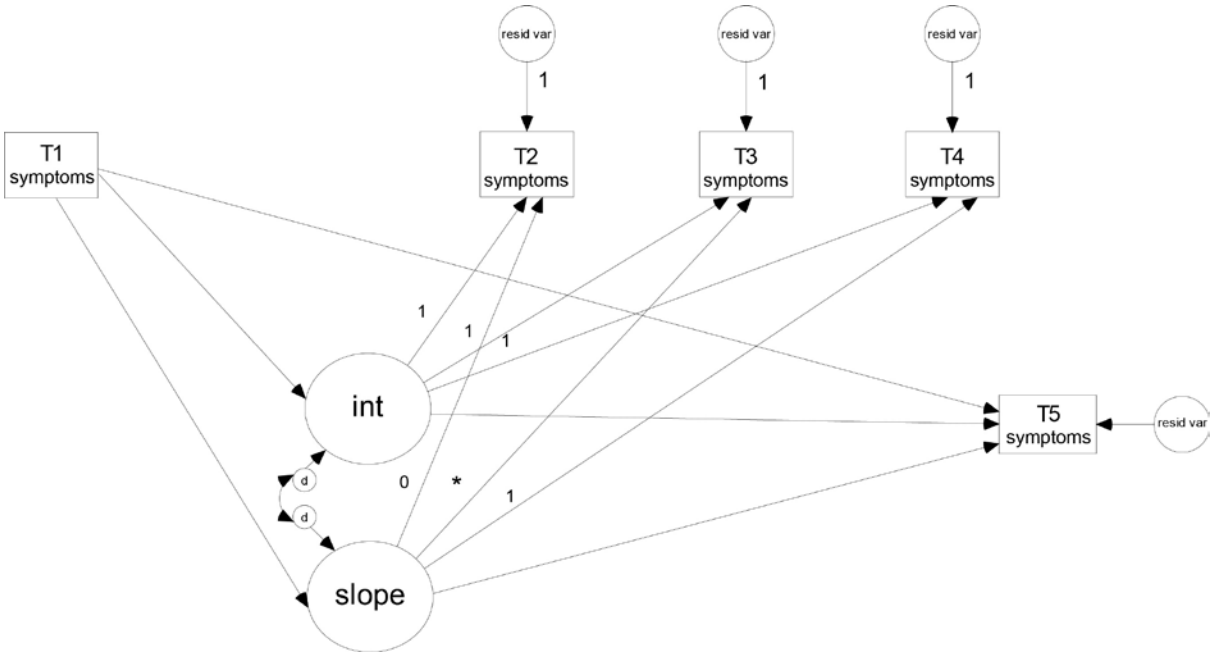


Figure 8.2. Conditional non-linear positive symptoms latent trajectory model, incorporating positive symptoms at admission as a covariate and long-term (7.3 year) positive symptom outcome.

The model in Figure 8.2 shows how positive symptoms at admission, when participants typically evidence florid psychosis, is specified as an exogenous covariate (i.e., it is not predicted by any other variable in the model). Positive symptoms score at long-term follow-up is specified as an endogenous distal outcome variable, and is predicted by positive symptoms at admission and by the two latent growth trajectory factors, the intercept and the slope. The parameters of the short-term growth trajectory (i.e. the 1-year interval subsequent to initial recovery) are predicted by positive symptoms at admission. Positive symptoms at admission was centred by subtracting the sample mean from each individual's observed value, to facilitate interpretability, as detailed in Statistical Methods (Chapter 5). When a variable is

centred on its sample mean, the model intercepts (for instance, the intercepts of the two latent growth variables and positive symptoms outcome at long-term follow-up) represent estimated values for an individual with average levels of positive symptoms at admission, instead of basing the estimated intercept values on individuals with zero positive symptoms at admission, a scenario which is neither plausible nor interpretable, given the usually florid nature of psychosis at intake.

The non-linear nature of the short-term symptom trajectory can be observed by inspecting the slope loadings. As specified above, the first loading (corresponding to the initial recovery point) is fixed to zero; the second (corresponding to 6-month follow-up) is freely estimated (indicated by *), and the third (corresponding to 1-year follow-up) is fixed to 1. The covariance between the disturbance terms of the intercept and slope was constrained to zero, in this and subsequent models, unless otherwise indicated. The fit of this non-linear model was very good as estimated using MLR (χ^2 = 7.813, df=5, p=0.1668; CFI = 0.981; RMSEA = 0.037 (95% CI <0.001, 0.084); SRMR = 0.040).

8.2.1 Model 2 Research Questions

There are two types of research questions in this section. In the first instance, questions which relate to direct effects for this model specification are presented, in particular, whether symptom severity at admission directly predicts: (a) the short-term latent growth trajectory; (b) long-term outcome; or (c) whether the short-term growth trajectory directly predicts long-term outcome. In the second part of this section, mediational investigations are presented, specifically, whether the effect of symptoms at admission on distal long-term symptom levels is mediated either fully or partly by the latent trajectory variables (i.e. symptom levels at initial recovery and the subsequent short-term change). If some form of mediation is found, then it would imply that the level of symptom severity at admission transmits its effect on long-term outcome via the short-term change that occurs over the 1-year interval following initial recovery; that is, through the mediating latent growth variable(s), the intercept and/or slope. These mediational questions are further elaborated in Mediation (Chapter 6), which contains a full description of criteria necessary to establish which one of four possible outcomes is applicable: full mediation; partial mediation; inconsistent mediation; or no mediation.

8.2.2 Direct effects

The magnitude and direction of direct effects in this model are presented in Table 8-1 below as regression coefficients (with robust standard errors and probability values) linking the following observed and latent variables: (i) symptom levels at admission; (ii) each of the latent growth factors (the intercept and slope); and (iii) observed long-term symptoms.

8.2.2.1 Does positive symptom severity at admission directly predict the short-term growth trajectory?

This question aims to identify whether admission positive symptom levels predict:

c) Initial positive symptom levels at the starting point of the trajectory (i.e. intercept) and/or;
d) the short-term change (i.e. slope) in positive symptoms that occurs over the subsequent 1-year interval.

Table 8-1 shows that higher levels of positive symptoms at admission were predictive of higher levels of positive symptoms at initial recovery ($\hat{\gamma}$= 0.114; 95% CI (0.005, 0.224)), but did not predict the short-term change in positive symptoms over the 1-year interval subsequent to initial recovery. A one-point increase in severity of positive symptoms at admission was associated with just over one-tenth of a point increase in severity of positive symptoms at initial recovery (i.e. the intercept latent factor).

8.2.2.2 Does positive symptom severity at admission directly predict long-term positive symptom severity?

Severity of positive symptoms at admission failed to predict long-term outcome ($\hat{\gamma}$= -0.107; 95% CI (-0.225, 0.011); p=0.075) when the effects of the other predictors of long-term outcome (i.e., intercept and slope latent growth factors) were taken into account.

8.2.2.3 Does the short-term growth trajectory directly predict long-term positive symptom severity?

This question asks if either of these latent variables predict long-term outcome:

a) Initial symptom levels at the starting point of the trajectory (i.e. intercept) and/or;
b) the short-term change (i.e. slope) that occurs over the subsequent 1-year interval.

Higher levels of positive symptoms at initial recovery (i.e., the starting point of the short-term trajectory) were predictive of more severe long-term outcome ($\hat{\gamma}$= 0.859; 95% CI (0.508, 1.210)) but the change in positive symptoms that occurred over the short-term trajectory subsequent to initial recovery was not. A one-point increase in severity of positive symptoms at initial recovery was associated with just over four-fifths of a point increase in severity of positive symptoms at long-term follow-up.

Table 8-1. Direct effects: Unstandardised coefficient estimates (with MLR standard errors) for (i) random intercepts and random slopes of the short-term positive symptom trajectory, regressed on admission positive symptoms; and (ii) long-term positive symptoms, regressed on (a) short-term trajectory random intercepts and (b) slopes, and (c) positive symptoms at admission.

Outcome	*Short-term change 1-year subsequent to initial recovery*				*Level of symptoms at long-term follow-up*	
	Intercept		*Slope*			
Direct effects	**Estimate (SE)**	***p-value***	**Estimate (SE)**	***p-value***	**Estimate (SE)**	***p-value***
Predictors						
Level of symptoms at admission	**0.114 (0.056)**	**0.040**	0.009 (0.056)	(0.869)	-0.107 (0.060)	0.075
Starting point of trajectory (Intercept factor)	-	-	-	-	**0.859 (0.179)**	**<0.001**
Short-term trajectory (Slope factor)	-	-	-	-	0.441 (0.726)	0.544

8.2.3 Indirect effects

The path diagram for the indirect effects is identical to the path diagram in Figure 8.2. Conditional non-linear positive symptoms latent trajectory model, incorporating positive symptoms at admission as a covariate and long-term (7.3 year) positive symptom outcome. (above). The model indirect effects are formalised as a two-part research question in Section 8.2.3.1. The presence of any mediated effects was established using the bias-corrected bootstrap, which is recommended as the method of choice (MacKinnon et al., 2004), as discussed in Mediation (Chapter 6). Bootstrapped 95% confidence intervals, which are not necessarily symmetric around the point estimate of the mediated effect, were used. These asymmetric intervals are particularly appropriate in establishing whether the mediated effect is significantly different from zero, since they accommodate the non-normality of the sampling of the mediation effect. Statistical significance of the effect was determined by

examining whether zero was included in the confidence interval; if the interval did not contain zero, then the result was regarded as statistically significant. The bias-corrected bootstrap procedure in Mplus was used for this two mediator model, using 10,000 bootstrap draws. A comprehensive overview of mediation analysis methodology is provided in Chapter 6.

8.2.3.1 Is the effect of severity of positive symptoms at admission on long-term symptom levels mediated in full or in part by either of the latent trajectory variables?

This question is concerned with whether the positive symptom levels at admission indirectly affects long-term positive symptoms, via its effect on the short-term change (represented by the intercept and/or slope latent variables) that occurs from initial recovery.

The effect of admission symptom levels on long-term positive symptoms was completely mediated by level of symptoms at initial recovery (i.e., the intercept latent variable); ab_i = 0.098; 95% CI (0.012, 0.225), as shown by the specific indirect effects in Table 8-2. This effect is statistically significant since the asymmetric 95% confidence interval does not include zero. There was no evidence that the short-term change that occurred subsequent to initial recovery (as represented by the slope latent factor, ab_s) mediated the effects of admission symptoms on long-term positive symptoms. This indirect effect is regarded as non-significant since the asymmetric 95% confidence interval contains zero. Since there was no compelling evidence of any direct effect of admission symptoms on long-term outcome (see direct effect in Table 8-1: c'= -0.107; 95% CI (-0.225, 0.011); p=0.075) whilst accounting for the mediators, a partial mediation scenario is ruled out. The implication of these results is that the effect of admission symptom levels is transmitted on long-term symptom levels solely through its effect on level of positive symptom levels at initial recovery following the psychotic episode.

Table 8-2. Indirect effects of severity of positive symptoms at admission on long-term symptom levels: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals. Statistically significant effects are presented in bolded text.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI[1]
Admission symptoms → intercept of STT → long-term symptoms	$\boldsymbol{ab_i}$	**0.098 (0.053)**	**0.012, 0.225**
Admission symptoms → slope of STT → long-term symptoms	ab_s	0.004 (0.126)	-0.129, 0.173

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval.

8.2.4 Model 2 Summary

These results provide answers to several questions of interest. Firstly, there is evidence that the level of positive symptoms at admission on long-term outcome is completely mediated by the starting point of the short-term trajectory (i.e. the intercept latent variable). In other words, level of admission symptoms transmits its effect on long-term positive symptom outcome solely through its effect on level of positive symptoms at the initial recovery point. Secondly, the status of positive symptoms at initial recovery (i.e. intercept) significantly predicts long-term outcome, but the short-term trajectory from this point onward (i.e. the slope) does not. Other questions, which will be asked later, relate to the possibility of incorporating baseline features and clinical predictors which might account for the characteristics of patients at admission, over the short-term trajectory and at long-term outcome. Four of these baseline predictors, all exogenous variables, will be introduced in the next stage, Model 3.

8.3 Model 3: Effects of Participants' Presenting Features on Short-Term and Long-Term Positive Symptom Levels ?

The next set of questions relates to the inclusion of four of the participants' baseline presenting features that might account for variability in severity of positive symptoms over the short-term and long-term. These are gender, age at onset of psychosis, duration of untreated psychosis (DUP) and pre-morbid functioning. A detailed description of these four variables is presented in Method (Chapter 4). The main difference between this model and the previous model is that these four presenting features are introduced specifically for the purpose of accounting for the positive symptoms of patients at admission, over the short-term trajectory and at long-term follow-up. The nature of any such effects will be examined, for instance, whether the effect of a particular presenting feature on a dependent variable (such as short-term or long-term positive symptoms) is a direct one, or whether the effect is mediated by intervening variable(s) in the model.

A path diagram representing the relationships between the observed and latent variables in this model is presented in Figure 8.3. These four new observed variables are exogenous. All paths in the preceding model are retained, with new model paths presented in bold type. In order to streamline the complexity of the diagram and to convey the idea of the model more simply, the four presenting features are placed in a single box instead of being specified as separate observed variables with paths emanating from each. In contrast with the previous model, positive symptoms at admission was specified as an endogenous covariate, since it is predicted by the four baseline predictors. Similar to the previous model, positive symptoms score at long-term follow-up was specified as an endogenous distal outcome variable, and was predicted by three groups of variables: (i) positive symptoms at admission (T1); (ii) the two latent growth trajectory factors underlying the short-term growth trajectory (the intercept and slope); and (iii) the four baseline predictors. The short-term growth trajectory (over the 1-year interval subsequent to initial recovery) was predicted by positive symptoms at admission and by the four baseline presenting features.

Positive symptoms at admission, age at onset of psychosis, and pre-morbid functioning were centred by subtracting the sample mean of each variable from each individual's observed value on that variable to facilitate interpretability, as detailed in Statistical Methods (Chapter 5). The reason for centring a particular variable on its sample mean is clearer if we consider, for example, age at onset of psychosis; by centring this predictor on its sample mean, the model

intercepts (for instance, the intercepts of the two latent growth variables and long-term outcome) represent estimated values for an individual with an average age at onset of psychosis instead of basing the estimated intercept values on individuals aged zero years at onset of psychosis, which is clearly implausible. The covariance between the disturbance terms of the intercept and slope was constrained to zero. The fit of this model was very good as estimated using MLR (χ^2 = 15.936, df=12, p=0.1942; CFI = 0.983; RMSEA = 0.028 (95% CI <0.001, 0.061); SRMR = 0.021).

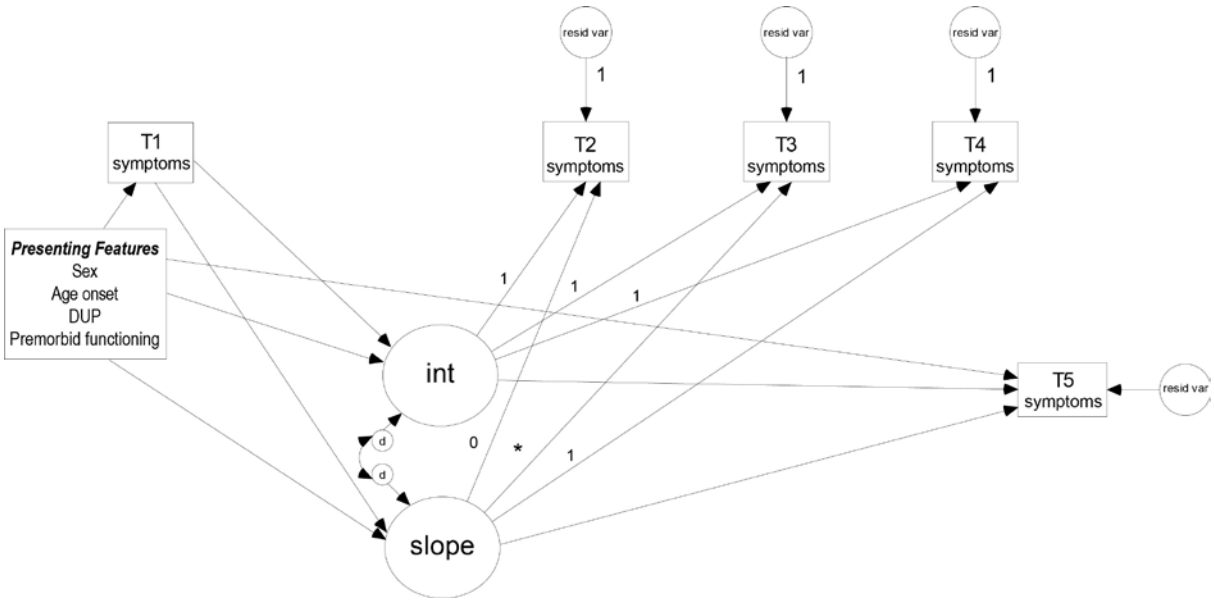


Figure 8.3. Conditional non-linear positive symptom latent trajectory model, incorporating direct effects of gender, age at onset of psychosis, DUP and pre-morbid functioning as predictors of severity of positive symptoms (i) at admission; (ii) across the short-term growth trajectory and (iii) at long-term follow-up. Each arrow actually represents multiple paths from the set of predictors to each dependent variable.

8.3.1 Model 3 Research Questions

Research questions in this section can be divided into two sections. The first comprises direct effects, whilst the second deals with indirect effects:

(i) Section 8.3.2: Identification of direct effects of participants' presenting features on short-term trajectories and long-term positive symptom outcome;

(ii) Section 8.3.3: Identification of indirect effects of presenting features on short-term trajectories and long-term positive symptom outcome.

Section 8.3.2 relates to direct effects for this model specification, in particular, whether any of the four presenting features (gender, age at onset of psychosis, DUP and pre-morbid functioning) directly predict: (a) positive symptom levels at admission; (b) the short-term trajectory (STT); or (c) long-term positive symptoms.

Section 8.3.3 comprises two distinct research questions regarding the possible presence of mediated effects, specifically: (a) whether the effect of each of the four presenting features on the STT in the 1-year interval subsequent to initial recovery point is mediated fully or partly by admission symptoms; and (b) whether the effect of each of these four presenting features on distal long-term symptom levels is mediated either fully or partly by level of symptoms at admission, and/or by the latent trajectory variables (i.e. symptom levels at the initial recovery point, represented by the intercept; and the short-term change subsequent to initial recovery, represented by the slope). These mediation issues were elaborated in Mediation (Chapter 6), which contains a full description of the criteria necessary to establish particular mediation mechanisms.

8.3.2 Direct effects

8.3.2.1 Do the four key presenting features (gender, age of onset, DUP or pre-morbid functioning) directly predict positive symptom levels at admission?

None of the four presenting features (gender, age at onset of psychosis, DUP or pre-morbid functioning) directly predicted severity of positive symptoms at admission, as indicated in Table 8-3 (see below).

8.3.2.2 Is there a direct effect of any presenting feature on the latent growth factors?

Do any of these four baseline characteristics directly predict:

c) Initial positive symptom levels at the starting point of the short-term trajectory (i.e. intercept) and/or;

d) the short-term change (i.e. slope) that occurs over the subsequent 1-year interval?

Pre-morbid functioning and DUP directly predicted symptom status at initial recovery (i.e. the intercept latent factor). Subjects with poorer pre-morbid functioning had significantly more severe levels of positive symptoms at initial recovery ($\hat{\gamma}$ = 2.964; 95% CI (0.588, 5.341) as shown in Table 8-3. A one-point increase in pre-morbid functioning (where the lowest score of 0 represents the best possible functioning and the highest score of 1 represents the worst possible functioning) was associated with an average increase of almost 3 points in severity of positive symptoms at initial recovery, the start of the STT. Each of the four DUP categories was compared with very long DUP in excess of one year, as detailed in Method chapter 4. Subjects presenting with a very short DUP of 0-7 days or a short DUP of 8-28 days (as compared to subjects with very long $DUP_{1+\ year}$) scored an average reduction in symptom severity of almost 3 points at initial recovery ($DUP_{0\text{-}7\ days}\ \hat{\gamma}$ = 2.738; 95% CI (-3.984, -1.491); $DUP_{8\text{-}28\ days}\ \hat{\gamma}$ =-2.825; 95% CI (-4.142,-1.509)), whilst subjects with a slightly longer DUP of 29-90 days scored an average reduction in symptom severity of 1.68 points at initial recovery than subjects with very long $DUP_{1+\ year}$ ($DUP_{29\text{-}90\ days}\ \hat{\gamma}$ = -1.680; 95% CI (-3.037; -0.323)). None of the four presenting features predicted the short-term change (i.e., the slope latent factor) in the 1-year STT subsequent to initial recovery.

8.3.2.3 Do any of the four presenting features directly predict long-term positive symptom outcome?

Table 8-3 shows that of the presenting features, only pre-morbid functioning directly predicted level of positive symptoms at long-term follow-up ($\hat{\gamma}$ = 3.524; 95% CI (0.391, 6.657)). A one-point increase in pre-morbid functioning (where the lowest score of 0 represents the best possible functioning and the highest score of 1 represents the worst possible functioning) was associated with a 3.5 point increase in severity of positive symptoms at long-term follow-up.

Table 8-3. Direct effects: Unstandardised estimates (regression coefficients, with MLR standard errors) for (i) admission positive symptoms, regressed on gender, age at onset, DUP and pre-morbid functioning; (ii) random intercepts and random slopes of the short-term positive symptom trajectory, regressed on gender, age at onset, DUP, pre-morbid functioning and admission positive symptoms; and (iii) long-term positive symptoms, regressed on (a) gender, age at onset, DUP and pre-morbid functioning; (b) short-term trajectory random intercepts and (c) slopes, and (d) admission symptoms .

Outcome:	***Admission symptoms***		***Short-term change 1-year subsequent to initial recovery***				***Level of symptoms at long-term follow-up***	
			Intercept		***Slope***			
	Estimate(SE)	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***
Predictors								
Gender:	-0.180 (0.426)	0.672	0.159 (0.393)	0.686	-0.046 (0.451)	0.918	-0.184 (0.477)	0.700
Age at onset:	0.017 (0.055)	0.755	-0.053 (0.052)	0.301	0.047 (0.053)	0.370	0.105 (0.066)	0.109
DUP[1]:								
0-7 days	-0.672 (0.663)	0.311	**-2.738 (0.636)**	**< 0.001**	0.480 (0.806)	0.552	-1.857 (1.142)	0.104
8-28 days	-0.856 (0.646)	0.185	**-2.825 (0.672)**	**< 0.001**	1.176 (0.861)	0.172	-1.671 (1.288)	0.195
29-90 days	-0.770 (0.595)	0.196	**-1.680 (0.692)**	**0.015**	0.448 (0.780)	0.566	-2.013 (1.055)	0.056
3-months-1 year	-0.296 (0.549)	0.589	-0.789 (0.642)	0.219	0.401 (0.788)	0.611	-1.114 (0.997)	0.264
Pre-morbid functioning:	0.895 (1.153)	0.438	**2.964 (1.213)**	**0.015**	-0.192 (1.196)	0.872	**3.524 (1.598)**	**0.027**
Admission symptoms	-	-	0.089 (0.054)	0.099	0.019 (0.059)	0.752	-0.105 (0.058)	0.070
Starting point of trajectory (Intercept factor)	-	-	-	-	-	-	**0.675 (0.207)**	**0.001**
Short-term trajectory: (Slope factor)	-	-	-	-	-	-	0.550 (0.567)	0.332

[1] The reference category against which each DUP category is compared is very long DUP $_{1+\text{ years}}$

8.3.3 Indirect effects

This is the second set of questions to be addressed for Model 3. Results of the mediational analyses are presented in two parts, and comprise research questions concerning: (i) whether the effects of the four presenting features on the STT are mediated by admission symptoms, and; (ii) whether the effects of the presenting features on long-term positive symptoms are mediated by short-term symptom outcomes (either by admission symptoms or by the STTs).

8.3.3.1 Are the effects of gender, age of onset, DUP and pre-morbid functioning on the short-term positive symptom trajectories mediated in full or in part by level of symptoms at admission?

This question examined whether each of the four presenting features indirectly affected the short-term change in positive symptoms (represented by the intercept and/or slope latent variables) that occurs from initial recovery point via their effect on level of positive symptoms at admission. Results of these mediation analyses are presented individually for each of the four presenting features.

Gender

There was no evidence that gender exerted any indirect effect on the positive symptom STT (represented by the intercept and slope latent variables) via admission symptoms, as indicated by the asymmetric confidence intervals of the specific indirect effects, each of which included zero (see Table 8-4). The implication of these results is that there appears to be no effect, either direct or indirect, of gender on the short-term symptom trajectory.

Table 8-4. Indirect effects of male gender on the short-term positive symptom trajectory (intercept and slope latent variables) via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI[1]
Male → admission symptoms → intercept of STT	ab_i	-0.016 (0.045)	-0.151, 0.046
Male → admission symptoms → slope of STT	ab_s	-0.003 (0.029)	-0.097, 0.035

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval.

Age at onset of psychosis

There was no evidence of any indirect effect of age at onset of psychosis on either the starting point of the short-term trajectory at initial recovery (i.e., the intercept latent variable) or on rates of change (i.e., the slope latent variable) via admission symptoms, as indicated by the asymmetric 95% confidence intervals for the specific indirect effects, each of which included zero (see Table 8-5).

Table 8-5. Indirect effects of age at onset of psychosis (Age at onset) on the short-term positive symptom trajectory (intercept and slope latent variables) via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI[1]
Age at onset → admission symptoms → intercept of STT	ab_i	0.002 (0.006)	-0.007, 0.018
Age at onset → admission symptoms → slope of STT	ab_s	<0.001 (0.004)	-0.005, 0.011

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval.

DUP

Table 8-6 presents the unstandardised indirect effects of each of the DUP categories on the STT latent variables: the intercept and the slope. Each DUP category was compared with the reference category, very long DUP in excess of one year ($DUP_{1+\ year}$).

There was no evidence of any indirect effect of DUP on either the starting point of the STT at initial recovery (i.e., the intercept latent variable) or on rates of change (i.e., the slope latent variable) via admission symptoms, as indicated by the asymmetric 95% confidence intervals for the specific indirect effects, each of which included zero. The implication of these results, taken along with the direct effects presented in Table 8-3, is that the effects of very short $DUP_{0\text{-}7\ days}$, short $DUP_{8\text{-}28\ days}$ and moderate $DUP_{29\text{-}90\ days}$ are transmitted on the short-term symptom trajectory solely through their direct effects on level of positive symptoms at initial recovery following the psychotic episode.

Table 8-6. Indirect effects of the four DUP categories (compared with very long DUP 1-year+) on the starting point (i.e., intercept) and rates of change (i.e., slope) of the short-term symptom trajectory, via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect		Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI[1]
DUP → admission symptoms → intercept of STT				
	$DUP_{0\text{-}7\ days}$	ab_{ia}	-0.060 (0.078)	-0.319, 0.028
	$DUP_{8\text{-}28\ days}$	ab_{ia}	-0.076 (0.083)	-0.341, 0.017
	$DUP_{29\text{-}90days}$	ab_{ia}	-0.068 (0.075)	-0.308, 0.018
	$DUP_{3mths\text{-}1yr}$	ab_{ia}	-0.026 (0.059)	-0.210, 0.052
DUP → admission symptoms → slope of STT				
	$DUP_{0\text{-}7\ days}$	ab_{ia}	-0.013, (0.060)	-0.210, 0.060
	$DUP_{8\text{-}28\ days}$	ab_{ia}	-0.016, (0.067)	-0.213, 0.077
	$DUP_{29\text{-}90days}$	ab_{ia}	-0.014 (0.062)	-0.218, 0.066
	$DUP_{3mths\text{-}1yr}$	ab_{ia}	-0.006 (0.040)	-0.142, 0.045

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval.

Pre-morbid functioning

There was no evidence of an indirect effect of pre-morbid functioning on the short-term symptom trajectory via admission symptoms, as indicated by the asymmetric 95% confidence intervals for the specific indirect effects, each of which included zero (Table 8-7). The results, along with previously presented direct effects (Table 8-3) suggest that the effect of pre-morbid functioning is transmitted on the short-term

symptom trajectory solely through its direct effect on level of positive symptoms at initial recovery.

Table 8-7. Indirect effects of pre-morbid functioning on the short-term symptom trajectory (intercept and slope latent variables) via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI
Pre-morbid functioning →admission symptoms → intercept of STT	ab_i	0.079 (0.133)	-0.088, 0.484
Pre-morbid functioning → admission symptoms → slope of STT	ab_s	0.017 (0.101)	-0.105, 0.361

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval.

8.3.3.2 Are the effects of gender, age of onset, DUP and pre-morbid functioning on long-term symptom levels mediated in full or in part by either the latent trajectory variables or by symptom levels at admission?

This question is concerned with whether any of the four presenting features indirectly affect long-term symptoms; (a) via their effect on level of symptoms at admission, or (b) via their effect on the short-term change (represented by the intercept and/or slope latent variables) that occurs from initial recovery. Results of these mediation analyses are presented individually for each of the four presenting features.

Gender

There was no evidence of any indirect effect of gender on severity of long-term positive symptoms, as indicated by the specific indirect effects displayed in Table 8-8. Of the five effects tested, all were non-significant, as indicated by their asymmetric 95% confidence intervals, each of which included zero.

Table 8-8. Indirect effects of gender on long-term symptom levels: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI
Male → intercept of STT → long-term positive symptoms	ab_i	0.107 (0.285)	-0.450, 0.695
Male → slope of STT → long-term positive symptoms	ab_s	-0.026 (0.689)	-1.519, 0.788
Male → Admission symptoms → long-term positive symptoms	ab_{ia}	0.019 (0.067)	-0.062, 0.210

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval.

Age at onset of psychosis

There was no evidence that age at onset of psychosis indirectly affected the severity of long-term positive symptoms, as indicated by the specific indirect effects displayed in Table 8-9, each of which were non-significant.

Table 8-9. Indirect effects of age at onset of psychosis (Age at onset) on long-term symptom levels: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI
Age at onset → intercept of STT -> long-term positive symptoms	ab_i	-0.036 (0.040)	-0.134, 0.027
Age at onset → slope of STT -> long-term positive symptoms	ab_s	0.026 (0.106)	-0.042, 0.433
Age at onset → Admission symptoms → long-term positive symptoms	ab_{ia}	-0.002 (0.008)	-0.024, 0.010

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval.

DUP

Table 8-10 presents the unstandardised indirect effects of each of the DUP categories on long-term positive symptoms for each model parameter. Each DUP category was compared with the reference category, very long DUP in excess of one year ($DUP_{1+\ year}$).

The effects of short to moderate DUP levels on long-term positive symptoms were completely mediated by the intercept latent variable (i.e. level of symptoms at initial

recovery). Thus, a very short $DUP_{0\text{-}7\ days}$ (as opposed to very long $DUP_{1+\ year}$) indirectly resulted in an average 1.849 point reduction (95% CI (-3.909, -0.668)) in severity of positive symptoms at long-term follow-up, via its effect on the intercept latent variable. Similarly, those individuals with a short $DUP_{8\text{-}28\ days}$ experienced an average reduction of 1.908 points (95% CI (-4.058, -0.725)) in severity of positive symptoms at long-term follow-up via the effect of DUP on the intercept, and those with a moderate $DUP_{29\text{-}90days}$ experienced an average reduction of 1.135 positive symptoms points (95% CI (-2.885, -0.232)) at long-term follow-up.

A partial mediation scenario is ruled out since there was no evidence of any direct effect of each of these DUP categories on long-term outcome whilst accounting for the mediators (refer direct effects presented in Table 8-3). There was no evidence of any other form of mediation: neither admission symptoms nor the short-term change that occurred subsequent to initial recovery (as represented by the slope latent factor) were significant mediators of DUP. The implication of these results is that the effects of short to moderate DUP levels of up to 90 days are transmitted on long-term symptom levels solely through their effect on level of positive symptoms at initial recovery following the psychotic episode.

Table 8-10. Indirect effects of the four DUP categories (compared with very long DUP 1-year+) on long-term symptom levels: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals. Significant effects are presented in bolded text.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI
DUP → intercept of STT → long-term positive symptoms			
$DUP_{0\text{-}7\ days}$	$\boldsymbol{ab_i}$	**-1.849 (0.804)**	**-3.909, -0.668**
$DUP_{8\text{-}28\ days}$	$\boldsymbol{ab_i}$	**-1.908 (0.820)**	**-4.058, -0.725**
$DUP_{29\text{-}90days}$	$\boldsymbol{ab_i}$	**-1.135 (0.660)**	**-2.885, -0.232**
$DUP_{3mths\text{-}1yr}$	ab_i	-0.533 (0.523)	-1.891, 0.244
DUP → slope of STT → long-term positive symptoms			
$DUP_{0\text{-}7\ days}$	ab_s	0.264 (1.136)	-0.718, 4.292
$DUP_{8\text{-}28\ days}$	ab_s	0.647 (1.822)	-0.896, 6.353
$DUP_{29\text{-}90days}$	ab_s	0.246 (1.289)	-0.712, 4.853
$DUP_{3mths\text{-}1yr}$	ab_s	0.220 (1.220)	-0.755, 4.296
DUP → admission symptoms → long-term positive symptoms			
$DUP_{0\text{-}7\ days}$	ab_{ia}	0.071 (0.125)	-0.050, 0.459
$DUP_{8\text{-}28\ days}$	ab_{ia}	0.090 (0.135)	-0.039, 0.459
$DUP_{29\text{-}90days}$	ab_{ia}	0.081 (0.118)	-0.036, 0.420
$DUP_{3mths\text{-}1yr}$	ab_{ia}	0.031 (0.087)	-0.073, 0.297

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval.

Pre-morbid functioning

The effect of pre-morbid functioning on long-term positive symptoms was partly mediated by the intercept latent variable (i.e. level of symptoms at initial recovery) as shown in Table 8-11 (ab_i = 2.002; 95% CI (0.374, 5.143)). The mediation effect is partial since there was a statistically significant direct effect of pre-morbid functioning on long-term outcome (c' = 3.524; 95% CI (0.391, 6.657)) whilst accounting for the mediators (see Table 8-3). There was no evidence that the short-term change that occurred subsequent to initial recovery (as represented by the slope latent factor) mediated the effects of pre-morbid functioning on long-term positive symptoms, nor was admission symptoms a significant mediator. The implication of these results is that the effect of pre-morbid functioning is transmitted on long-term symptom levels

both directly and indirectly, with the indirect effect manifested via its impact on the intercept latent variable (i.e. level of symptoms at initial recovery).

Table 8-11. Indirect effects of pre-morbid functioning on long-term symptom levels: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals. Significant effects are presented in bolded text.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI
Pre-morbid functioning → intercept of STT → long-term symptoms	$\boldsymbol{ab_i}$	**2.002 (1.176)**	**0.374, 5.143**
Pre-morbid functioning → slope of STT → long-term symptoms	ab_s	-0.106 (1.690)	-4.923, 1.839
Pre-morbid functioning→ Admission symptoms → long-term symptoms	ab_{ia}	-0.094 (0.205)	-0.713, 0.126

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval.

8.3.4 Model 3 Summary

There were several notable findings emanating from these analyses:

Prediction of long-term outcome

Firstly, the effect of pre-morbid functioning on long-term positive symptoms was partially mediated by the level of positive symptoms at initial recovery point, as represented by the intercept latent variable. This mediation effect was partial, since pre-morbid functioning also directly predicted long-term outcome, with poorer pre-morbid functioning predictive of greater severity of long-term positive symptoms. Secondly, the effect of DUP on long-term outcome was completely mediated by the intercept latent variable, with effects of shorter DUP levels (0-7 days; 8-28 days; 29-90 days duration of untreated psychosis) transmitted on long-term symptom levels solely through their effect on level of positive symptoms at initial recovery following the psychotic episode.

No direct or indirect effects of gender or age at onset of psychosis on long-term outcome were detected. Level of positive symptoms at initial recovery (represented by the intercept latent variable) remained a significant predictor of long-term outcome

when the four baseline characteristics were taken into account. The short-term change that occurred subsequent to initial recovery (i.e. the slope latent variable) was not predictive of long-term outcome, regardless of whether the four presenting features were considered or not.

Prediction of short-term outcome

Better pre-morbid functioning and shorter DUP levels of up to 90 days, as compared with DUP in excess of one year, each directly and independently predicted lower psychotic symptom levels at initial recovery (represented by the intercept latent variable). Symptom levels at admission no longer predicted short-term symptom levels at initial recovery once participant presenting features were controlled. There was no evidence that these baseline features transmitted their effects on the short-term symptom trajectory indirectly, thus ruling out mediation scenarios.

8.4 Model 4 : Effects of Baseline DSM-IV Psychotic Diagnosis on Short and Long-Term Positive Symptoms

The next set of questions relates to the inclusion of a predictor, DSM-IV diagnosis of the first episode of psychosis, which was ascertained shortly after entry to the service. This predictor has the potential to differentiate positive symptom trajectories and final long-term outcome, over and above the capacity of other baseline clinical and demographic predictors. The main difference between this model and the previous model is the addition of baseline DSM-IV diagnosis as a predictor of these outcomes. A detailed description of DSM-IV diagnosis is presented in Method (Chapter 4). Diagnoses were grouped into six broad categories:

(vii) Schizophrenia (reference category);
(viii) Schizophreniform;
(ix) Schizoaffective disorder;
(x) Bipolar psychotic disorder;
(xi) Depressive Psychosis;
(xii) Other psychotic disorders (comprising psychotic disorder NOS, delusional disorder, brief Psychotic disorder).

The nature of diagnostic effects on the severity of positive symptoms at different stages of the illness was examined, for instance, whether the effect of a particular diagnostic category (relative to schizophrenia, which was the reference category) on a dependent variable (such as short-term or long-term symptoms) was direct in nature, or whether the effect was mediated by intervening variable(s) in the model.

A path diagram representing the relationships between the observed and latent variables in this final model is presented in Figure 8.4. The single DSM-IV diagnosis box is actually a series of dummy variables, each with its own set of parameters. Model coefficients for each diagnostic dummy variable indicate the differential effect of that diagnosis (as opposed to being assigned a diagnosis of schizophrenia) on the dependent variable(s), adjusting for other variables in the model. This new observed variable is exogenous. All paths in the preceding model were retained. Similar to the previous model, positive symptoms score at long-term follow-up was specified as an endogenous distal outcome variable, and was predicted by four groups of variables:

(i) positive symptoms at admission;

(ii) the two latent growth trajectory factors underlying the short-term growth trajectory (i.e. the intercept and slope);

(iii) the four participant presenting features, and;

(iv) the five DSM-IV diagnostic dummy variables.

This figure also depicts the short-term trajectory (over the 1-year interval subsequent to initial recovery) being predicted by: positive symptoms at admission, the four presenting features and DSM-IV diagnosis. Level of symptoms at admission is predicted by the four presenting features and DSM-IV diagnosis.

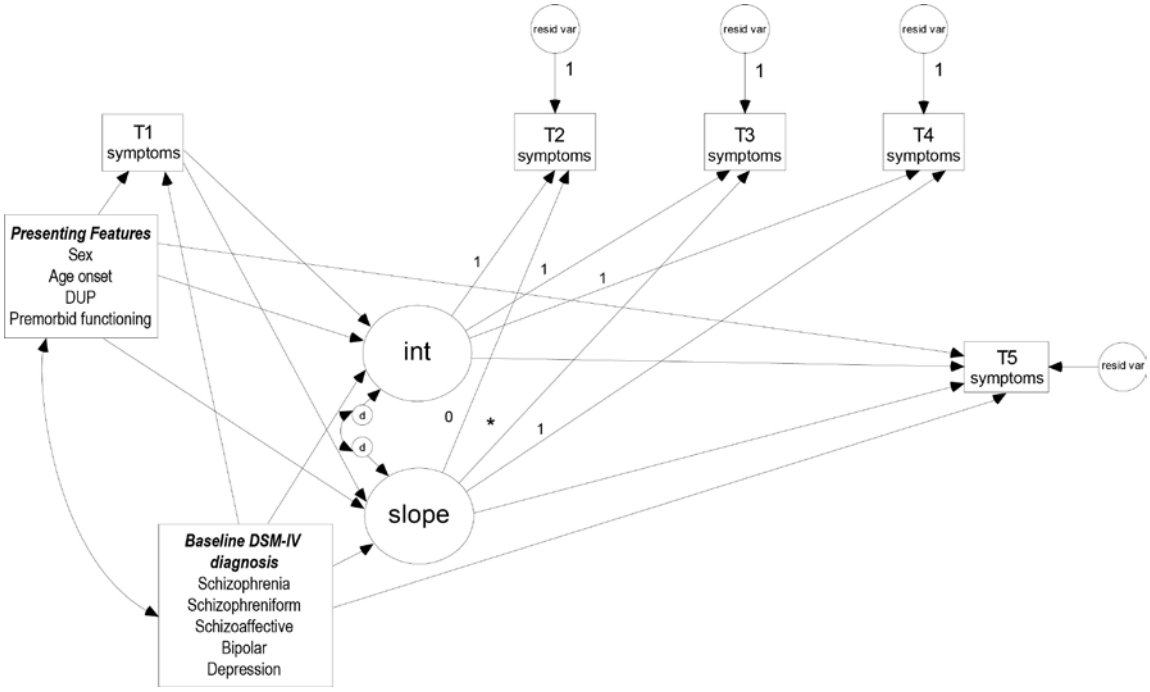


Figure 8.4. Conditional non-linear positive symptom latent trajectory model, incorporating direct effects of DSM-IV diagnosis (bolded), gender, age at onset of psychosis, DUP and pre-morbid functioning as predictors of severity of symptoms (i) at admission; (ii) the short-term growth trajectory and (iii) long-term follow-up. Each arrow actually represents multiple paths from the multi-category DSM-IV diagnosis predictor to each dependent variable.

As in model 3, positive symptoms at admission, age at onset of psychosis, and pre-morbid functioning were centred by subtracting the sample mean of each variable from each individual's observed value on that variable to facilitate interpretability. The covariance between the disturbance terms of the intercept and slope was constrained

to zero. The fit of this model was very good as estimated using MLR (χ^2 = 22.040, df=17, p=0.1832; CFI = 0.982; RMSEA = 0.027 (95% CI <0.001, 0.055); SRMR = 0.016).

8.4.1 Model 4 Research Questions

Similar to Model 3, the research questions are divided into two sections:

(i) Section 8.4.2: identification of direct effects of DSM-IV diagnosis on short-term positive symptom trajectories and long-term outcome;

(ii) Section 8.4.3: identification of indirect effects of DSM-IV diagnosis on short-term trajectories and long-term outcome.

Section 8.4.2 relates to direct effects for this model specification, in particular, whether DSM-IV diagnosis is able to differentiate: (a) symptom levels at admission; (b) the short-term latent growth trajectory; or (c) long-term outcome.

Section 8.4.3 comprises two distinct research questions regarding the possibility of the presence of mediated effects, specifically: (a) whether the effect of each diagnostic category on the short-term trajectory (STT) in the 1-year interval subsequent to initial recovery is mediated fully or partly by admission symptoms, and; (b) whether the effect of each diagnostic category (relative to schizophrenia) on distal long-term symptom levels is mediated either fully or partly by level of symptoms at admission, and/or by the latent trajectory variables (i.e. intercept and slope).

8.4.2 Direct effects

8.4.2.1 Does baseline diagnosis directly predict symptom levels at admission?

Individuals who received a diagnosis of bipolar psychotic disorder at baseline were rated with significantly less severe positive symptoms at admission compared with subjects with schizophrenia ($\hat{\gamma}$ = -1.568; 95% CI (-2.989, -0.147)), as did individuals diagnosed with other psychotic disorders ($\hat{\gamma}$ = -2.861; 95% CI (-4.711, -1.011)); see Table 8-12. Those diagnosed with schizophreniform disorder, schizoaffective disorder or depressive psychosis disorder did not differ significantly from those diagnosed with schizophrenia, with respect to positive symptom levels at admission.

8.4.2.2 Does baseline DSM-IV diagnosis directly predict the latent growth factors?

This question aims to identify whether particular psychotic diagnoses directly predict:

c) Initial symptom levels at the starting point of the trajectory (i.e. intercept) and/or;

d) the short-term change (i.e. slope) that occurs over the subsequent 1-year interval.

Subjects with schizophreniform disorder, bipolar psychotic disorder, depressive psychosis and other psychotic disorders (comprising psychotic disorder NOS, delusional disorder and, brief psychotic disorder) exhibited significantly less severe levels of positive symptoms at the starting point of the short-term trajectory (i.e., the intercept) compared with subjects diagnosed with schizophrenia (see Table 8-12). For instance, subjects with bipolar disorder scored an average of 2.5 points less compared with subjects with schizophrenia ($\hat{\gamma}$ = -2.517; 95% CI (-3.606, -1.428)), with a similar effect for subjects with other psychotic disorders ($\hat{\gamma}$ = -2.117; 95% CI (-3.616, -0.619)). The effect for subjects with depressive psychosis was slightly more modest in comparison ($\hat{\gamma}$ = -1.493; 95% CI (-2.573, -0.413)), and was similar to the effect for subjects with schizophreniform disorder ($\hat{\gamma}$ = -1.532; 95% CI (-2.649, -0.415)). Individuals with a baseline diagnosis of other psychotic disorders (comprising delusional disorder, psychotic disorder NOS or brief psychotic disorder) appeared to experience an overall increase in positive symptom levels over the 1-year short-term trajectory ($\hat{\gamma}$ = 1.276; 95% CI (0.068, 2.483)) compared to subjects with schizophrenia.

8.4.2.3 Does baseline DSM-IV psychotic diagnosis directly predict long-term outcome?

Table 8-12 shows that baseline psychotic diagnosis did not directly predict level of positive symptoms at long-term follow-up (see final column in table). These direct paths to long-term outcome were characterised by small unstandardised coefficients and probability values in excess of p> 0.251.

Table 8-12. Direct effects: Unstandardised estimates (regression coefficients, with MLR standard errors) for (i) admission positive symptoms, regressed on gender, age at onset, DUP, pre-morbid functioning and DSM-IV diagnosis ; (ii) random intercepts and random slopes of the short-term positive symptom trajectory, regressed on gender, age at onset, DUP, pre-morbid functioning, admission positive symptoms and DSM-IV diagnosis ; and (iii) long-term positive symptoms, regressed on (a) gender, age at onset, DUP, pre-morbid functioning and DSM-IV diagnosis; (b) short-term trajectory random intercepts and (c) slopes; (d) positive symptoms at admission, and; (e) DSM-IV diagnosis.

Outcome:	***Admission symptoms***		***Short-term change 1-year subsequent to initial recovery***				***Level of symptoms at long-term follow-up***	
			Intercept		***Slope***			
	Estimate(SE)	***p-value***	**Estimate(SE)**		**Estimate(SE)**	***p-value***	**Estimate(SE)**	
Predictors								
DSM-IV diagnosis[1]								
Schizophreniform	-0.691	0.282	**-1.532**	**0.007**	0.841	0.205	-1.221	0.251
	(0.642)		**(0.570)**		(0.664)		(1.062)	
Schizoaffective	-0.423	0.436	-0.483	0.483	-0.149	0.850	0.803	0.364
	(0.544)		(0.688)		(0.789)		(0.885)	
Bipolar disorder	**-1.568**	**0.031**	**-2.517**	**<0.001**	0.854	0.197	-0.745	0.497
	(0.725)		**(0.555)**		(0.662)		(1.097)	
Depressive psychosis	-0.969	0.174	**-1.493**	**0.007**	0.027	0.964	0.275	0.775
	(0.713)		**(0.551)**		(0.594)		(0.961)	
Other psychotic disorders	**-2.861**	**0.002**	**-2.117**	**0.006**	**1.276**	**(0.038)**	-0.800	0.562
	(0.944)		**(0.765)**		**(0.616)**		(1.379)	
Gender:	-0.185	0.660	0.012	0.973	-0.026	0.955	-0.105	0.826
	(0.419)		(0.373)		(0.451)		(0.477)	
Age at onset:	0.026	0.634	-0.043	0.389	0.047	0.381	0.108	0.097
	(0.054)		(0.050)		(0.053)		(0.065)	
DUP[2]:								
0-7 days	0.155	0.837	-1.368	0.055	<0.001	>0.999	-1.561	0.148

Outcome:	*Admission symptoms*		*Short-term change 1-year subsequent to initial recovery*				*Level of symptoms at long-term follow-up*	
			Intercept		*Slope*			
	Estimate(SE)	***p-value***	**Estimate(SE)**		**Estimate(SE)**	***p-value***	**Estimate(SE)**	
Predictors								
	(0.753)		(0.712)		(0.888)		(1.078)	
8-28 days	-0.062	0.931	**-1.694**	**0.023**	0.743	0.413	-1.574	0.153
	(0.714)		**(0.744)**		(0.908)		(1.102)	
29-90 days	-0.353	0.577	-1.010	0.176	0.245	0.765	-1.892	0.071
	(0.633)		(0.747)		(0.823)		(1.047)	
3-months-1 year	-0.265	0.631	-0.707	0.268	0.431	0.592	-1.241	0.216
	(0.551)		(0.638)		(0.804)		(1.003)	
Pre-morbid functioning:	0.699	0.557	**2.520**	**0.035**	0.045 (1.273)	0.972	**3.611**	**0.023**
	(1.191)		**(1.195)**				**(1.590)**	
Admission symptoms	-	-	0.058	0.264	0.033	0.578	-0.114	0.064
			(0.052)		(0.059)		(0.062)	
Starting point of trajectory (Intercept factor)	-	-	-	-	-	-	**0.625**	**0.007**
							(0.231)	
Short-term trajectory: (Slope factor)	-	-	-	-	-	-	0.620	0.256
							(0.546)	

[1] The reference category against which each DSM-IV category is compared is schizophrenia.

[2] The reference category against which each research question category is compared is very long DUP $_{1+\text{ years}}$

8.4.3 Indirect effects

8.4.3.1 Are the effects of baseline psychotic diagnosis on the short-term symptom trajectories mediated in full or in part by level of symptoms at admission?

This question examined whether DSM-IV baseline diagnosis indirectly affects the short-term change (represented by the intercept and/or slope latent variables) that occurs from initial recovery via its effect on level of symptoms at admission. Table 8-13 presents the unstandardised indirect effects of each of the diagnostic categories on the short-term trajectory latent variables: the intercept and the slope. Each diagnostic category was compared with the reference category, schizophrenia disorder.

There was no evidence that baseline DSM-IV diagnosis indirectly impacted on either the starting point of the short-term trajectory at initial recovery (i.e., the intercept latent variable, or on rates of change (i.e., the slope latent variable) via admission symptoms, as indicated by the asymmetric 95% confidence intervals for the specific indirect effects, each of which included zero. Therefore, as presented in Table 8-12, the effects of schizophreniform disorder, bipolar psychotic disorder and depressive psychosis were transmitted on the short-term symptom trajectory solely through their direct effects on level of positive symptoms at initial recovery following the psychotic episode. The effect of other psychotic disorders on the other hand, was transmitted directly to the short-term symptom trajectory via its impact on the starting point of the trajectory (intercept) and on rates of change (slope).

Table 8-13. Indirect effects of the DSM-IV diagnoses (compared with schizophrenia disorder) on the starting point (i.e., intercept) and rates of change (i.e., slope) of the short-term positive symptom trajectory, via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI [1]
DSM-IV diagnosis[2] → admission symptoms → intercept of STT			
Schizophreniform	ab_{ia}	-0.040 (0.065)	-0.258, 0.027
Schizoaffective	ab_{ia}	-0.024 (0.050)	-0.199, 0.029
Bipolar	ab_{ia}	-0.091 (0.102)	-0.381, 0.037
Depressive psychosis	ab_{ia}	-0.056 (0.077)	-0.314, 0.026
Other psychotic disorder	ab_{ia}	-0.165 (0.167)	-0.592, 0.085
DSM-IV diagnosis[2] → admission symptoms → slope of STT			
Schizophreniform	ab_{ia}	-0.023(0.063)	-0.251, 0.045
Schizoaffective	ab_{ia}	-0.014(0.047)	-0.196, 0.035
Bipolar	ab_{ia}	-0.052(0.109)	-0.357, 0.114
Depressive psychosis	ab_{ia}	-0.032(0.079)	-0.306, 0.062
Other psychotic disorder	ab_{ia}	-0.094(0.192)	-0.583, 0.229

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval.

[2] The reference category against which each DSM-IV category is compared is schizophrenia.

8.4.3.2 Are the effects of baseline diagnosis on long-term symptom levels mediated in full or in part by the latent trajectory variables or by positive symptom levels at admission?

This question concerns whether baseline psychotic diagnosis indirectly impacts on long-term positive symptom outcome via two possible pathways: (i) via its effect on level of symptoms at admission, and/or (ii) via its effect on the short-term change (represented by the intercept and/or slope latent variables) that occurs after initial recovery. Table 8-14 presents the unstandardised indirect effects of each of the diagnostic categories on long-term positive symptoms for each model parameter. Each diagnostic category was compared with the reference category, schizophrenia.

Table 8-14. Indirect effects of the five DSM-IV baseline diagnostic categories (compared with schizophrenia) on long-term symptom levels: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals. Significant effects are presented in bolded text.

Specific indirect effect	Mediation notation	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI
DSM-IV diagnosis → intercept of STT → long-term symptoms			
Schizophreniform	$\boldsymbol{ab_i}$	**-0.957 (0.576)**	**-2.516, -0.158**
Schizoaffective	ab_i	-0.302 (0.503)	-1.632, 0.490
Bipolar	$\boldsymbol{ab_i}$	**-1.572 (0.765)**	**-3.439, -0.400**
Depressive psychosis	$\boldsymbol{ab_i}$	**-0.933 (0.523)**	**-2.300, -0.179**
Other psychotic disorder	$\boldsymbol{ab_i}$	**-1.323 (0.795)**	**-3.543, -0.249**
DSM-IV diagnosis → slope of STT → long-term symptoms			
Schizophreniform	ab_s	0.522 (1.378)	-0.553, 5.891
Schizoaffective	ab_s	-0.093 (1.160)	-3.093, 1.192
Bipolar	ab_s	0.529 (1.429)	-0.548, 5.645
Depressive psychosis	ab_s	0.017 (0.852)	-1.237, 1.832
Other psychotic disorder	ab_s	0.791 (1.811)	-0.640, 6.675
DSM-IV diagnosis → admission symptoms → long-term symptoms			
Schizophreniform	ab_{ia}	0.079 (0.120)	-0.049, 0.454
Schizoaffective	ab_{ia}	0.048 (0.095)	-0.062, 0.331
Bipolar	ab_{ia}	0.178 (0.195)	-0.033, 0.681
Depressive psychosis	ab_{ia}	0.110 (0.150)	-0.043, 0.531
Other psychotic disorder	ab_{ia}	0.325 (0.326)	-0.082, 1.076

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval.

[2] The reference category against which each DSM-IV category is compared is schizophrenia.

Four DSM-IV diagnostic categories impacted indirectly on long-term positive symptoms via the intercept latent variable (i.e., at the starting point of the STT) as shown in Table 8-14. For instance, subjects diagnosed with bipolar psychotic disorder at baseline experienced an average 1.572 point reduction (95% CI (-3.439, -0.400)) in severity of positive symptoms at long-term follow-up as compared to subjects with schizophrenia disorder, via its impact on the intercept latent variable. Other diagnostic categories which indirectly resulted in a reduction in severity of positive symptoms at

long-term follow-up via the intercept included other psychotic disorders (ab_i = -1.323; 95% CI (-3.543, -0.249), schizophreniform disorder (ab_i = -0.957; 95% CI (-2.516, -0.158)) and depressive psychosis (ab_i =-0.933; 95% CI (-2.300, -0.179)). Partial mediation is ruled out since there was no evidence of any direct effect of each of these diagnostic categories on long-term outcome whilst accounting for the mediators (see Table 8-12). There was no evidence of any other form of mediation: neither admission symptoms nor the short-term change that occurred subsequent to initial recovery (as represented by the slope latent factor) were significant mediators of baseline diagnosis. The implication of these results is that the effects of diagnosis are transmitted on long-term symptom levels solely through their effect on level of positive symptoms at initial recovery following the psychotic episode.

8.4.4 Model 4 Summary

Prediction of long-term outcome

There was evidence that baseline psychotic diagnosis transmits its effect on long-term outcome solely through its effect on level of positive symptoms at initial recovery following the psychotic episode. These diagnoses included schizophreniform disorder, bipolar psychotic disorder, depressive psychosis and other psychotic disorder. Better pre-morbid functioning and lower levels of psychotic symptoms at initial recovery (i.e., the intercept) remained significant direct predictors of better long-term symptomatic outcome when the effects of all other variables in the model, including psychotic diagnosis, were accounted for. There was no effect of admission symptoms on long-term outcome when effects of all other variables were accounted for, nor did the short-term change that occurred subsequent to initial recovery (i.e. the slope latent variable) predict long-term outcome.

Prediction of short-term outcome

Firstly, baseline psychotic diagnosis directly predicted short-term positive symptoms: participants diagnosed with bipolar psychotic disorder and other psychotic disorders exhibited significantly less severe symptoms at admission compared with subjects diagnosed with schizophrenia, whilst schizophreniform, bipolar, depressive and other psychotic disorders were each significantly differentiated from schizophrenia disorder by exhibiting less severe positive symptoms at initial recovery (i.e., intercept).

Furthermore, individuals diagnosed with other psychotic disorders (comprising psychotic disorder NOS, delusional disorder and brief psychotic disorder) experienced an overall increase in symptoms over the short-term trajectory (i.e. the slope latent variable) as compared with individuals with schizophrenia.

Secondly, effects of participants' presenting features on short-term outcome obtained in the previous model were attenuated when DSM-IV diagnosis was included; only pre-morbid functioning and short DUP of 8-28 days remained significant predictors of level of positive symptoms at initial recovery (i.e., the starting point of the STT). As in Model 3, none of the four presenting features predicted the short-term change (i.e. slope) that occurred subsequent to initial recovery, nor did they predict admission symptom levels, which in turn did not predict the short-term change represented by the intercept or slope latent variable. None of the baseline psychotic diagnosis categories transmitted their effects on the short-term symptom trajectory indirectly, via admission symptoms.

8.5 Summary of Model Fitting Results for Positive Symptoms

The unconditional model presented in Section 8.1 demonstrated that the average short-term trajectory (STT) measured on up to three occasions over the 1-year interval subsequent to initial recovery from the first psychotic episode was essentially non-linear. Individuals varied significantly in their initial symptom levels at the starting point of the trajectory, but individual variability in rates of change over the short-term trajectory failed to be captured by the model.

Section 8.2 focused on the prediction of short-term symptom trajectories and long-term outcomes; results indicated that the effect of level of symptoms at admission on long-term symptom levels was completely mediated by the starting point of the short-term trajectory (i.e. the intercept latent factor). In other words, positive symptom levels at admission appeared to transmit their effect on long-term positive symptom outcome solely through their effect on level of symptoms at initial recovery, which itself directly predicted long-term outcome. No predictive effect of short-term change occurring in the 1-year interval subsequent to initial recovery (slope variable) was detected.

Section 8.3 examined effects of four participant presenting features on short- and long-term symptoms; age at onset of psychosis, gender, duration of untreated psychotic symptoms (DUP) and pre-morbid functioning. Findings emerging from these analyses were five-fold: (i) effects of DUP and pre-morbid functioning on the short-term trajectory were direct in nature, with shorter DUP and better pre-morbid functioning predictive of less severe psychotic symptoms at initial recovery (i.e., intercept latent variable); (ii) admission symptoms no longer predicted short-term symptom levels once the four presenting features were taken into account; (iii) pre-morbid functioning exerted its effects on long-term symptoms in a dual manner, with its effect being partially mediated by symptom levels at initial recovery (i.e. the intercept) in addition to a direct predictive effect on long-term outcome; (iv) the effect of DUP on long-term outcome was completely mediated by the intercept latent variable, with shorter DUP categories (0-7 days; 8-28 days; 29-90 days duration of untreated psychosis, as compared with very long DUP in excess of one year) conferring beneficial effects on long-term symptom levels solely through their effect on level of positive symptoms at the starting point of the short-term trajectory, initial recovery; (v) level of positive symptoms at initial recovery remained a significant predictor of long-term outcome, but the short-term change that occurred in the 1-year interval subsequent to initial recovery was not.

Section 8.4 introduced baseline DSM-IV psychotic diagnosis as an independent predictor of short-term and long-term outcome, taking into account the effect of the other factors. There were four main findings. Firstly, the nature of the effect of diagnosis on the short-term symptom trajectory was direct, with schizophreniform disorder, bipolar psychotic disorder, depressive psychosis and other psychotic disorder groups experiencing significantly less severe levels of positive symptoms at initial recovery compared with subjects diagnosed with schizophrenia. Interestingly, individuals diagnosed with other psychotic disorders experienced an overall *increase* in symptoms over the short-term trajectory (i.e. the slope latent variable) compared with subjects diagnosed with schizophrenia. Subjects diagnosed with bipolar psychotic disorder and other psychotic disorders had significantly less severe symptoms at admission.

Secondly, effects of participant presenting features on short-term outcome were attenuated when diagnosis was taken into account; only pre-morbid functioning and short DUP of 8-28 days remained significant predictors of the intercept latent variable. As in model 3, none of the four baseline characteristics predicted the short-term change (i.e. slope) that occurred subsequent to initial recovery, nor did they predict admission symptom levels, which in turn did not predict the short-term trajectory represented by the intercept or slope latent variable.

Thirdly, the effects of particular psychotic diagnoses on long-term outcome were significantly and fully mediated by the level of positive symptoms at initial recovery, as represented by the intercept latent variable. Diagnoses which indirectly impacted on long-term outcome via this mechanism included schizophreniform disorder, bipolar psychotic disorder, depressive psychosis and other psychotic disorder. This provides some evidence that baseline psychotic diagnosis transmits its effect on long-term outcome solely through its effect on level of positive symptoms at initial recovery following the psychotic episode, with no evidence of any direct effect of psychotic diagnosis on long-term outcome.

Fourthly, pre-morbid functioning remained a significant predictor of long-term outcome when the effects of all other variables in the model, including psychotic diagnosis, were accounted for, with poorer pre-morbid functioning predictive of greater severity of long-term positive symptoms. Consistent with results obtained in the previous model 3, pre-morbid functioning was the only baseline characteristic to directly impact on long-term outcome, along with the intercept latent variable (i.e. level of symptoms at initial recovery).

8.6 General conclusion

The change in mean positive symptoms over the 1-year interval subsequent to initial recovery (remission/stabilisation of symptoms) from the initial psychotic episode conformed optimally to a non-linear trajectory. Study participants scored a mean equivalent of 'very mild' on positive symptoms at the point of initial recovery, with a statistically significant decrease in symptoms over the STT. Individuals varied significantly in their initial symptom levels at the beginning of the trajectory, but not

in their rates of change. The starting point of the trajectory significantly mediated the effects of DUP, premorbid functioning, and diagnosis on long-term positive symptoms. It also directly predicted long-term symptoms, thus serving a dual role as mediator and predictor. Only one other variable directly predicted long-term symptoms; premorbid functioning. Predictors of the short-term trajectory included the four participant presenting features; gender, age at onset of psychosis, DUP, premorbid functioning, along with DSM-IV diagnosis. Effects of the four presenting features were substantially attenuated when diagnosis was included.

9 NEGATIVE SYMPTOMS

This chapter reports the characteristics and predictors of short-term trajectories (STTs) and long-term outcome for each of four negative symptom subscales of the Scale for the Assessment of Negative Symptoms (SANS): affective flattening, alogia, avolition and anhedonia. The approach taken in the modelling of these four scales is identical to that presented in Positive Symptoms (Chapter 8), with the latent growth curve models developed in four incremental stages in order to address the defined research questions. Results from each of these stages are presented sequentially, with the chapter partitioned in four distinct sections, each corresponding to a particular stage of the model.

The unconditional model presented in Section 9.1 demonstrates that the shape of the affective flattening, alogia, avolition, and anhedonia trajectories is linear. Section 9.2 focuses on the prediction of short-term negative symptom trajectories and long-term symptomatic outcomes by the severity of negative symptoms at admission. Section 9.3 examines the nature of the effects of four presenting features of participants on short-term and long-term negative symptoms; age at onset of psychosis, gender, duration of psychotic symptoms (DUP) and pre-morbid functioning. Section 9.4 introduces baseline DSM-IV psychotic diagnosis as a final predictor of short-term and long-term negative symptom outcomes. A summary of the findings is provided at the end of the chapter.

The modelling presented below repeats the evolution described for positive symptoms in Chapter 8 for each of the four negative symptom subscales, and as such, is necessarily repetitious. Except where noted, all technical details are identical. Outcomes of the models are summarised in **Section 9.5** (Press Ctrl + click on hyperlink to go directly to summary).

9.1 Model 1: Growth Characteristics of Negative Symptoms Over Short-Term Follow-Up

A base model for each of the four types of negative symptoms, affective flattening, alogia, avolition and anhedonia, was developed as the framework for subsequent model stages. This model fitted an unconditional growth curve to the negative

symptoms data at the starting point of the trajectory (initial recovery), 6-month and 1-year follow-up. The unconditional models capture two aspects of symptom presentation and change: firstly, the characteristics of the short-term psychopathology growth trajectory for the overall group were identified; secondly, the degree to which there was individual variability in psychopathology trajectory estimates across individuals was assessed. These questions are detailed in sections 9.1.1 and 9.1.2 below.

The four negative symptoms subscales were scaled to a common metric of 0 to 5 (achieved by dividing each subscale score by the number of items in the scale), where 0 = 'None'; 1 = 'Questionable'; 2 = 'Mild'; 3 = 'Moderate'; 4 = 'Marked'; 5 = 'Severe'. This was done to facilitate comparisons between the different subscales, which contained differing numbers of items. The latent growth factors and observed variables are shown in Figure 9.1 below, which represents the unconditional model for each of the four negative symptoms. The first factor represents the intercept component of the trajectory and the second factor represents the slope component.

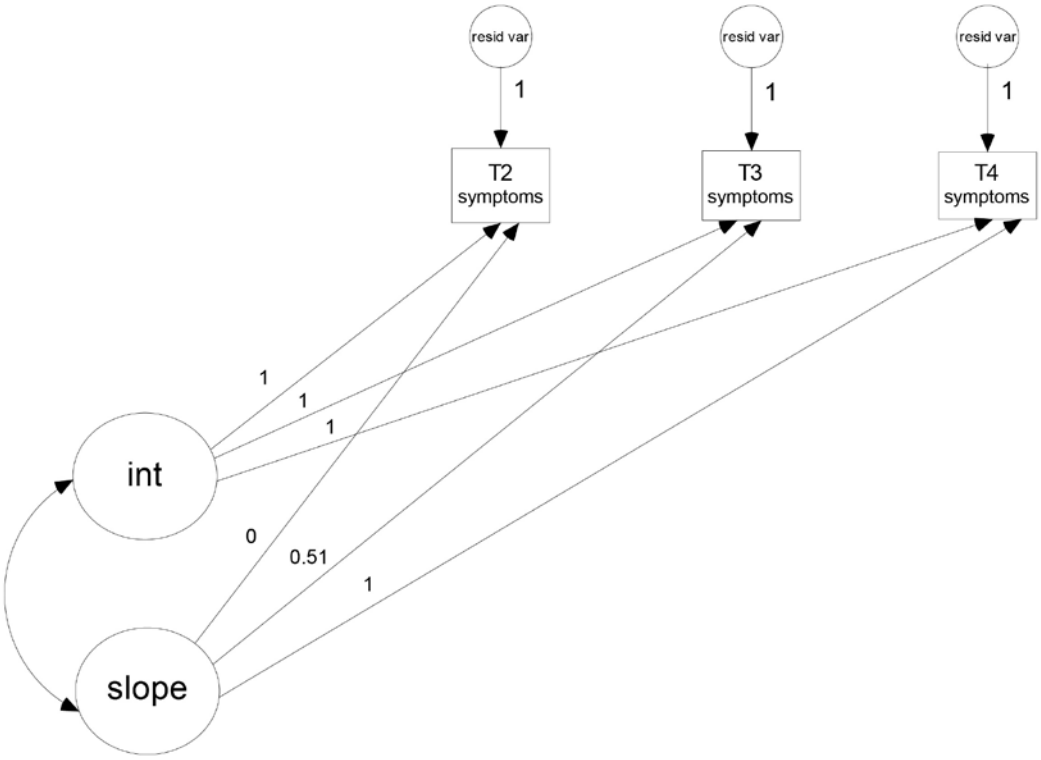


Figure 9.1. Unconditional linear latent trajectory model for Negative symptoms measured at the starting point of the short-term trajectory; 6-month follow-up and 1-year follow-up; latent and observed variables.

9.1.1 What is the overall short-term trajectory for the sample?

This sought to identify:

d) the average initial level of severity at the starting point of each negative symptom trajectory;
e) whether the average symptom severity changes significantly over the 1-year interval subsequent to the starting point, and if so;
f) whether the change over time is best described as linear or non-linear.

The simplest form of model, the linear model, was initially fitted to each of the affective flattening, alogia, avolition and anhedonia subscales. Judging by multiple indices, the linear model fitted well for affective flattening and alogia (see Table 9-1). However, the fit of the linear model for the avolition subscale was marginal (χ^2 = 11.225, df=3, p=0.0106; CFI = 0.944; RMSEA = 0.087 (95% CI = 0.037, 0.145); SRMR = 0.064), and the fit for anhedonia was only minimally improved (χ^2 = 7.687, df=3, p=0.0530; CFI = 0.974; RMSEA = 0.063 (95% CI < 0.001, 0.120); SRMR = 0.041).

Removal of parameter constraints was required to achieve an acceptable fit to these models. This involved allowing the residual variance of one observed variable to be freely estimated (at 6-month follow-up for avolition, and at 1-year follow-up for anhedonia). These model adjustments were identified by inspecting the modification indices (MI) for each model (defined in Statistical Methods, Chapter 5). Of the eight MI values produced for the avolition model, one in particular appeared reasonable in a theoretical sense; inspection of this MI suggested that the residual variance for the observed avolition variable measured at 6-month follow-up be freely estimated (MI=7.974), rather than fixed as per the model default. The fit of the linear model for avolition was greatly improved as a result of this adjustment, with the Satorra-Bentler scaled chi-square difference test (TRd) (refer Statistical Methods, Chapter 5) indicating that this model specification provided a significantly better fit than the simpler linear model (TRd=10.615; df = 1). This model adjustment made little substantive difference to the majority of the model parameters, with the exception of the covariance between the intercept and slope, which became statistically significant (r=-0.338; p=0.003). Thus, individuals with higher initial scores at the starting point of the trajectory showed greater decline in severity over time.

Likewise, for anhedonia, inspection of the MI values for the initial linear model revealed one parameter in particular the freeing of which was theoretically justifiable; the residual variance for the observed anhedonia variable measured at 1-year follow-up (MI=7.354). Freeing up this parameter resulted in a significantly improved fit compared with the simple linear model, as indicated by the Satorra-Bentler scaled chi-square difference test (TRd=6.327, df=1). This adjustment made no substantive difference to model parameters. Fit indices for these modified models are presented in Table 9-1.

Table 9-1. Fit indices of linear unconditional model fitted for affective flattening, alogia, avolition and anhedonia symptoms at initial recovery, 6-months and 1-year follow-up.

	Affective flattening	Alogia	Avolition [1]	Anhedonia [2]
Fit indices for linear model				
Chi-square	1.557	1.465	2.880	0.133
(df)	3	3	2	2
p-value	0.6692	0.6904	0.2369	0.9355
CFI	1.000	1.000	0.994	1.00
RMSEA	< 0.001	<0.001	0.035	< 0.001
95% CI RMSEA	<0.001, 0.066	< 0.001, 0.064	< 0.001, 0.116	<0.001, 0.026
SRMR	0.022	0.017	0.023	0.009

[1] Degrees of freedom are reduced due to the residual variance of avolition at 6-month follow-up being freed to improve fit

[2]Degrees of freedom are reduced due to the residual variance of anhedonia at 1 year follow-up being freed to improve fit

Model estimates relating to question 9.1.1 (a) identification of average initial level of severity at starting point (i.e., intercept latent variable) and question 9.1.1 (b) the average change in symptom severity over the 1-year interval subsequent to starting point (i.e., slope latent variable), are presented for each of the four negative symptoms in Table 9-2.

Table 9-2. Short-term trajectory estimates (SE) for each of the four negative symptoms: Average initial symptom severity at starting point (intercept) and average symptom severity change (slope) over the 1-year interval following starting point, with probability values.

	Affective flattening	Alogia	Avolition	Anhedonia
Mean intercept	0.892	0.597	1.103	1.598
(SE)	(0.045)	(0.035)	(0.051)	(0.058)
p-value	< 0.001	< 0.001	< 0.001	< 0.001
Mean slope	-0.226	-0.081	0.007	-0.105
(SE)	(0.052)	(0.047)	(0.073)	(0.071)
p-value	< 0.001	0.083	0.926	0.141

Estimates of the mean intercept of the trajectories for the four negative symptoms ranged from 0.597 (alogia) to 1.598 (anhedonia), as shown in Table 9-2. These estimates correspond to average ratings at the trajectory starting point of 'None' to 'Questionable' for alogia and affective flattening, and ratings of 'Questionable' to 'Mild' for avolition and anhedonia. Estimates of the mean slopes of the trajectories were not significantly different from zero for alogia, avolition and anhedonia, reflecting that there was little change in these symptoms over the 1-year short-term trajectory. Conversely, the change in affective flattening over the 1-year interval was significantly different from zero, with an average decrease of 0.226 points over this period.

9.1.2 What is the nature of variation of short-term trajectories between individuals?

This question aims to identify whether this unconditional model is able to capture the individual variability in trajectory estimates, specifically:

c) initial levels of symptom severity at the starting point of the trajectory (i.e., intercept latent factor)

d) rates of change in symptom severity over the 1-year interval subsequent to the starting point (i.e., slope latent factor).

Model fitting provided estimates of the variance of the intercepts and the slopes for each of the four negative trajectories. These estimates are presented in Table 9-3.

Table 9-3. Intercept and slope variance estimates, and covariance estimates (SE) for the four negative symptom trajectories, with probability values.

	Affective flattening	Alogia	Avolition	Anhedonia
Intercept variance (SE)	0.498 (0.064)	0.282 (0.045)	0.662 (0.096)	0.774 (0.094)
p-value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Slope variance (SE)	0.216 (0.112)	0.263 (0.086)	1.050 (0.214)	0.770 (0.177)
p-value	0.054	**0.002**	**< 0.001**	**< 0.001**
Intercept and slope covariance	-0.568 (0.083)	-0.411 (0.125)	-0.405 (0.081)	-0.203 (0.102)
p-value	**<0.001**	**0.001**	**<0.001**	**0.048**

For each of the four symptom trajectories, there was significant individual variability of the intercept around its mean value. There was also significant variability of the slope around its mean value for each symptom subscale, with the exception of affective flattening; the individual variability in affective flattening trajectories failed to be captured by the model, resulting in a marginally non-significant value (p=0.054). In other words, patients varied significantly in their starting point scores on four types of negative symptoms, and in their rates of change in the subsequent 1-year interval on all negative symptoms except for affective flattening. The significant negative covariance between the intercept and slope, for all subscales, implies that individuals with higher initial scores at the starting point of the trajectory show greater decline in severity over time.

9.1.3 Model 1 Summary

These results provide answers to two questions of interest. Firstly, the average starting points of each of the four negative symptom trajectories at the point of stabilisation of the illness were identified; these range from 'Zero' to 'Mild'. On average, there was little change detected in the severity of alogia, avolition and anhedonia symptoms across the 1-year interval. The shape of the trajectories could best be described as linear for all negative symptom subscales. Secondly, the evidence suggests that there is substantial individual variability in initial starting values of the short-term trajectory for each of the four negative symptoms, and also significant individual variability around the mean slope for all symptoms except for affective flattening. In other words, FEP patients varied significantly in their initial score on all negative symptoms and in

their rates of change in the 1-year interval subsequent to that point for most types of negative symptoms.

9.2 Model 2: Negative Symptoms at Admission and Long-term Follow-up

Measurements of negative symptoms made on two other occasions—at admission to the service and at long-term follow-up—were incorporated in models based on the unconditional linear models from Section 9.1. A path diagram representing the relationships between the observed and latent variables in this model is presented in Figure 9.2. Each subscale at admission was centred by subtracting its sample mean from each individual's observed value, to facilitate interpretability, as detailed in Statistical Methods (Chapter 5).

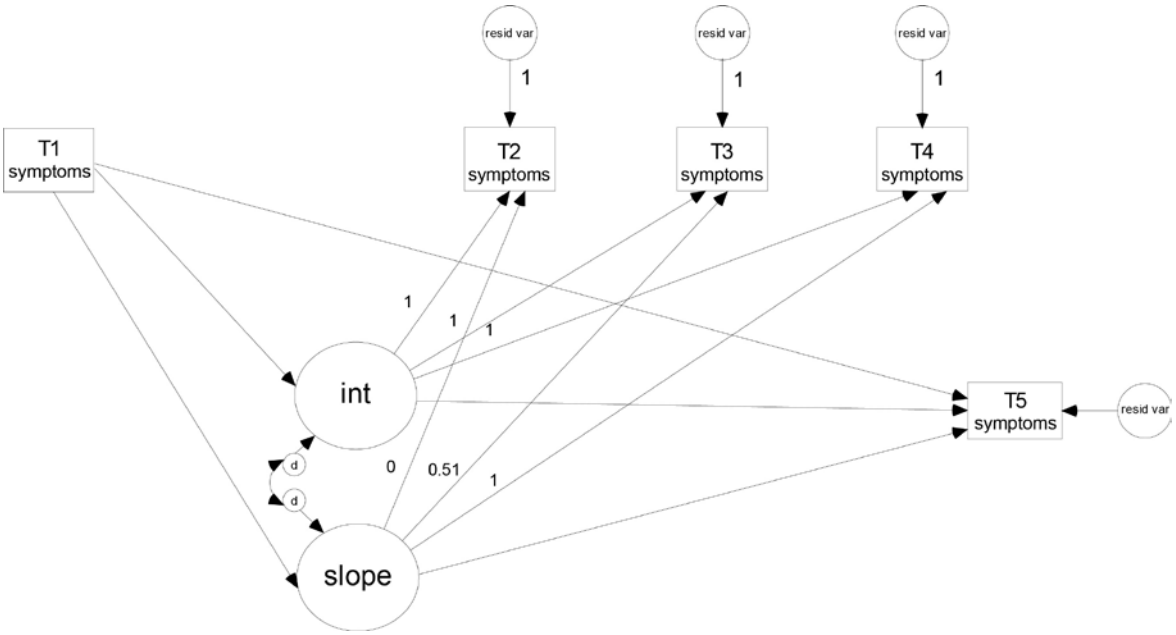


Figure 9.2. Conditional linear latent trajectory model for severity of negative symptoms, incorporating symptom levels at admission as a covariate and long-term (7.3 year) outcome.

The specification of the linear form of the short-term symptom trajectories of all negative symptom scales can be seen from the parameterisation of the slope loadings in Figure 9.2; the first loading (corresponding to the starting point) is fixed to zero; the

second (corresponding to 6-month follow-up) is fixed to 0.51, and the third (corresponding to 1-year follow-up) is fixed to 1. The covariance between the disturbance terms of the intercept and slope was constrained to zero (in this and subsequent models), for all negative symptom scales except for alogia, where the freeing of this parameter resulted in a significant improvement in the fit of the model as indicated by the Satorro-Bentler scaled chi-square difference test (TRd=4.715, df=1). The residual covariance of the observed avolition variable at 6-month follow-up and the anhedonia variable at 1-year follow-up were freely estimated in this and subsequent models, as per the unconditional model specification in Model 1. Model fit indices for each of the four negative symptoms are presented in Table 9-4.

Table 9-4. Fit indices of conditional model 2 for affective flattening, alogia, avolition and anhedonia symptoms.

	Affective flattening	Alogia [1]	Avolition [2]	Anhedonia [3]
Slope factor loadings	0, 0.51, 1	0, 0.51, 1	0, 0.51, 1	0, 0.51, 1
Fit indices				
Chi-square	6.922	7.496	12.886	6.590
(df)	6	5	5	5
p-value	0.3281	0.1863	0.0245	0.2529
CFI	0.997	0.987	0.967	0.995
RMSEA	0.019	0.035	0.063	0.028
95% CI RMSEA	<0.001, 0.069	< 0.001, 0.083	0.021, 0.107	<0.001, 0.078
SRMR	0.022	0.026	0.037	0.024

[1] Degrees of freedom are reduced due to covariance between disturbance terms of intercept and slope for alogia being freely estimated in this model

[2] Degrees of freedom are reduced due to the residual variance of avolition at 6-month follow-up being freely estimated to improve fit, as per previous model

[3] Degrees of freedom are reduced due to the residual variance of anhedonia at 1 year follow-up being freely estimated to improve fit, as per previous model

9.2.1 Model 2 Research Questions

Firstly, questions which relate to direct effects for this model specification will be presented. These questions concern whether negative symptom severity at admission directly predicts: (a) the short-term latent growth trajectory; (b) long-term negative symptoms outcome; or (c) whether the short-term growth trajectory directly predicts long-term outcome. Secondly, mediational investigations will be presented. These analyses examine whether the effect of symptoms at admission on distal long-term

symptom levels is mediated either fully or partly by the latent trajectory variables (i.e. the starting point of the trajectory and/or the subsequent change over the 1-year trajectory). These mediational questions are further elaborated in Mediation (Chapter 6), which contains a full description of criteria necessary to establish the presence of indirect effects.

9.2.2 Direct effects

The magnitude and direction of direct effects in this model are presented in Table 9-5 below as regression coefficients (with robust standard errors and probability values) linking the following observed and latent variables with each other: (i) negative symptom levels at admission; (ii) each of the latent growth factors (the intercept and slope); and (iii) observed long-term negative symptoms.

9.2.2.1 Does symptom severity at admission directly predict the short-term growth trajectory?

This question aims to identify whether admission symptom levels predict:

e) Initial symptom levels at the starting point of the trajectory (i.e. intercept) and/or:

f) the short-term change (i.e. slope) that occurs over the subsequent 1-year interval.

Table 9-5 shows that alogia, avolition and anhedonia symptoms at admission were predictive of higher levels of symptoms at the starting point of the trajectory; a one-point increase in severity of each type of symptom at admission was associated with average increases at each starting point of between 0.259 and 0.523 points. Affective flattening and anhedonia levels at admission additionally predicted the short-term change over the 1-year interval subsequent to their starting points, with higher levels of symptoms at admission significantly associated with decreasing rates of change in symptoms over the short-term trajectory.

9.2.2.2 Does negative symptom severity at admission directly predict long-term negative symptom outcome?

Severity of avolition symptoms at admission was a statistically significant predictor of long-term avolition symptoms when the effects of the other predictors of long-term

outcome (i.e., intercept and slope factors) were controlled; a one-point increase in avolition at admission led to approximately a one-third of a point increase at long-term follow-up, as displayed in Table 9-5. There was no evidence that other types of negative symptoms at admission were directly associated with severity of long-term follow-up symptoms.

9.2.2.3 Does the short-term growth trajectory directly predict long-term symptom severity?

This question sought to investigate whether either of these latent variables predicted long-term negative symptom outcome:

c) Initial symptom levels at the starting point (i.e. intercept) and/or;
d) the short-term change (i.e. slope) that occurs over the 1-year interval subsequent to starting point .

Higher levels of affective flattening, alogia, avolition and anhedonia symptoms at the starting point (i.e., intercept) predicted severity of long-term outcome; a one-point increase in severity of each symptom at the starting point was associated with increases of between 0.406 and 0.872 of a point of the same symptom at long-term follow-up (refer Table 9-5). The slope latent variable for all negative symptom subscales, except for affective flattening, predicted each of their respective long-term outcomes; increasing symptom severity over the short-term trajectory was associated with increased severity of long-term outcomes for these subscales.

Table 9-5. Direct effects: Unstandardised coefficient estimates (with MLR standard errors) for (i) random intercepts and random slopes of the short-term negative symptom trajectories, regressed on admission symptoms; and (ii) long-term negative symptoms, regressed on (a) short-term trajectory random intercepts and (b) slopes, and (c) negative symptoms at admission. Significant effects are presented in bold text.

Outcome	*Short-term change 1-year subsequent to initial recovery*				*Level of symptoms at long-term follow-up*	
Predictors	*Intercept*		*Slope*			
Direct effects	**Estimate (SE)**	***p-value***	**Estimate (SE)**	***p-value***	**Estimate (SE)**	***p-value***
Admission symptoms						
Affective flattening	**0.523 (0.048)**	**< 0.001**	**-0.256 (0.057)**	**< 0.001**	-0.190 (0.351)	0.588
Alogia	**0.259 (0.044)**	**< 0.001**	-0.111 (0.057)	0.054	0.050 (0.050)	0.312
Avolition	**0.359 (0.049)**	**< 0.001**	-0.125 (0.078)	0.108	**0.300 (0.120)**	**0.013**
Anhedonia	**0.467 (0.043)**	**< 0.001**	**-0.152 (0.061)**	**0.013**	0.128 (0.118)	0.278
Starting point of trajectory (Intercept factor)						
Affective flattening	-	-	-	-	**0.616 (0.174)**	**<0.001**
Alogia	-	-	-	-	**0.698 (0.120)**	**< 0.001**
Avolition	-	-	-	-	**0.406 (0.189)**	**0.032**
Anhedonia	-	-	-	-	**0.872 (0.171)**	**< 0.001**
Short-term trajectory (Slope factor)						
Affective flattening	-	-	-	-	-0.742 (1.206)	0.538
Alogia	-	-	-	-	**0.501 (0.151)**	**0.001**
Avolition	-	-	-	-	**0.663 (0.195)**	**0.001**
Anhedonia	-	-	-	-	**0.415 (0.167)**	**0.013**

9.2.3 Indirect effects

The path diagram for the indirect effects is identical to the path diagram in Figure 9.2. The model indirect effects are formalised as a single research question in section 9.2.3.1. Bootstrapped asymmetric 95% confidence intervals were used to detect the presence of mediated effects. Statistical significance of the effect was determined by examining whether zero was included in the confidence interval; if the interval did not

contain zero, then the result was regarded as statistically significant. The bias-corrected bootstrap procedure in MPlus was used for this two mediator model, using 10,000 bootstrap draws. A comprehensive overview of mediation analysis methodology and the bias-corrected bootstrap is provided in Mediation (Chapter 6).

9.2.3.1 Is the effect of severity of symptoms at admission on long-term symptom levels mediated in full or in part by either of the latent trajectory variables?

The effect of admission symptom levels on long-term symptom severity of alogia and anhedonia was completely mediated by level of symptoms at the starting point (i.e., intercept latent variable; alogia ab_i =0.181; 95% CI (0.107, 0.285); anhedonia ab_i = 0.407; 95% CI (0.242, 0.633)), and the short-term change that occurred in the 1-year interval subsequent to starting point (i.e., slope; alogia ab_s = -0.055; 95% CI (-0.162, -0.002); anhedonia ab_s =-0.063; 95% CI (-0.177, -0.010)), as shown by the specific indirect effects in Table 9-6. These effects can be regarded as being statistically significant since the asymmetric 95% bias-corrected bootstrap confidence intervals did not include zero. As described in Mediation (Chapter 6), complete mediation occurs when a predictor variable such as admission symptoms transmits its effect to the outcome variable (i.e., long-term negative symptom levels) solely through the mediator (i.e., intercept and/or slope latent trajectory variables), with no direct effect of the predictor on long-term outcome.

Regarding the mediating mechanism for alogia and anhedonia, higher levels of symptoms at admission were linked with higher levels of symptoms at the trajectory starting point ($\hat{\gamma}$ = 0.259 and 0.467 respectively; both p-values < 0.001; see direct effects in Table 9-5), which in turn was linked with more severe symptom levels at long-term follow-up ($\hat{\gamma}$ = 0.698 and 0.872 respectively, p-values < 0.001; see Table 9-5). In parallel, higher levels of symptoms at admission were linked with modestly decreasing severity of symptoms over the alogia trajectory ($\hat{\gamma}$ = -0.111; p=0.054; Table 9-5) and the anhedonia trajectory ($\hat{\gamma}$ = -0.152; p=0.013; Table 9-5), which in turn led to lower symptom levels at long-term follow-up ($\hat{\gamma}$ = 0.501; p=0.001 and $\hat{\gamma}$ = 0.415; p=0.013, respectively; Table 9-5). Hence, the effect of higher levels of admission symptoms on long-term alogia and anhedonia symptom levels was mediated in opposite ways by the intercept and slope of each of these symptoms.

As for affective flattening, the effect of admission symptoms on long-term severity was completely mediated by symptom levels at initial recovery from the psychotic episode (i.e., intercept; ab_i = 0.322; 95% CI (0.164, 0.556)); higher affective flattening symptom levels at admission were linked with higher symptom levels at the starting point of the trajectory ($\hat{\gamma}$ = 0.523; p< 0.001), which in turn led to more severe symptoms at long-term follow-up ($\hat{\gamma}$ = 0.616; p< 0.001). Finally, the effect of admission symptoms on long-term avolition symptom levels was direct in nature, as reported in an earlier section, and not mediated by either the intercept or by the slope latent variables.

Table 9-6. Specific indirect effects of severity of symptoms at admission on long-term symptom levels for the four types of negative symptoms: (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals. Significant effects are presented in bolded text.

Specific indirect effects	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Admission symptoms → i → long-term symptoms			
Affective flattening	**0.322 (0.097)**	**0.164, 0.556**	**Sig; p<0.05**
Alogia	**0.181 (0.045)**	**0.107, 0.285**	**Sig; p<0.05**
Avolition	0.146 (0.075)	-0.002, 0.295	NS; > 0.05
Anhedonia	**0.407 (0.099)**	**0.242, 0.633**	**Sig; p<0.05**
Admission symptoms → s→ long-term symptoms			
Affective flattening	0.190 (0.433)	-0.071, 2.587	NS; > 0.05
Alogia	**-0.055 (0.042)**	**-0.162, -0.002**	**Sig; p<0.05**
Avolition	-0.083 (0.062)	-0.236, 0.011	NS; > 0.05
Anhedonia	**-0.063 (0.041)**	**-0.177, -0.010**	**Sig; p<0.05**

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

9.2.4 Model 2 Summary

Firstly, higher symptom levels at admission directly predicted greater severity in symptom levels at the starting point of the trajectory for all negative symptom scales, and also predicted the decreasing rates of short-term change in affective flattening and anhedonia over the 1-year interval subsequent to the starting point.

Secondly, the effect of alogia and anhedonia symptom levels at admission on their long-term symptom levels was completely mediated by their trajectories at the starting point and subsequent 1-year interval (i.e., intercept and slope latent variables), whilst affective flattening was completely mediated by the intercept only (i.e., status on affective flattening at the starting point). In contrast, severity of avolition at admission directly predicted long-term avolition outcome, with no mediation occurring.

Thirdly, short-term trajectories of alogia, avolition and anhedonia directly predicted long-term outcome, with higher levels of these symptoms at the starting point, along with more rapid increases over the short-term trajectory, being statistically significant predictors of worse long-term outcome. For affective flattening, only the starting point of the trajectory predicted long-term outcome.

The next stage, Model 3, builds on this conditional model by incorporating four baseline characteristics: gender, age at onset of psychosis, duration of untreated psychosis (DUP) and pre-morbid functioning to assess whether it is possible to further differentiate the negative symptom trajectories, in addition to predicting long-term outcome.

9.3 Model 3: Effects Of Participants' Presenting Attributes on Short and Long-Term Negative Symptom Levels

The next set of questions relates to the inclusion of four of the participants' presenting attributes/characteristics that have the potential to differentiate negative symptom trajectories and predict final long-term outcome. These are gender, age at onset of psychosis, duration of untreated psychosis (DUP) and pre-morbid functioning. A detailed description of these four variables is presented in Method (Chapter 4). The nature of any such identified effects of these predictors on the short-term negative symptom outcomes (i.e., at admission and the short-term trajectories) and long-term symptom outcomes will be examined, for instance, whether the effect of a particular baseline characteristic on these dependent variables is direct or whether the effect is mediated by intervening variable(s) in the model.

A path diagram representing the relationships between the observed and latent variables in this model is presented in Figure 9.3. Negative symptoms at admission, age at onset of psychosis, and pre-morbid functioning were centred by subtracting the sample mean of each variable from each individual's observed value on that variable to facilitate interpretability, as detailed in Statistical Methods (Chapter 5). The covariance between the disturbance terms of the intercept and slope was constrained to zero for all negative symptom scales except for alogia, as per the specification in the previous model, Model 2. Model fit indices for each of the four negative symptoms are presented in Table 9-7; these indices indicate that each of the four models fit reasonably well.

Table 9-7. Fit indices of conditional model 3 for affective flattening, alogia, avolition and anhedonia symptoms.

	Affective flattening	Alogia [1]	Avolition [2]	Anhedonia [3]
Slope factor loadings	0, 0.51, 1	0, 0.51, 1	0, 0.51, 1	0, 0.51, 1
Fit indices				
Chi-square	10.339	15.402	15.679	16.298
(df)	13	12	12	12
p-value	0.6660	0.2202	0.2064	0.1780
CFI	1.000	0.987	0.989	0.992
RMSEA	< 0.001	0.026	0.028	0.029
95% CI RMSEA	<0.001, 0.040	< 0.001, 0.060	< 0.001, 0.062	<0.001, 0.062
SRMR	0.012	0.017	0.017	0.015

[1] Degrees of freedom are reduced due to covariance between disturbance terms of intercept and slope for alogia being freely estimated.

[2] Degrees of freedom are reduced due to the residual variance of avolition at 6-month follow-up being freely estimated to improve fit, as per unconditional model.

[3] Degrees of freedom are reduced due to the residual variance of anhedonia at 1 year follow-up being freely estimated to improve fit, as per unconditional model.

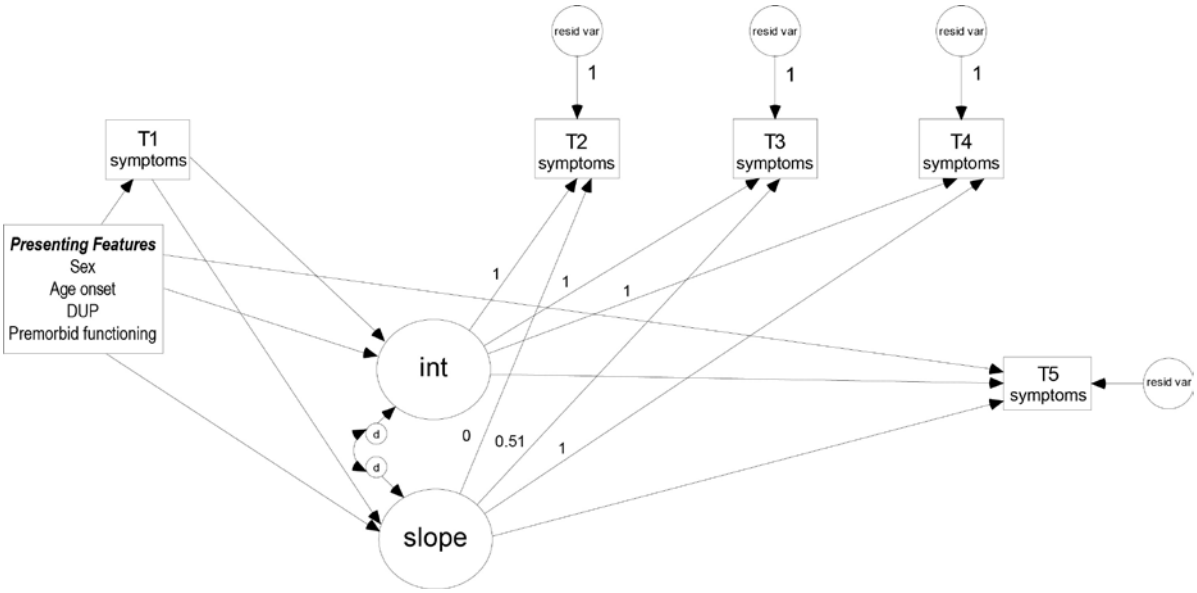


Figure 9.3. Conditional linear latent trajectory model, incorporating direct effects of gender, age at onset of psychosis, DUP and pre-morbid functioning (bolded) as predictors of severity of negative symptoms (i) at admission; (ii) across the short-term growth trajectory and (iii) at long-term follow-up. Each arrow actually represents multiple paths from the set of predictors to each dependent variable.

9.3.1 Model 3 Research Questions

Research questions in this section are divided into two sections:

(iii) Section 9.3.2: Identification of direct effects of participants presenting attributes on short-term negative symptom trajectories and long-term symptom outcomes;

(iv) Section 9.3.3: Identification of indirect effects of participants presenting attributes on short-term negative symptom trajectories and long-term symptom outcomes;

The first of these (Section 9.3.2) relates to direct effects for this model specification, in particular, whether any of the four participant presenting attributes (gender, age at onset of psychosis, DUP and pre-morbid functioning directly predict: (a) negative symptom levels at admission; (b) the short-term trajectory (STT); or (c) long-term negative symptoms.

Section 9.3.3 comprises two distinct research questions regarding the presence of mediated effects, specifically: (a) whether the effect of each of the four presenting attributes on the STT in the 1-year interval subsequent to initial recovery is mediated fully or partly by admission symptoms and; (b) whether the effect of these four presenting features on distal long-term symptom levels is mediated either fully or partly by admission symptoms, or by the latent trajectory variables (i.e. initial status at initial recovery, represented by the intercept; and the subsequent short-term change, represented by the slope).

9.3.2 Direct effects

9.3.2.1 Do the four key presenting features (gender, age of onset, DUP or pre-morbid functioning) directly predict symptom levels at admission?

DUP and pre-morbid functioning directly predicted severity of affective flattening, avolition and anhedonia symptoms at admission, as indicated in Table 9-8 (see below), but did not predict alogia. Neither gender nor age at onset of psychosis directly predicted any of the four negative symptom subscales at admission.

9.3.2.2 Is there a direct effect of any presenting feature on the latent growth factors?

This question investigates whether these four baseline characteristics directly predict:

e) negative symptom status at the starting point of the short-term trajectory (i.e. intercept) and/or;

f) the short-term change (i.e. slope) that occurs over the subsequent 1-year interval?

The four presenting features directly predicted the latent growth factors in a variety of ways, as displayed in Table 9-8:

(i) Pre-morbid functioning directly predicted symptom status on alogia and anhedonia symptoms at the starting point of the STT (i.e. intercept). A one-point increase in pre-morbid functioning (where a score of 0 represents the best possible functioning and a score of 1 represents the worst possible functioning) was associated with an average increase of almost 1.5 points ($p< 0.001$) in severity of anhedonia at the start of the short-term trajectory, and almost half a point on alogia ($p=0.038$);

(ii) Subjects with very short $DUP_{0\text{-}7\ days}$ or short $DUP_{8\text{-}28\ days}$ experienced significantly less severe anhedonia symptoms at the starting point compared with subjects with subjects in the very long DUP reference category $DUP_{1+\ years}$, whilst subjects with short $DUP_{8\text{-}28\ days}$ experienced significantly less severe affective flattening and avolition symptoms at starting point compared with the reference category;

(iii) Being older at the onset of psychosis directly predicted less severe affective flattening and alogia symptoms at the starting point, with each additional year of age accounting for a modest decrement in symptoms (affective flattening: $\hat{\gamma}$ = -0.024; $p=0.033$) (alogia: $\hat{\gamma}$ = -0.030; $p=0.001$). Conversely, being older at onset of the illness was linked with increasing severity of symptoms over the short-term avolition slope ($\hat{\gamma}$ = 0.048; $p=0.020$).

(iv) male participants experienced increased severity of avolition symptoms (0.253 of a point) at the starting point of the trajectory compared with female participants.

9.3.2.3 Do any of the four presenting features directly predict long-term outcome?

Table 9-8 shows that of the four presenting features, only gender directly predicted long-term outcome. Male subjects experienced significantly worse levels of avolition (0.441 points; p=0.009) and anhedonia (0.423 points; p=0.010) symptoms at long-term follow-up compared with females. Pre-morbid functioning, DUP and age at onset of psychosis failed to directly predict any of the four long-term negative symptom subscales.

Table 9-8. Direct effects: Unstandardised estimates (regression coefficients, with standard errors) for affective flattening, alogia, avolition and anhedonia (i) admission symptoms, regressed on gender, age at onset, DUP and pre-morbid functioning; (ii) random intercepts and random slopes of the short-term trajectory, regressed on gender, age at onset, DUP, pre-morbid functioning and admission symptoms; and (iii) long-term symptoms, regressed on (a) gender, age at onset, DUP and pre-morbid functioning; (b) short-term trajectory random intercepts and (c) slopes, and (d) admission symptoms.

Outcome:	*Admission symptoms*		*Short-term trajectory*				*Level of symptoms at long-term follow-up*	
			Intercept		*Slope*			
	Estimate (SE)	***p-value***	**Estimate (SE)**	***p-value***	**Estimate (SE)**	***p-value***	**Estimate (SE)**	***p-value***
Predictors								
Gender:								
Affective flattening	0.179 (0.094)	0.057	0.108 (0.079)	0.171	0.169 (0.104)	0.104	0.293 (0.415)	0.480
Alogia	0.181 (0.104)	0.082	-0.022 (0.066)	0.735	0.105 (0.095)	0.266	0.059 (0.068)	0.387
Avolition	0.126 (0.116)	0.281	**0.253 (0.096)**	**0.008**	0.175 (0.157)	0.264	**0.441 (0.169)**	**0.009**
Anhedonia	0.131 (0.128)	0.305	0.148 (0.106)	0.162	0.114 (0.153)	0.455	**0.423 (0.164)**	**0.010**
Age at onset:								
Affective flattening	0.010 (0.013)	0.454	**-0.024 (0.011)**	**0.033**	0.003 (0.014)	0.851	0.023 (0.026)	0.368
Alogia	0.019 (0.013)	0.147	**-0.030 (0.009)**	**0.001**	0.009 (0.012)	0.456	0.010 (0.010)	0.324
Avolition	-0.004 (0.015)	0.785	-0.019 (0.013)	0.155	**0.048 (0.020)**	**0.015**	0.012 (0.025)	0.633
Anhedonia	0.015 (0.015)	0.331	0.018 (0.015)	0.224	0.025 (0.020)	0.224	0.018 (0.021)	0.398

Outcome:	*Admission symptoms*		*Short-term trajectory*				*Level of symptoms at long-term follow-up*	
			Intercept		*Slope*			
DUP								
Affective flattening								
$DUP_{0\text{-}7\ days}$	**-0.353 (0.167)**	**0.035**	-0.250 (0.151)	0.097	0.045 (0.193)	0.815	0.289 (0.355)	0.415
$DUP_{8\text{-}28\ days}$	-0.247 (0.154)	0.110	**-0.315 (0.155)**	**0.042**	0.089 (0.198)	0.653	0.461 (0.387)	0.234
$DUP_{29\text{-}90days}$	**-0.321 (0.159)**	**0.043**	-0.049 (0.151)	0.748	-0.130 (0.184)	0.480	0.052 (0.484)	0.914
$DUP_{3mths\text{-}1yr}$	-0.146 (0.156)	0.352	-0.070 (0.149)	0.636	0.046 (0.185)	0.805	0.037 (0.336)	0.912
$DUP_{1+\ year}$ [1]	0							
Alogia								
$DUP_{0\text{-}7\ days}$	-0.025 (0.172)	0.883	-0.206 (0.128)	0.109	-0.010 (0.180)	0.957	0.079 (0.120)	0.512
$DUP_{8\text{-}28\ days}$	-0.027 (0.167)	0.871	-0.121 (0.126)	0.336	0.035 (0.189)	0.853	0.029 (0.119)	0.804
$DUP_{29\text{-}90days}$	-0.151 (0.160)	0.346	0.013 (0.129)	0.920	-0.027 (0.188)	0.885	0.073 (0.123)	0.553
$DUP_{3mths\text{-}1yr}$	-0.012 (0.159)	0.938	0.015 (0.126)	0.908	-0.154 (0.186)	0.405	0.035 (0.121)	0.768
$DUP_{1+\ year}$ [1]	0							
Avolition								
$DUP_{0\text{-}7\ days}$	**-1.105 (0.209)**	**< 0.001**	-0.343 (0.190)	0.071	-0.312 (0.272)	0.252	0.279 (0.308)	0.365
$DUP_{8\text{-}28\ days}$	**-0.700 (0.213)**	**0.001**	**-0.464 (0.185)**	**0.012**	0.027 (0.266)	0.919	-0.147 (0.317)	0.643
$DUP_{29\text{-}90days}$	**-0.785 (0.208)**	**< 0.001**	-0.234 (0.187)	0.210	-0.290 (0.249)	0.246	0.298 (0.289)	0.303
$DUP_{3mths\text{-}1yr}$	**-0.478 (0.203)**	**0.018**	-0.200 (0.183)	0.274	-0.169 (0.240)	0.482	-0.063 (0.290)	0.828
$DUP_{1+\ year}$ [1]	0							

Outcome:	*Admission symptoms*		*Short-term trajectory*				*Level of symptoms at long-term follow-up*	
			Intercept		*Slope*			
Anhedonia								
$DUP_{0\text{-}7\ days}$	**-0.913 (0.218)**	**< 0.001**	**-0.515 (0.173)**	**0.003**	-0.256 (0.244)	0.294	0.004 (0.304)	0.988
$DUP_{8\text{-}28\ days}$	**-0.838 (0.213)**	**< 0.001**	**-0.505 (0.188)**	**0.007**	-0.068 (0.269)	0.800	0.091 (0.315)	0.772
$DUP_{29\text{-}90days}$	**-0.586 (0.215)**	**0.006**	-0.292 (0.172)	0.089	-0.256 (0.239)	0.283	0.196 (2.268)	0.466
$DUP_{3mths\text{-}1yr}$	-0.129 (0.198)	0.516	-0.174 (0.164)	0.286	-0.236 (0.221)	0.286	-0.217 (0.262)	0.408
$DUP_{1+\ year}$ [1]	0							
Pre-morbid functioning								
Affective flattening	**0.599 (0.268)**	**0.025**	0.246 (0.254)	0.333	0.134 (0.309)	0.665	0.467 (0.656)	0.476
Alogia	0.106 (0.268)	0.693	**0.434 (0.210)**	**0.038**	0.218 (0.281)	0.436	0.173 (0.251)	0.492
Avolition	**0.872 (0.293)**	**0.003**	0.424 (0.299)	0.156	0.615 (0.450)	0.172	0.773 (0.480)	0.107
Anhedonia	**1.533 (0.338)**	**< 0.001**	**1.461 (0.332)**	**< 0.001**	-0.131 (0.496)	0.791	0.274 (0.547)	0.616
Admission symptoms								
Affective flattening	-	-	**0.498 (0.047)**	**< 0.001**	**-0.266 (0.059)**	**< 0.001**	-0.371 (0.685)	0.588
Alogia	-	-	**0.259 (0.042)**	**< 0.001**	**-0.116 (0.058)**	**0.046**	0.043 (0.052)	0.406
Avolition	-	-	**0.294 (0.053)**	**< 0.001**	**-0.164 (0.082)**	**0.046**	**0.317 (0.135)**	**0.019**
Anhedonia	-	-	**0.345 (0.048)**	**< 0.001**	**-0.163 (0.071)**	**0.022**	0.146 (0.115)	0.203
Starting point of trajectory: (Intercept factor)								
Affective flattening	-	-	-	-	-	-	**0.666 (0.193)**	**0.001**
Alogia	-	-	-	-	-	-	**0.682 (0.127)**	**< 0.001**

Outcome:	*Admission symptoms*		*Short-term trajectory*				*Level of symptoms at long-term follow-up*	
			Intercept		*Slope*			
Avolition	-	-	-	-	-	-	0.222 (0.228)	0.329
Anhedonia	-	-	-	-	-	-	**0.794 (0.207)**	**< 0.001**
Short-term trajectory : (Slope factor)								
Affective flattening	-	-	-	-	-	-	-1.270 (2.443)	0.603
Alogia	-	-	-	-	-	-	**0.462 (0.151)**	**0.002**
Avolition	-	-	-	-	-	-	**0.666 (0.225)**	**0.003**
Anhedonia	-	-	-	-	-	-	**0.425 (0.179)**	**0.017**

[1] The reference category against which each DUP category is compared is very long DUP $_{1+\text{ years}}$

9.3.3 Indirect effects

This is the second set of questions to be addressed for Model 3. Results of the mediational analyses are presented in two parts, and comprise research questions concerning: (i) whether the effects of the four presenting features on the STTs are mediated by admission symptoms, and; (ii) whether the effects of these presenting features on long-term negative symptoms are mediated by short-term negative symptoms (either by admission symptoms or by the STTs). The path diagram for the indirect effects is identical to the path diagram in Figure 9.3.

9.3.3.1 Are the effects of gender, age of onset, DUP and pre-morbid functioning on the short-term negative symptom trajectories mediated in full or in part by level of symptoms at admission?

This question examined whether each of the four presenting features indirectly impacted the short-term change in negative symptoms (represented by the intercept and/or slope latent variables) via their effect on level of negative symptoms at admission. Results of these mediation analyses are presented individually for each of the four presenting features.

Gender

The effect of gender on the rate of change in affective flattening (i.e., slope) was completely mediated by admission symptoms, as indicated by the asymmetric confidence intervals of the specific indirect effects (see Table 9-9). Being male was linked with higher symptom levels at admission (0.179 points higher than for females), which led to decreased rates of change (slope coefficient = -0.266) across the short-term affective flattening trajectory (refer direct effects presented in Table 9-8). The net effect was a small decrease in severity of symptoms over the trajectory of 0.048 of a point (Table 9-9), compared with females. No indirect effects of gender were observed for any other negative symptom subscale.

Table 9-9. Indirect effects of male gender on the short-term negative symptom trajectories (intercept and slope latent variables), via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects. Significant effects are presented in bolded text.

Specific indirect effects	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Male → admission symptoms → intercept of STT			
Affective flattening	0.089 (0.048)	-0.004, 0.185	NS; > 0.05
Alogia	0.047 (0.028)	-0.005, 0.105	NS; > 0.05
Avolition	0.037 (0.036)	-0.030, 0.115	NS; > 0.05
Anhedonia	0.045 (0.046)	-0.042, 0.139	NS; > 0.05
Male → admission symptoms → slope of STT			
Affective flattening	**-0.048 (0.028)**	**-0.112,-0.001**	**Sig; p<0.05**
Alogia	-0.021 (0.018)	-0.071, 0.002	NS; > 0.05
Avolition	-0.021 (0.024)	-0.089, 0.011	NS; > 0.05
Anhedonia	-0.021 (0.025)	-0.089, 0.014	NS; > 0.05

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

Age at onset of psychosis

There was no evidence that age at onset of psychosis indirectly predicted the starting point of the trajectory (i.e. intercept) or rates of change (i.e. slope) via admission symptoms for any of the negative symptom subscales (see Table 9-10). Thus, the effects of age at onset of psychosis were transmitted to short-term affective flattening and alogia outcomes solely by its direct predictive effect (see direct effects in Table 9-8) on their respective intercepts, and likewise, to short-term avolition via its direct effect on the slope latent variable.

Table 9-10. Indirect effects of age at onset of psychosis on the short-term negative symptom trajectories (intercept and slope latent variables), via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects.

Specific indirect effects	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Ageons→ admission symptoms → intercept of STT			
Affective flattening	0.005 (0.007)	-0.008, 0.017	NS; > 0.05
Alogia	0.005 (0.003)	-0.002, 0.012	NS; > 0.05
Avolition	-0.001 (0.005)	-0.010, 0.008	NS; > 0.05
Anhedonia	0.005 (0.006)	-0.005, 0.017	NS; > 0.05
Ageons→ admission symptoms→ slope of STT			
Affective flattening	-0.003 (0.004)	-0.010, 0.004	NS; > 0.05
Alogia	-0.002 (0.002)	-0.008,<0.001	NS; > 0.05
Avolition	0.001 (0.003)	-0.004, 0.008	NS; > 0.05
Anhedonia	-0.002 (0.003)	-0.011, 0.002	NS; > 0.05

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals presented in third column; effect is regarded as significant if zero is excluded from the interval

Duration of Untreated Psychosis (DUP)

Table 9-11 and Table 9-12 present the unstandardised indirect effects of each of the DUP categories on the short-term trajectory latent variables: the intercept (presented in Table 9-11) and the slope (presented in Table 9-12), via admission symptom levels. Each DUP category was compared with the reference category, very long DUP in excess of one year ($DUP_{1+\ year}$). Treatment delay indirectly predicted the STTs (intercept and slope) of affective flattening, avolition and anhedonia (but not alogia) via its effect on admission symptoms, which consequently impacted on the starting point and rate of change over the 1-year interval. Specifically, shorter DUP was linked with less severe affective flattening, avolition and anhedonia symptoms at admission, which in turn led to less severe negative symptoms at the starting point of the trajectory (see Table 9-11) and modest increases in severity of symptoms across the subsequent 1-year interval (see Table 9-12).

This latter effect, whereby shorter DUP levels were associated with an increase in the slopes of affective flattening, avolition, and anhedonia, is possibly a form of floor effect. There is a clear link between shorter DUP and lower intercepts. Under these circumstances, there is less possibility for symptoms to fall further, leading to the increased likelihood of observing stability or an increase over time. This is partially a consequence of the design of the study in which participants were not assessed until symptoms from their psychotic episode had stabilised or remitted.

The effects of predictors also need to be considered in the context of the fixed effects for the intercept and slope. For affective flattening, the mean slope is clearly negative (in model 1 = -0.226; p< 0.001, and in model 3 = -0.361; p=0.031), and the magnitude of path coefficients from DUP to the slope, as observed in Table 9.8 (hovering around zero/small positive magnitude) would generally leave slopes going down, but less so. For avolition, the mean slope is effectively zero, which means that so this is a 'going up' situation. One interpretation of this, is the effect of DUP on the intercept outweighs any subsequent increase in avolition, as captured by a positive slope. This is speculative, and the main point would seem to be that intercept effects generally outweigh slope effects, which generally don't have long-term consequences. This point will be engaged further in Discussion (Chapter 10).

The mediating effects of admission symptoms on the starting point of the anhedonia and avolition trajectories (i.e., the intercept) were partial, since treatment delay (DUP) also directly predicted the intercept latent variable for these subscales.

Table 9-11. Indirect effects of the four DUP categories (compared with very long DUP $_{1\text{-year+}}$) on the starting point (i.e., intercept) of the short-term negative symptom trajectories, via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects. Significant effects are presented in bolded text.

Specific indirect effect	Unstandardised ab coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
DUP → admission symptoms → intercept of STT			
Affective flattening			
$DUP_{0\text{-}7\ days}$	**-0.176 (0.086)**	**-0.350, -0.012**	**Sig; p<0.05**
$DUP_{8\text{-}28\ days}$	-0.123 (0.081)	-0.296, 0.021	NS > 0.05
$DUP_{29\text{-}90days}$	**-0.160 (0.082)**	**-0.328, -0.008**	**Sig; p<0.05**
$DUP_{3mths\text{-}1yr}$	-0.073 (0.080)	-0.233, 0.080	NS > 0.05
$DUP_{1+\ year}$ [2]	0		
Alogia			
$DUP_{0\text{-}7\ days}$	-0.007 (0.046)	-0.106, 0.083	NS > 0.05
$DUP_{8\text{-}28\ days}$	-0.007 (0.045)	-0.106, 0.083	NS > 0.05
$DUP_{29\text{-}90days}$	-0.039 (0.045)	-0.142, 0.037	NS > 0.05
$DUP_{3mths\text{-}1yr}$	-0.003 (0.043)	-0.094, 0.076	NS > 0.05
$DUP_{1+\ year}$ [2]	0		
Avolition			
$DUP_{0\text{-}7\ days}$	**-0.325 (0.090)**	**-0.528, -0.172**	**Sig; p<0.05**
$DUP_{8\text{-}28\ days}$	**-0.206 (0.075)**	**-0.379, -0.080**	**Sig; p<0.05**
$DUP_{29\text{-}90days}$	**-0.231 (0.075)**	**-0.401, -0.103**	**Sig; p<0.05**
$DUP_{3mths\text{-}1yr}$	**-0.140 (0.067)**	**-0.288, -0.024**	**Sig; p<0.05**
$DUP_{1+\ year}$ [2]	0		
Anhedonia			
$DUP_{0\text{-}7\ days}$	**-0.315 (0.091)**	**-0.512, -0.156**	**Sig; p<0.05**
$DUP_{8\text{-}28\ days}$	**-0.289 (0.089)**	**-0.491, -0.135**	**Sig; p<0.05**
$DUP_{29\text{-}90days}$	**-0.202 (0.082)**	**-0.378, -0.058**	**Sig; p<0.05**
$DUP_{3mths\text{-}1yr}$	-0.044 (0.070)	-0.190, 0.085	NS > 0.05
$DUP_{1+\ year}$ [2]	0		

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

[2] Reference category against which other DUP levels are compared.

Table 9-12. Indirect effects of the four DUP categories (compared with very long DUP $_{1\text{-year+}}$) on rates of change (i.e., slope) of the short-term symptom trajectory, via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects. Significant effects are presented in bolded text.

Specific indirect effect	Unstandardised ab coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
DUP → admission symptoms → slope of STT			
Affective flattening			
$DUP_{0\text{-}7\ days}$	**0.094 (0.05)**	**0.013, 0.216**	**Sig; p<0.05**
$DUP_{8\text{-}28\ days}$	0.066 (0.046)	-0.008, 0.177	NS > 0.05
$DUP_{29\text{-}90days}$	**0.085 (0.049)**	**0.007, 0.203**	**Sig; p<0.05**
$DUP_{3mths\text{-}1yr}$	0.039 (0.044)	-0.041, 0.140	NS > 0.05
$DUP_{1+\ year}$ [2]	0		
Alogia			
$DUP_{0\text{-}7\ days}$	0.003 (0.023)	-0.039, 0.059	NS > 0.05
$DUP_{8\text{-}28\ days}$	0.003 (0.023)	-0.035, 0.061	NS > 0.05
$DUP_{29\text{-}90days}$	0.017 (0.024)	-0.013, 0.088	NS > 0.05
$DUP_{3mths\text{-}1yr}$	0.001 (0.022)	-0.039, 0.052	NS > 0.05
$DUP_{1+\ year}$ [2]	0		
Avolition			
$DUP_{0\text{-}7\ days}$	**0.181 (0.104)**	**0.009, 0.417**	**Sig; p<0.05**
$DUP_{8\text{-}28\ days}$	**0.115 (0.072)**	**0.009, 0.301**	**Sig; p<0.05**
$DUP_{29\text{-}90days}$	**0.128 (0.076)**	**0.010, 0.316**	**Sig; p<0.05**
$DUP_{3mths\text{-}1yr}$	**0.078 (0.056)**	**0.003, 0.232**	**Sig; p<0.05**
$DUP_{1+\ year}$ [2]	0		
Anhedonia			
$DUP_{0\text{-}7\ days}$	**0.149 (0.078)**	**0.027, 0.342**	**Sig; p<0.05**
$DUP_{8\text{-}28\ days}$	**0.137 (0.074)**	**0.023, 0.321**	**Sig; p<0.05**
$DUP_{29\text{-}90days}$	**0.096 (0.058)**	**0.014, 0.248**	**Sig; p<0.05**
$DUP_{3mths\text{-}1yr}$	0.021 (0.038)	-0.033, 0.128	NS > 0.05
$DUP_{1+\ year}$ [2]	0		

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

[3] Reference category against which other DUP levels are compared.

Pre-morbid functioning

The effects of pre-morbid functioning on the STTs of affective flattening, avolition and anhedonia symptoms (intercept and slope latent variables) were mediated by admission symptoms, as indicated by the specific indirect effects in Table 9-13. Mediation was complete for affective flattening and avolition, given the absence of a direct effect of pre-morbid functioning on the intercept and slope latent variables of these symptoms. In contrast, the effect of pre-morbid functioning on the STT for anhedonia was only partly mediated by admission symptoms, since pre-morbid functioning also directly predicted anhedonia symptom levels at the starting point (i.e., the intercept).

Direct effects presented in Table 9-8 indicated that for each of affective flattening, avolition and anhedonia symptoms, poorer pre-morbid functioning was linked with more severe symptom levels at admission, which in turn transmitted its effects to (i) the starting point (intercept) of the short-term trajectory, resulting in increased symptom severity, and (ii) the rate of change (slope) in the trajectory, resulting in decreasing severity of symptoms over the subsequent 1-year interval. This latter effect, whereby poorer premorbid functioning was associated with a decrease in the slopes of affective flattening, avolition, and anhedonia (and, conversely, better premorbid functioning was associated with an increase in the slopes), is similar to the result for DUP presented above, where shorter DUP levels were linked with an increase in the slopes of affective flattening, avolition, and anhedonia. The same speculative commentary that was made for DUP applies here, along with the point that the intercept effects generally outweigh slope effects, which tend not to have long-term consequences.

Table 9-13. Indirect effects of pre-morbid functioning on the short-term negative symptom trajectories (intercept and slope latent variables), via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects. Significant effects are presented in bolded text.

Specific indirect effects	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Pre-morbid functioning → admission symptoms → intercept of STT			
Affective flattening	**0.299 (0.144)**	**0.033, 0.602**	**Sig; p<0.05**
Alogia	0.027 (0.073)	-0.115, 0.175	NS; > 0.05
Avolition	**0.256 (0.098)**	**0.092, 0.491**	**Sig; p<0.05**
Anhedonia	**0.529 (0.140)**	**0.283, 0.833**	**Sig; p<0.05**
Pre-morbid functioning → admission symptoms → slope of STT			
Affective flattening	**-0.160 (0.084)**	**-0.361,-0.024**	**Sig; p<0.05**
Alogia	-0.012 (0.037)	-0.113,-0.048	NS; > 0.05
Avolition	**-0.143 (0.088)**	**-0.374,-0.014**	**Sig; p<0.05**
Anhedonia	**-0.251 (0.127)**	**-0.543,-0.041**	**Sig; p<0.05**

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

9.3.3.2 Are the effects of gender, age of onset, DUP and pre-morbid functioning on long-term symptom levels mediated in full or in part by symptom levels at admission or by the latent trajectory variables?

This question investigated whether any of the four presenting features indirectly affected long-term symptoms; (i) via their effect on level of symptoms at admission, or (ii) via their effect on the short-term change (represented by the intercept and/or slope latent variables) across the 1-year trajectory. Results of these mediation analyses are presented individually for each of the four presenting features.

Gender

There was no evidence that gender indirectly impacted on severity of long-term negative symptoms, as indicated by the asymmetric 95% confidence intervals in Table 9-14, each of which included zero. The presence of direct effects (as shown in Table

9-8) indicates that the adverse effects of male gender on long-term avolition and anhedonia outcomes were transmitted directly, with no evidence of any mediating mechanism.

Table 9-14. Indirect effects of male gender on long-term symptom levels via admission and the short-term latent trajectory variables: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Male → admission symptoms → long-term outcome			
Affective flattening	-0.066 (0.109)	-0.776, 0.008	NS; > 0.05
Alogia	0.008 (0.014)	-0.008, 0.050	NS; > 0.05
Avolition	0.040 (0.045)	-0.025, 0.160	NS; > 0.05
Anhedonia	0.019 (0.030)	-0.015, 0.124	NS; > 0.05
Male → intercept of STT → long-term outcome			
Affective flattening	0.072 (0.060)	-0.022, 0.218	NS; > 0.05
Alogia	0.015 (0.048)	-0.081, 0.113	NS; > 0.05
Avolition	0.056 (0.070)	-0.061, 0.220	NS; > 0.05
Anhedonia	0.117 (0.099)	-0.037, 0.361	NS; > 0.05
Male → slope of STT → long-term outcome			
Affective flattening	-0.214 (0.333)	-2.653, 0.002	NS; > 0.05
Alogia	0.049 (0.061)	-0.039, 0.199	NS; > 0.05
Avolition	0.117 (0.119)	-0.077, 0.414	NS; > 0.05
Anhedonia	0.049 (0.078)	-0.076, 0.248	NS; > 0.05

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

Age at onset of psychosis

The effects of age at onset of psychosis on long-term affective flattening and alogia symptoms were completely mediated by the intercept latent variable (i.e. symptom levels at the starting point) as shown in Table 9-15, whilst its effects on long-term

avolition were completely mediated by the slope (i.e., rate of change over the trajectory). Being older at onset of psychosis was linked with less severe affective flattening and alogia symptom levels at the starting point of the trajectory (i.e. intercept), which in turn led to less severe affective flattening and alogia symptoms at long-term follow-up. In contrast, being older at onset of psychosis was linked with a modest increase in severity of avolition symptoms over the short-term trajectory (i.e. slope), which in turn led to more severe avolition symptoms at long-term follow-up.

Table 9-15. Indirect effects of age at onset of psychosis (Age at onset) on long-term symptom levels via admission and the short-term latent trajectory variables: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals. Significant effects are presented in bolded text.

Specific indirect effect	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Ageons → admission symptoms → long-term outcome			
Affective flattening	-0.004 (0.010)	-0.075, 0.002	NS; > 0.05
Alogia	0.001 (0.002)	-0.001, 0.006	NS; > 0.05
Avolition	-0.001 (0.006)	-0.015, 0.008	NS; > 0.05
Anhedonia	0.002 (0.004)	-0.002, 0.015	NS; > 0.05
Ageons → intercept of STT → long-term outcome			
Affective flattening	**-0.016 (0.010)**	**-0.043,-0.002**	**Sig; p<0.05**
Alogia	**-0.021 (0.008)**	**-0.040,-0.008**	**Sig; p<0.05**
Avolition	-0.004 (0.007)	-0.025, 0.004	NS; > 0.05
Anhedonia	0.014 (0.014)	-0.007, 0.047	NS; > 0.05
Ageons → slope of STT → long-term outcome			
Affective flattening	-0.003 (0.031)	-0.164, 0.017	NS; > 0.05
Alogia	0.004 (0.007)	-0.007, 0.021	NS; > 0.05
Avolition	**0.032 (0.020)**	**0.005, 0.085**	**Sig; p<0.05**
Anhedonia	0.010 (0.012)	-0.005, 0.042	NS; > 0.05

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

DUP

Table 9-16, Table 9-17, and Table 9-18 present the unstandardised indirect effects of the DUP categories on long-term negative symptoms via three present the unstandardised indirect effects of the DUP categories on long-term negative symptoms via three potential mediators: admission symptoms (presented in Table 9-16); and the short-term symptom trajectory latent variables, comprising the intercept (presented in Table 9-17) and the slope (presented in Table 9-18). Each DUP category was compared with the reference category (very long $DUP_{1+\ years}$).

Results indicated that: (i) effects of all levels of DUP on long-term avolition symptoms were completely mediated by level of symptoms at admission; (ii) effects of shorter DUP levels (28 days and less) on long-term anhedonia symptoms were completely mediated by the starting point of the trajectory, and; (iii) effects of short DUP (8-28 days) on long-term affective flattening were completely mediated by the starting point of the trajectory. Details are presented separately for each mediating variable:

Mediating variable: admission symptoms

The effects of each successive DUP level on long-term avolition symptoms were completely mediated by level of symptoms at admission (see Table 9-16). The unstandardised coefficients indicate that each consecutive DUP level indirectly resulted in a reduction in severity of avolition symptoms at long-term follow-up, relative to the reference category (very long $DUP_{1+\ years}$). As for the mediating mechanism, shorter DUP levels ranging from zero days up to one year (as compared with the reference category) were linked with lower avolition levels at admission, which in turn was linked with milder avolition symptoms at long-term follow-up. Thus, the protective effects of shorter DUP levels were conferred on long-term avolition symptom levels solely through their impact on level of avolition symptoms at admission.

Mediating variable: Starting point of the STT (i.e. intercept)

Very short and short levels of DUP (up to 28 days duration) indirectly predicted less severe long-term anhedonia via their effects on the starting point of the short-term trajectory (i.e., the intercept) (see Table 9-17). Specifically, these shorter DUP levels were linked with less severe anhedonia symptoms at the starting point of the

trajectory, which in turn was linked with less severe anhedonia at long-term follow-up. Mediation was complete, since DUP did not directly predict long-term anhedonia. In addition, short $DUP_{8\text{-}28\ days}$ indirectly predicted long-term affective flattening via its effect on the starting point of the short-term trajectory (i.e., intercept), resulting in a reduction in long-term symptoms compared with the reference category, very long $DUP_{1+\ years}$.

Mediating variable: Rate of change across the STT (slope)

Table 9-18 indicates that the effects of DUP on the long-term negative symptom outcomes were not significantly mediated by the rate of change over the short-term trajectory (i.e., slope).

Table 9-16. Indirect effects of the four DUP categories (compared with very long DUP $_{1\text{-}year+}$) on long-term negative symptom levels via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals. Significant effects are presented in bolded text.

Specific indirect effect	Unstandardised ab coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
DUP → admission symptoms → long-term outcome			
Affective flattening			
$DUP_{0\text{-}7\ days}$	0.131 (0.214)	-0.016, 1.494	NS; > 0.05
$DUP_{8\text{-}28\ days}$	0.091 (0.163)	-0.010, 1.274	NS; > 0.05
$DUP_{29\text{-}90days}$	0.119 (0.199)	-0.016, 1.462	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	0.054 (0.125)	-0.015, 0.937	NS; > 0.05
$DUP_{1+\ year}$ [2]			
Alogia			
$DUP_{0\text{-}7\ days}$	-0.001 (0.014)	-0.044, 0.017	NS; > 0.05
$DUP_{8\text{-}28\ days}$	-0.001 (0.013)	-0.045, 0.015	NS; > 0.05
$DUP_{29\text{-}90days}$	-0.007 (0.016)	-0.074, 0.008	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	-0.001 (0.013)	-0.036, 0.020	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		
Avolition			
$DUP_{0\text{-}7\ days}$	**-0.350 (0.180)**	**-0.780,-0.064**	**Sig; p<0.05**

Specific indirect effect	Unstandardised ab coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
$DUP_{8\text{-}28\ days}$	**-0.222 (0.128)**	**-0.554,-0.041**	**Sig; p<0.05**
$DUP_{29\text{-}90days}$	**-0.249 (0.137)**	**-0.600,-0.045**	**Sig; p<0.05**
$DUP_{3mths\text{-}1yr}$	**-0.152 (0.103)**	**-0.433,-0.014**	**Sig; p<0.05**
$DUP_{1+\ year}$ [2]	0		
Anhedonia			
$DUP_{0\text{-}7\ days}$	-0.134 (0.125)	-0.410, 0.091	NS; > 0.05
$DUP_{8\text{-}28\ days}$	-0.123 (0.116)	-0.387, 0.083	NS; > 0.05
$DUP_{29\text{-}90days}$	-0.086 (0.087)	-0.323, 0.044	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	-0.019 (0.041)	-0.162, 0.028	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

[2] The reference category against which each DUP category is compared is very long $DUP_{1+\ years}$

Table 9-17. Indirect effects of the four DUP categories (compared with very long $DUP_{1\text{-}year+}$) on long-term symptom levels via the starting point of the short-term trajectory (intercept latent variable): unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect	Unstandardised ab coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
DUP → intercept of STT→ long-term outcome			
Affective flattening			
$DUP_{0\text{-}7\ days}$	-0.167 (0.113)	-0.459, 0.012	NS; > 0.05
$DUP_{8\text{-}28\ days}$	**-0.210 (0.117)**	**-0.511, -0.031**	**Sig; p<0.05**
$DUP_{29\text{-}90days}$	-0.032 (0.107)	-0.249, 0.179	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	-0.047 (0.662)	-0.277, 0.157	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		
Alogia			
$DUP_{0\text{-}7\ days}$	-0.140 (0.099)	-0.360, 0.029	NS; > 0.05
$DUP_{8\text{-}28\ days}$	-0.083 (0.094)	-0.291, 0.083	NS; > 0.05

Specific indirect effect	Unstandardised ab coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
$DUP_{29\text{-}90days}$	-0.009 (0.093)	-0.181, 0.190	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	-0.010 (0.091)	-0.175, 0.185	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		
Avolition			
$DUP_{0\text{-}7\ days}$	-0.076 (0.110)	-0.396, 0.069	NS; > 0.05
$DUP_{8\text{-}28\ days}$	-0.103 (0.133)	-0.428, 0.114	NS; > 0.05
$DUP_{29\text{-}90days}$	-0.052 (0.087)	-0.345, 0.048	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	-0.044 (0.080)	-0.301, 0.048	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		
Anhedonia			
$DUP_{0\text{-}7\ days}$	**-0.409 (0.197)**	**-0.889,-0.115**	**Sig; p<0.05**
$DUP_{8\text{-}28\ days}$	**-0.401 (0.208)**	**-0.934, -0.094**	**Sig; p<0.05**
$DUP_{29\text{-}90days}$	-0.232 (0.161)	-0.634, 0.014	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	-0.139 (0.150)	-0.494, 0.107	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

[2] The reference category against which each DUP category is compared is very long $DUP_{1+\ years}$

Table 9-18. Indirect effects of the four DUP categories (compared with very long $DUP_{1\text{-}year+}$) on long-term symptom levels via the rate of change symptoms over the short-term trajectory (slope latent variable): unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals.

Specific indirect effect	Unstandardised ab coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
DUP → slope of STT→ long-term outcome			
Affective flattening			
$DUP_{0\text{-}7\ days}$	-0.057 (0.431)	-2.532, 0.164	NS; > 0.05
$DUP_{8\text{-}28\ days}$	-0.113 (0.428)	-2.980, 0.081	NS; > 0.05
$DUP_{29\text{-}90days}$	0.166 (0.475)	-0.040, 3.970	NS; > 0.05

Specific indirect effect	Unstandardised ab coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
$DUP_{3mths\text{-}1yr}$	-0.058 (0.405)	-2.258, 0.176	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		
Alogia			
$DUP_{0\text{-}7\ days}$	-0.005 (0.106)	-0.233, 0.175	NS; > 0.05
$DUP_{8\text{-}28\ days}$	0.016 (0.113)	-0.191, 0.233	NS; > 0.05
$DUP_{29\text{-}90days}$	-0.013 (0.109)	-0.258, 0.178	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	-0.071 (0.119)	-0.374, 0.089	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		
Avolition			
$DUP_{0\text{-}7\ days}$	-0.208 (0.219)	-0.777, 0.131	NS; > 0.05
$DUP_{8\text{-}28\ days}$	0.018 (0.203)	-0.422, 0.416	NS; > 0.05
$DUP_{29\text{-}90days}$	-0.193 (0.201)	-0.737, 0.114	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	-0.113 (0.190)	-0.584, 0.198	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		
Anhedonia			
$DUP_{0\text{-}7\ days}$	-0.109 (0.132)	-0.482, 0.069	NS; > 0.05
$DUP_{8\text{-}28\ days}$	-0.029 (0.140)	-0.348, 0.220	NS; > 0.05
$DUP_{29\text{-}90days}$	-0.109 (0.133)	-0.482, 0.072	NS; > 0.05
$DUP_{3mths\text{-}1yr}$	-0.100 (0.122)	-0.440, 0.065	NS; > 0.05
$DUP_{1+\ year}$ [2]	0		

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

[2] The reference category against which each DUP category is compared is very long $DUP_{1+\ years}$

Pre-morbid functioning

The effect of pre-morbid functioning on long-term avolition symptoms was completely mediated by level of symptoms at admission, as shown in Table 9-19. Similarly, its effects on long-term alogia and anhedonia were completely mediated by level of symptoms at the starting point of the trajectory (i.e., the intercept). For each of these negative symptom subscales, poorer pre-morbid functioning was linked with greater severity of symptoms in the short-term (at admission for avolition, and at the starting

point of the trajectory for alogia and anhedonia), which in turn predicted greater severity of symptoms at long-term follow-up.

Table 9-19. Indirect effects of pre-morbid functioning on long-term symptom levels via admission and the short-term latent trajectory variables: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals. Significant effects are presented in bolded text.

Specific indirect effect	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Pre-morbid functioning → admission symptoms → long-term outcome			
Affective flattening	-0.222 (0.363)	-2.528, 0.027	NS; > 0.05
Alogia	0.005 (0.023)	-0.020, 0.085	NS; > 0.05
Avolition	**0.277 (0.157)**	**0.051, 0.694**	**Sig; p<0.05**
Anhedonia	0.224 (0.207)	-0.168, 0.662	NS; > 0.05
Pre-morbid functioning → intercept of STT → long-term outcome			
Affective flattening	0.164 (0.193)	-0.147, 0.639	NS; > 0.05
Alogia	**0.296 (0.165)**	**0.019, 0.669**	**Sig; p<0.05**
Avolition	0.094 (0.148)	-0.084, 0.550	NS; > 0.05
Anhedonia	**1.160 (0.432)**	**0.538, 2.246**	**Sig; p<0.05**
Pre-morbid functioning → slope of STT → long-term outcome			
Affective flattening	-0.170 (0.685)	-5.518, 0.019	NS; > 0.05
Alogia	0.101 (0.173)	-0.160, 0.502	NS; > 0.05
Avolition	0.410 (0.378)	-0.148, 1.387	NS; > 0.05
Anhedonia	-0.056 (0.259)	-0.746, 0.330	NS; > 0.05

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

9.3.4 Model 3 Summary

A primary finding was that the short-term trajectory (STT) predicted long-term negative symptom outcome independently of the effects of participants' presenting

attributes. This suggests that the negative symptom STT is not simply a surrogate for the effects of these baseline characteristics. Specifically, elevated levels of affective flattening, alogia and anhedonia at the start of the STT (i.e., intercept) directly predicted more severe symptom levels at long-term follow-up, whilst increased rates of change in the alogia, avolition and anhedonia growth trajectories predicted greater severity of long-term symptoms.

Furthermore, the STT appeared to play a dual role in the prediction of long-term negative symptoms: not only did it directly predict long-term negative symptom outcomes, it also mediated the effects of the presenting features of participants on long-term outcome, including age at onset of psychosis, pre-morbid functioning and DUP.

Similar to role of the STT, admission symptom levels played both a direct and indirect role in the prediction of long-term symptoms, mediating the effects of all DUP levels on long-term avolition. Unlike the STT however, the effect of admission symptoms on long-term outcome as a predictor and mediator was confined to this single negative symptom. The sole other direct predictor of long-term outcome was male gender, which directly predicted poorer long-term avolition and anhedonia symptom levels.

Predictors of the STT were also identified. admission symptoms predicted the trajectories (intercept and slope) of each of the four negative symptoms, with higher levels of symptoms at admission linked more severe symptom levels at the start of the trajectory and decreased rates of change over the subsequent 1-year interval. Each of the four participant presenting features variously predicted the starting point of specific symptom trajectories but not others. The effects of pre-morbid functioning and DUP on the STTs (intercept and slope) of affective flattening, avolition and anhedonia were mediated by admission symptoms, which also mediated the effects of male gender on the affective flattening trajectory.

The next and final stage, Model 4, builds on this model by incorporating DSM-IV diagnosis to assess whether further differentiation of the negative symptom trajectories is possible, in addition to predicting long-term outcome.

9.4 Model 4 : Effects of Baseline DSM-IV Psychotic Diagnosis on Short and Long-Term Negative Symptoms

The final model included one additional predictor: baseline DSM-IV diagnosis of the first episode of psychosis. Based on previous research, this predictor has the theoretical potential to differentiate negative symptom trajectories and final long-term outcome, over and above the capacity of other baseline clinical and demographic predictors. Diagnoses were grouped into six broad categories: schizophrenia (reference category); schizophreniform; schizoaffective disorder; bipolar psychotic disorder; depressive psychosis, and other psychotic disorders (comprising psychotic disorder not otherwise specified (NOS), delusional disorder, brief psychotic disorder).

A path diagram representing the relationships between the observed and latent variables in this final model is presented in Figure 9.4. The single DSM-IV diagnosis box represents a series of dummy variables, each with its own set of parameters. Model coefficients for each diagnostic dummy variable indicate the differential effect of that particular diagnosis on the dependent variable(s) (with schizophrenia as the reference diagnosis), adjusting for other variables in the model. Model specifications detailed in previous models remained the same (for instance, centring of selected observed variables). Model fit indices for each of the four negative symptoms are presented in Table 9-20; these indicate that each of the four models fit reasonably well.

Table 9-20. Fit indices of conditional model 4 for affective flattening, alogia, avolition and anhedonia symptoms.

	Affective flattening	Alogia [1]	Avolition [2]	Anhedonia [3]
Slope factor loadings	0, 0.51, 1	0, 0.51, 1	0, 0.51, 1	0, 0.51, 1
Fit indices				
Chi-square	12.750	18.205	25.012	17.486
(df)	18	17	17	17
p-value	0.8062	0.3760	0.0944	0.4219
CFI	1.000	0.996	0.978	0.999
RMSEA	< 0.001	0.013	0.034	0.008
95% CI RMSEA	<0.001, 0.028	< 0.001, 0.047	< 0.001, 0.062	<0.001, 0.046
SRMR	0.010	0.013	0.015	0.012

[1] Degrees of freedom are reduced due to covariance between disturbance terms of intercept and slope for alogia being freely estimated

[2] Degrees of freedom are reduced due to the residual variance of avolition at 6-month follow-up being freely estimated to improve fit, as per unconditional model

[3] Degrees of freedom are reduced due to the residual variance of anhedonia at 1 year follow-up being freely estimated to improve fit, as per unconditional model

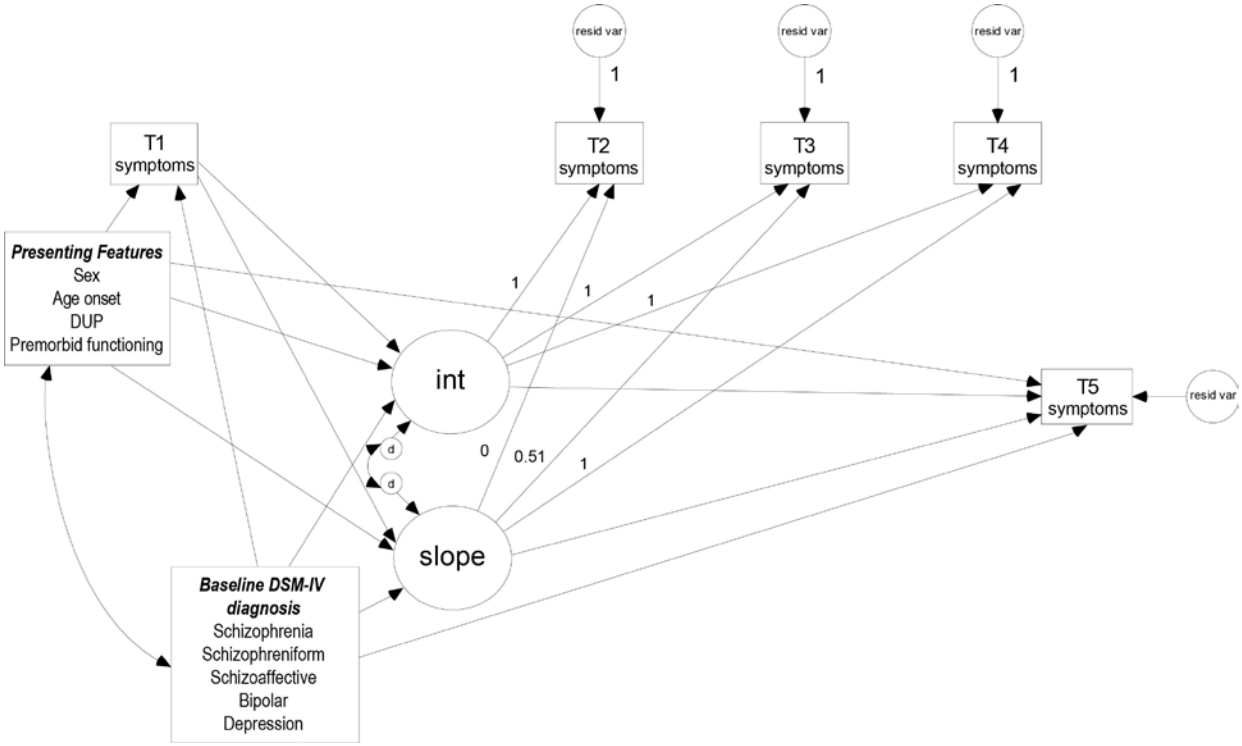


Figure 9.4. Conditional linear latent trajectory model, incorporating direct effects of DSM-IV diagnosis (bolded), gender, age at onset of psychosis, DUP and pre-morbid functioning as predictors of severity of symptoms (i) at admission; (ii) across the short-term growth trajectory and (iii) at long-term follow-up. Each arrow actually represents multiple paths from the multi-category DSM-IV diagnosis predictor to each dependent variable.

9.4.1 Model 4 Research Questions

Research questions for this model are divided into two sections:

(i) Section 9.4.2: Identification of direct effects of DSM-IV diagnosis on short-term negative symptom trajectories and long-term outcome;

(ii) Section 9.4.3: Identification of indirect effects of DSM-IV diagnosis on short-term trajectories and long-term outcome;

The first of these (Section 9.4.2) relates to direct effects for this model specification, in particular, whether DSM-IV diagnosis is able to differentiate: (a) symptom levels at admission; (b) the short-term latent growth trajectory; or (c) long-term outcome.

Section 9.4.3 comprises two distinct research questions regarding the possibility of the presence of mediated effects, specifically: (a) whether the effect of each diagnostic category on the short-term symptom trajectory (STT) is mediated fully or partly by admission symptoms, and; (b) whether the effect of each diagnostic category (relative to schizophrenia) on distal long-term symptom levels is mediated either fully or partly by level of symptoms at admission, and/or by the latent trajectory variables (intercept and slope).

9.4.2 Direct effects

9.4.2.1 Does baseline diagnosis directly predict negative symptom levels at admission?

Subjects with a baseline diagnosis of bipolar psychotic disorder experienced significantly less severe symptoms on all four negative subscales at admission than subjects with schizophrenia (the reference group), as displayed in Table 9-21, after accounting for the effects of all other variables in the model. The largest difference observed was on the anhedonia subscale ($\hat{\gamma}$ = -1.264; 95% CI (-1.563, -0.964)). Individuals diagnosed with schizophreniform disorder experienced significantly less severe alogia and anhedonia symptoms on average than participants with schizophrenia, whilst those diagnosed with other psychotic disorders (comprising delusional disorder, psychotic disorder NOS or brief psychotic disorder) experienced less severe affective flattening and anhedonia symptoms compared with the schizophrenia reference group.

9.4.2.2 Does baseline DSM-IV diagnosis directly predict the latent growth factors?

This question aims to identify whether particular psychotic diagnoses directly predict:

e) Initial symptom levels at the starting point (i.e. intercept) and/or;
f) the short-term change (i.e. slope) that occurs over the 1-year interval subsequent to starting point.

Participants with bipolar psychotic disorder exhibited significantly less severe levels of symptoms at the starting point of the trajectories of affective flattening ($\hat{\gamma}$ = -0.240; p=0.048), alogia ($\hat{\gamma}$ = -0.289; p=0.008) and avolition ($\hat{\gamma}$ = -0.361; p=0.022) compared with subjects diagnosed with schizophrenia (see Table 9-21). Subjects with schizophreniform disorder ($\hat{\gamma}$ = -0.233; p=0.047) had less severe levels of symptoms at the starting point of the affective flattening trajectory, whilst subjects with other psychotic disorders ($\hat{\gamma}$ = -0.276; p=0.015) had less severe alogia symptoms at the starting point, as compared with the schizophrenia reference group.

Diagnostic effects on the slope latent variables were less apparent. Being diagnosed with bipolar psychotic disorder was linked with significant decreased change in anhedonia symptoms (λ= -0.574; p=0.036) across the short-term trajectory, whilst a diagnosis of depressive psychosis was linked with significantly decreased change in the anhedonia STT (λ= - 0.540; p=0.017), compared with the schizophrenia reference category.

9.4.2.3 Does baseline DSM-IV psychotic diagnosis directly predict long-term outcome?

Baseline psychotic diagnosis did not directly predict level of negative symptoms at long-term follow-up (refer final column in Table 9-21) for any of the four negative symptom subscales. These direct paths to long-term outcome were generally characterised by small unstandardised coefficients.

Table 9-21. Direct effects: Unstandardised estimates (regression coefficients, with MLR standard errors) for affective flattening, alogia, avolition and anhedonia; (i) admission negative symptoms, regressed on gender, age at onset, DUP, pre-morbid functioning and DSM-IV diagnosis ; (ii) random intercepts and random slopes of the short-term negative symptom trajectories, regressed on gender, age at onset, DUP, pre-morbid functioning, admission negative symptoms and DSM-IV diagnosis ; and (iii) long-term negative symptoms, regressed on (a) gender, age at onset, DUP, pre-morbid functioning and DSM-IV diagnosis; (b) short-term trajectory random intercepts and (c) slopes; (d) negative symptoms at admission, and; (e) DSM-IV diagnosis.

Outcome:	***Admission symptoms***		***Short-term trajectory***				***Level of symptoms at long-term follow-up***	
			Intercept		***Slope***			
	Estimate(SE)	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***
Predictors								
DSM-IV diagnosis[1]								
Schizophreniform								
Affective flattening	-0.095 (0.139)	0.496	**-0.233** (**0.118**)	**0.047**	-0.120 (0.160)	0.451	-0.028 (0.492)	0.955
Alogia	**-0.300** (**0.134**)	**0.025**	-0.125 (0.100)	0.212	0.030 (0.148)	0.841	0.188 (0.133)	0.159
Avolition	-0.307 (0.167)	0.067	-0.102 (0.145)	0.481	-0.345 (0.238)	0.148	0.383 (0.267)	0.152
Anhedonia	**-0.352** (**0.179**)	**0.050**	-0.213 (0.166)	0.200	-0.364 (0.243)	0.134	0.181 (0.254)	0.476
Schizoaffective								
Affective flattening	0.038 (0.161)	0.813	-0.021 (0.129)	0.869	-0.170 (0.152)	0.262	-0.479 (0.658)	0.466
Alogia	-0.214 (0.162)	0.187	-0.114 (0.111)	0.303	0.007 (0.138)	0.959	0.062 (0.116)	0.590
Avolition	-0.267 (0.195)	0.170	-0.158 (0.164)	0.336	0.021 (0.264)	0.665	-0.112 (0.294)	0.704
Anhedonia	-0.206 (0.183)	0.259	0.074 (0.159)	0.640	-0.439 (0.225)	0.051	0.041 (0.311)	0.896
Bipolar disorder								

Outcome:	*Admission symptoms*		*Short-term trajectory*				*Level of symptoms at long-term follow-up*	
			Intercept		*Slope*			
	Estimate(SE)	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***
Predictors								
Affective flattening	**-0.493** (**0.146**)	**0.001**	**-0.240** (**0.121**)	**0.048**	-0.098 (0.165)	0.551	0.050 (0.477)	0.917
Alogia	**-0.674** (**0.146**)	**< 0.001**	**-0.289** (**0.109**)	**0.008**	0.134 (0.159)	0.402	0.201 (0.104)	0.054
Avolition	**-0.759** (**0.158**)	**< 0.001**	**-0.361** (**0.157**)	**0.022**	0.114 (0.264)	0.665	-0.080 (0.317)	0.801
Anhedonia	**-1.264** (**0.153**)	**< 0.001**	0.059 (0.176)	0.736	**-0.574** (**0.274**)	**0.036**	-0.124 (0.325)	0.703
Depressive psychosis								
Affective flattening	0.128 (0.151)	0.396	-0.015 (0.134)	0.913	-0.236 (0.176)	0.180	-0.532 (0.903)	0.556
Alogia	-0.011 (0.168)	0.947	-0.142 (0.117)	0.225	-0.003 (0.157)	0.984	-0.023 (0.104)	0.825
Avolition	0.079 (0.167)	0.635	-0.155 (0.159)	0.330	-0.063 (0.245)	0.796	-0.063 (0.272)	0.816
Anhedonia	-0.034 (0.166)	0.839	-0.032 (0.157)	0.840	**-0.540** (**0.227**)	**0.017**	-0.010 (0.299)	0.972
Other psychotic disorders								
Affective flattening	**-0.423** (**0.152**)	**0.005**	-0.144 (0.183)	0.434	-0.095 (0.201)	0.636	-0.225 (0.495)	0.649
Alogia	-0.415 (0.240)	0.083	**-0.276** (**0.114**)	**0.015**	0.185 (0.169)	0.273	0.079 (0.144)	0.584
Avolition	-0.588 (0.337)	0.081	-0.185 (0.235)	0.432	-0.465 (0.380)	0.221	-0.125 (0.437)	0.775
Anhedonia	**-0.880** (**0.246**)	**< 0.001**	-0.007 (0.248)	0.979	-0.765 (0.395)	0.053	-0.122 (0.346)	0.725
Gender:								
Affective flattening	0.168 (0.091)	0.063	0.104 (0.078)	0.183	0.153 (0.106)	0.149	0.317 (0.543)	0.560
Alogia	0.154 (0.101)	0.129	0.013 (0.066)	0.844	0.107 (0.095)	0.260	0.062 (0.068)	0.359
Avolition	0.081 (0.112)	0.469	**0.228** (**0.095**)	**0.016**	0.173 (0.160)	0.281	**0.471** (**0.170**)	**0.005**

Outcome:	*Admission symptoms*		*Short-term trajectory*				*Level of symptoms at long-term follow-up*	
			Intercept		*Slope*			
	Estimate(SE)	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***
Predictors								
Anhedonia	0.075 (0.118)	0.522	0.157 (0.106)	0.137	0.063 (0.154)	0.684	**0.436** (**0.168**)	**0.009**
Age at onset:								
Affective flattening	0.011 (0.013)	0.368	-0.022 (0.012)	0.052	0.002 (0.014)	0.899	0.023 (0.030)	0.440
Alogia	0.021 (0.013)	0.110	**-0.029** (**0.009**)	**0.002**	0.008 (0.012)	0.484	0.010 (0.010)	0.322
Avolition	-0.003 (0.015)	0.843	-0.019 (0.013)	0.142	**0.050** (**0.020**)	**0.012**	0.011 (0.025)	0.662
Anhedonia	0.018 (0.014)	0.216	0.020 (0.015)	0.172	0.025 (0.020)	0.205	0.018 (0.022)	0.399
DUP:								
Affective flattening								
$DUP_{0\text{-}7\ days}$	-0.165 (0.203)	0.417	-0.109 (0.162)	0.501	0.122 (0.208)	0.558	0.347 (0.587)	0.554
$DUP_{8\text{-}28\ days}$	-0.106 (0.166)	0.521	-0.204 (0.165)	0.216	0.156 (0.210)	0.459	0.572 (0.651)	0.379
$DUP_{29\text{-}90days}$	-0.274 (0.170)	0.107	0.020 (0.157)	0.898	-0.069 (0.193)	0.722	0.094 (0.511)	0.853
$DUP_{3mths\text{-}1yr}$	-0.166 (0.158)	0.294	-0.068 (0.149)	0.647	0.065 (0.187)	0.729	0.102 (0.438)	0.815
$DUP_{1+\ year}$ [2]	0							
Alogia								
$DUP_{0\text{-}7\ days}$	0.280 (0.193)	0.146	-0.062 (0.147)	0.671	-0.068 (0.204)	0.740	-0.032 (0.132)	0.811
$DUP_{8\text{-}28\ days}$	0.203 (0.180)	0.259	-0.003 (0.142)	0.986	-0.019 (0.202)	0.925	-0.052 (0.130)	0.687
$DUP_{29\text{-}90days}$	-0.023 (0.169)	0.892	0.077 (0.137)	0.575	-0.041 (0.198)	0.836	0.014 (0.131)	0.916
$DUP_{3mths\text{-}1yr}$	-0.023 (0.163)	0.890	0.019 (0.126)	0.878	-0.149 (0.186)	0.424	0.033 (0.120)	0.786

Outcome:	*Admission symptoms*		*Short-term trajectory*				*Level of symptoms at long-term follow-up*	
			Intercept		*Slope*			
	Estimate(SE)	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***
Predictors								
$DUP_{1+\ year}$ [2]	0							
Avolition								
$DUP_{0\text{-}7\ days}$	**-0.763** (**0.230**)	**0.001**	-0.194 (0.203)	0.339	-0.281 (0.309)	0.363	0.224 (0.333)	0.501
$DUP_{8\text{-}28\ days}$	-0.432 (0.229)	0.059	-0.344 (0.195)	0.077	0.122 (0.285)	0.670	-0.216 (0.333)	0.516
$DUP_{29\text{-}90days}$	**-0.662** (**0.214**)	**0.002**	-0.179 (0.196)	0.361	-0.228 (0.263)	0.386	0.233 (0.298)	0.435
$DUP_{3mths\text{-}1yr}$	**-0.495** (**0.207**)	**0.017**	-0.203 (0.182)	0.265	-0.165 (0.240)	0.492	-0.074 (0.294)	0.801
$DUP_{1+\ year}$ [2]	0							
Anhedonia								
$DUP_{0\text{-}7\ days}$	-0.386 (0.225)	0.086	**-0.465** (**0.192**)	**0.016**	0.013 (0.287)	0.963	-0.006 (0.349)	0.987
$DUP_{8\text{-}28\ days}$	**-0.441** (**0.215**)	**0.041**	**-0.456** (**0.197**)	**0.021**	0.189 (0.286)	0.508	0.074 (0.352)	0.833
$DUP_{29\text{-}90days}$	-0.383 (0.217)	0.079	-0.240 (0.179)	0.180	-0.105 (0.249)	0.672	0.155 (0.300)	0.604
$DUP_{3mths\text{-}1yr}$	-0.142 (0.199)	0.476	-0.159 (0.164)	0.334	-0.220 (0.221)	0.320	-0.228 (0.268)	0.395
$DUP_{1+\ year}$ [2]	0							
Pre-morbid functioning :								
Affective flattening	0.444 (0.275)	0.106	0.188 (0.257)	0.465	0.177 (0.320)	0.580	0.627 (0.952)	0.510
Alogia	-0.070 (0.275)	0.800	0.366 (0.212)	0.084	0.261 (0.293)	0.372	0.201 (0.266)	0.451
Avolition	**0.648** (**0.286**)	**0.023**	0.357 (0.296)	0.228	0.736 (0.452)	0.104	0.634 (0.498)	0.203
Anhedonia	**1.135** (**0.327**)	**0.001**	**1.490** (**0.336**)	**< 0.001**	-0.021 (0.487)	0.966	0.202 (0.554)	0.715

Outcome:	*Admission symptoms*		*Short-term trajectory*				*Level of symptoms at long-term follow-up*	
			Intercept		*Slope*			
	Estimate(SE)	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***	**Estimate(SE)**	***p-value***
Predictors								
Admission symptoms								
Affective flattening	-		**0.483** (**0.048**)	**< 0.001**	**-0.264** (**0.061**)	**< 0.001**	-0.458 (0.970)	0.637
Alogia	-		**0.238** (**0.042**)	**< 0.001**	-0.101 (0.059)	0.084	0.058 (0.053)	0.273
Avolition	-		**0.273** (**0.055**)	**< 0.001**	**-0.175** (**0.083**)	**0.034**	**0.329** (**0.134**)	**0.014**
Anhedonia	-		**0.353** (**0.050**)	**< 0.001**	**-0.219** (**0.071**)	**0.002**	0.129 (0.124)	0.301
Starting point of trajectory (Intercept factor)								
Affective flattening	-		-		-		**0.700** (**0.200**)	**< 0.001**
Alogia	-		-		-		**0.692** (**0.134**)	**< 0.001**
Avolition	-		-		-		0.208 (0.228)	0.362
Anhedonia	-		-		-		**0.793** (**0.207**)	**< 0.001**
Slope of the STT:								
Affective flattening	-		-		-		-1.620 (3.585)	0.651
Alogia	-		-		-		**0.459** (**0.149**)	**0.002**
Avolition	-		-		-		**0.673** (**0.231**)	**0.004**
Anhedonia	-		-		-		**0.411** (**0.186**)	**0.027**

[1] The reference category against which each DSM-IV diagnostic category is compared is schizophrenia.

[2] The reference category against which each DUP category is compared is very long DUP $_{1+\text{ years}}$

9.4.3 Indirect effects

9.4.3.1 Are the effects of baseline psychotic diagnosis on the short-term symptom trajectories mediated in full or in part by level of symptoms at admission?

This question examined whether DSM-IV baseline diagnosis indirectly affected the short-term negative symptom trajectory (represented by the intercept and/or slope latent variables) via its effect on level of symptoms at admission. The tables below present the unstandardised indirect effects of each of the diagnostic categories on the trajectory latent variables: the intercept (presented in Table 9-22) and the slope (presented in Table 9-23). Specific indirect effects, along with their 95% confidence intervals and the statistical significance are displayed. Each diagnostic category was compared with the reference category, schizophrenia disorder.

The results indicate that baseline DSM-IV bipolar psychotic disorder, other psychotic disorders and schizophreniform (relative to schizophrenia disorder) indirectly predicted the starting point (i.e., intercept) of some or all of the negative symptom trajectories via their effect on admission symptoms (see Table 9-22). These three diagnostic categories also variously indirectly predicted rates of change (i.e., the slope latent variable; see Table 9-23) of affective flattening, avolition and anhedonia. Details of these results follow:

Bipolar psychotic disorder

The effect of bipolar psychotic disorder was indirectly transmitted to the starting point of all four negative symptom trajectories, and on rates of change of affective flattening, avolition and anhedonia. Mediated effects on the starting points of affective flattening, alogia and avolition were partial, since this bipolar psychotic disorder also directly predicted the starting point of these symptom trajectories; conversely, mediation was complete for anhedonia, since bipolar psychotic disorder did not directly predict its starting point. The effect of bipolar psychotic disorder on the rate of change (i.e., slope) in anhedonia was partly mediated by admission symptoms, since this disorder also directly predicted the rate of change in anhedonia. Conversely, mediation was complete for affective flattening and avolition, given the absence of direct effects between bipolar psychotic disorder and each of the affective flattening and avolition slopes.

Of interest was the differential impact of the direct and indirect effects of bipolar psychotic disorder on the anhedonia slope. On the one hand, this disorder directly predicted decreased rates of change (i.e., slope) in anhedonia over the 1-year trajectory (see direct effects in Table 9.21: c' = -0.574; p=0.036). On the other hand, bipolar psychotic disorder also indirectly predicted increased rates of change in anhedonia (ab_{slope}= 0.276; 95% CI (0.096, 0.490) via its effect on admission symptoms. Overall however, the total effect of bipolar psychotic disorder on the anhedonia slope was negative (c = -0.298), hence this disorder was associated with decreased rates of change.

The duality of the diagnostic effect of bipolar psychotic disorder on the slope of the anhedonia STT is illustrated by the single mediator model. In this scenario, bipolar psychotic disorder is linked with reduced anhedonia symptom levels at admission (a = -1.264; p<0.001). When this is considered along with the parameter indicating that each one-point increase in symptoms at admission led to a reduction in rates of change in the anhedonia trajectory (b= -0.219; p=0.002), the mechanism behind bipolar psychotic disorder being indirectly associated with increased rates of change in anhedonia via admission symptoms is thus explained. The mediated effect (ab_{slope}) is derived by multiplying each of these path coefficients: a(-1.264) * b(-0.219) = ab_{slope} 0.276. The *total* effect of bipolar psychotic disorder on rates of change in anhedonia is equivalent to c = -0.298; this can be decomposed into a direct effect c' (-0.574) which is the parameter relating the diagnosis to the anhedonia slope (adjusting for the effects of the mediator), and the indirect effect: ab_{slope} (0.276), which is equivalent to $c - c'$, as outlined in Mediation (Chapter 6).

Other psychotic disorders

Table 9-22 and Table 9-23 show that the effect of other psychotic disorders on the starting points and rates of change of the affective flattening and anhedonia trajectories was indirectly transmitted via its effect on admission symptoms. Mediation was complete, given the absence of direct effects of this class of DSM-IV disorders on the latent variables.

Schizophreniform disorder

As indicated in Table 9-22 and Table 9-23, the effect of schizophreniform was indirectly transmitted to the starting point of the alogia trajectory via admission symptoms, and also indirectly predicted the rate of change in anhedonia. Mediation was complete for both. As regards the mechanism of mediation for other psychotic disorders and schizophreniform disorder, each diagnostic category was (relative to a diagnosis of schizophrenia) linked with lower levels of symptoms at admission, which in turn transmitted its effect to the latent variables, resulting in lower symptom levels at the starting point and increased rates of change across the short-term trajectories.

Table 9-22. Indirect effects of the five diagnostic categories (compared with schizophrenia) on the starting point (i.e., intercept) of the short-term symptom trajectory, via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects. Significant effects are presented in bolded text.

Specific indirect effect	Unstandardised ab coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Baseline diagnosis → admission symptoms → intercept of STT			
Schizophreniform			
Affective flattening	-0.046 (0.070)	-0.186, 0.086	NS; > 0.05
Alogia	**-0.071 (0.036)**	**-0.153, -0.011**	**Sig; p<0.05**
Avolition	-0.084 (0.050)	-0.192, 0.008	NS; > 0.05
Anhedonia	-0.124 (0.070)	-0.279, 0.001	NS; > 0.05
Schizoaffective			
Affective flattening	0.018 (0.080)	-0.140, 0.170	NS; > 0.05
Alogia	-0.051 (0.042)	-0.139, 0.026	NS; > 0.05
Avolition	-0.073 (0.056)	-0.195, 0.030	NS; > 0.05
Anhedonia	-0.073 (0.068)	-0.222, 0.046	NS; > 0.05
Depressive psychosis			
Affective flattening	0.062 (0.074)	-0.081, 0.213	NS; > 0.05
Alogia	-0.003 (0.042)	-0.089, 0.078	NS; > 0.05
Avolition	0.022 (0.048)	-0.068, 0.125	NS; > 0.05
Anhedonia	-0.012 (0.061)	-0.138, 0.108	NS; > 0.05
Bipolar psychotic disorder			
Affective flattening	**-0.238 (0.077)**	**-0.396, -0.093**	**Sig; p<0.05**
Alogia	**-0.160 (0.047)**	**-0.268, -0.083**	**Sig; p<0.05**
Avolition	**-0.207 (0.064)**	**-0.354, -0.101**	**Sig; p<0.05**
Anhedonia	**-0.446 (0.088)**	**-0.633, -0.129**	**Sig; p<0.05**
Other psychotic disorders			
Affective flattening	**-0.204 (0.080)**	**-0.377, -0.058**	**Sig; p<0.05**
Alogia	-0.099 (0.063)	-0.229, 0.024	NS; > 0.05
Avolition	-0.161 (0.106)	-0.392, 0.026	NS; > 0.05
Anhedonia	**-0.310 (0.098)**	**-0.525, -0.135**	**Sig; p<0.05**

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

Table 9-23. Indirect effects of the five diagnostic categories (compared with schizophrenia) on the rates of change (i.e., slope) of the short-term symptom trajectory, via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects. Significant effects are presented in bolded text.

Specific indirect effect	Unstandardised *ab* coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Baseline diagnosis → admission symptoms → slope of STT			
Schizophreniform			
Affective flattening	0.025 (0.040)	-0.045, 0.113	NS; > 0.05
Alogia	0.030 (0.153)	-0.001, 0.099	NS; > 0.05
Avolition	0.054 (0.042)	-0.002, 0.175	NS; > 0.05
Anhedonia	**0.077 (0.051)**	**0.003, 0.207**	**Sig; p<0.05**
Schizoaffective			
Affective flattening	-0.010 (0.045)	-0.100, 0.079	NS; > 0.05
Alogia	0.022 (0.024)	-0.007, 0.096	NS; > 0.05
Avolition	0.047 (0.044)	-0.011, 0.173	NS; > 0.05
Anhedonia	0.045 (0.046)	-0.024, 0.166	NS; > 0.05
Depressive psychosis			
Affective flattening	-0.034 (0.042)	-0.127, 0.042	NS; > 0.05
Alogia	0.001 (0.021)	-0.038, 0.050	NS; > 0.05
Avolition	-0.014 (0.034)	-0.111, 0.037	NS; > 0.05
Anhedonia	0.007 (0.040)	-0.070, 0.095	NS; > 0.05
Bipolar psychotic disorder			
Affective flattening	**0.130 (0.054)**	**0.042, 0.257**	**Sig; p<0.05**
Alogia	0.068 (0.046)	-0.007, 0.175	NS; > 0.05
Avolition	**0.133 (0.072)**	**0.015, 0.307**	**Sig; p<0.05**
Anhedonia	**0.276 (0.099)**	**0.096, 0.490**	**Sig; p<0.05**
Other psychotic disorders			
Affective flattening	**0.112 (0.052)**	**0.030, 0.237**	**Sig; p<0.05**
Alogia	0.042 (0.040)	-0.009, 0.151	NS; > 0.05
Avolition	0.103 (0.087)	-0.008, 0.351	NS; > 0.05
Anhedonia	**0.192 (0.085)**	**0.061, 0.405**	**Sig; p<0.05**

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval

9.4.3.2 Are the effects of baseline diagnosis on long-term symptom levels mediated in full or in part by the latent trajectory variables or by symptom levels at admission?

This question investigated whether DSM-IV baseline psychotic diagnosis indirectly impacted on long-term negative symptom outcomes through one or both of two possible pathways: (i) via its effect on level of negative symptoms at admission, and/or (ii) via its effect on the short-term trajectory (represented by the intercept and/or slope latent variables). Table 9-24, Table 9-25, and Table 9-26 present the unstandardised specific indirect effects for each of these three potential mediators, along with 95% confidence intervals. Each diagnostic category was compared with the reference category, schizophrenia.

The results indicate that each baseline DSM-IV disorder (relative to schizophrenia) indirectly predicted particular long-term negative symptoms via their effects on either admission symptoms or on one of the latent variables comprising the short-term symptom trajectory. Conversely, all four negative symptom subscales at long-term follow-up were indirectly predicted by at least one diagnostic category. Mediating mechanisms are detailed separately for each diagnostic group, as follows:

Schizophreniform disorder

The effect of schizophreniform disorder was indirectly transmitted to long-term affective flattening via the starting point (i.e., intercept) of the short-term trajectory (see Table 9-25); subjects diagnosed with this disorder experienced an average 0.163 point reduction (95% CI (-0.457, -0.014)) in affective flattening symptoms at long-term follow-up compared with subjects with schizophrenia disorder, via its impact on the intercept latent variable. As regards the mediating mechanism, receiving a diagnosis of schizophreniform disorder was linked with lower affective flattening levels at the starting point of the trajectory (i.e. intercept), which in turn was linked with less severe affective flattening at long-term follow-up. Mediation was complete, since schizophreniform disorder did not directly predict long-term affective flattening symptom levels.

Schizoaffective disorder

Schizoaffective disorder indirectly transmitted its effects to long-term anhedonia levels via its impact on the rate of change (i.e., slope) across the STT (see Table 9-26);

subjects with schizoaffective disorder were rated with significantly lower levels of anhedonia symptoms than subjects with schizophrenia at long-term follow-up (ab_s = -0.180; 95% CI (-0.608, -0.001). This indirect effect occurred via decreased rates of change in the short-term anhedonia trajectory (-0.439; p=0.051; see direct effects in Table 9-21), which in turn was linked with lower severity levels of anhedonia at long-term follow-up (0.411; p=0.027; Table 9-21). Mediation was complete, since schizoaffective disorder did not directly predict long-term anhedonia.

Bipolar psychotic disorder

Effects of bipolar psychotic disorder were indirectly transmitted to long-term levels of avolition via its impact on level of symptoms at admission (see Table 9-24). The effects of this disorder were also transmitted to long-term levels of affective flattening and alogia via its impact on the starting points of their respective short-term trajectories (i.e., intercept latent variables; see Table 9-25). Thus, subjects diagnosed with bipolar psychotic disorder experienced an average 0.250 point decrease in avolition, a 0.200 point decrease in alogia and a 0.168 decrease in affective flattening at long-term follow-up compared to subjects with schizophrenia disorder. Receiving a diagnosis of bipolar psychotic disorder led to lower levels of symptoms at admission (for avolition) and at the starting point of the trajectory (for affective flattening and alogia), which in turn led to lower symptom levels at long-term follow-up for each of these three symptom types. Mediated effects were complete, since bipolar psychotic disorder did not directly predict any of these long-term negative symptoms.

Depressive psychosis

The effect of depressive psychosis was indirectly transmitted to long-term affective flattening via its impact on the rate of change (i.e., slope) over its short-term trajectory (see Table 9-26). Subjects diagnosed with this disorder experienced an average 0.383 point increase in affective flattening severity (95% CI (0.004, 4.957)) at long-term follow-up compared with the schizophrenia reference group (note the width of the confidence interval around this point estimate). As for the mediation mechanism underpinning the association between depressive psychosis and long-term affective flattening, neither of the direct effects (see Table 9-21) involved were statistically significant. For instance, the link between depressive psychosis and decreased average rates of change of affective flattening over the STT did not attain significance ($\hat{\gamma}$ = -

0.236; p=0.180), nor was the corresponding link between rates of change in the STT and long-term affective flattening ($\hat{\gamma}$ = -1.620; p=0.651) statistically significant. In this instance, the coexistence of the two non-significant direct effects, taken in conjunction with the significant indirect effect, demonstrates a point that was detailed in Mediation (Chapter 6); that although uncommon, the scenario is possible.

The effect of depressive psychosis was also indirectly transmitted to long-term anhedonia. Subjects diagnosed with depressive psychosis disorder experienced an average 0.222 point decrease in anhedonia severity (95% CI (-0.729, -0.018) at long-term follow-up compared with subjects with schizophrenia disorder. This occurred via decreased rates of change in the short-term anhedonia trajectory (-0.540; p=0.017; see direct effects in Table 9-21), and positive changes in severity over the STT being linked with increased severity of anhedonia at long-term follow-up (0.411; p=0.027; Table 9-21). As with affective flattening, mediation was complete for each of these effects.

Other psychotic disorders

The impact of this group of disorders was indirectly transmitted to long-term alogia symptom levels via the starting point of the short-term trajectory (see Table 9-25). Subjects in this diagnostic group experienced an average 0.191 point decrease in alogia (95% CI (-0.424, -0.020)) at long-term follow-up as compared with subjects diagnosed with schizophrenia. Regarding the mediating mechanism, a diagnosis of other psychotic disorder was linked with lower severity levels of alogia at the starting point of the trajectory (-0.276; p=0.015; see direct effects in Table 9-21), which in turn was linked with lower levels of alogia at long-term follow-up (0.692; p=0.134; Table 9-21). Mediation was complete, given the absence of any direct effect of this diagnostic group on long-term symptom levels.

Table 9-24. Indirect effects of the five diagnostic categories (compared with schizophrenia) on long-term symptom levels, via admission symptoms: unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects. Significant effects are presented in bolded text.

Specific indirect effect	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Baseline diagnosis → admission symptoms → long-term symptoms			
Schizophreniform			
Affective flattening	0.043 (0.105)	-0.012, 0.835	NS; > 0.05
Alogia	-0.017 (0.023)	-0.084, 0.001	NS; > 0.05
Avolition	-0.101 (0.080)	-0.314, 0.006	NS; > 0.05
Anhedonia	-0.045 (0.064)	-0.242, 0.036	NS; > 0.05
Schizoaffective			
Affective flattening	-0.018 (0.107)	-0.615, 0.048	NS; > 0.05
Alogia	-0.012 (0.020)	-0.083, 0.009	NS; > 0.05
Avolition	-0.088 (0.086)	-0.319, 0.027	NS; > 0.05
Anhedonia	-0.027 (0.047)	-0.202, 0.022	NS; > 0.05
Depressive psychosis			
Affective flattening	-0.059 (0.119)	-0.972, 0.010	NS; > 0.05
Alogia	-0.011 (0.015)	-0.040, 0.024	NS; > 0.05
Avolition	0.026 (0.067)	-0.078, 0.201	NS; > 0.05
Anhedonia	-0.004 (0.032)	-0.104, 0.042	NS; > 0.05
Bipolar psychotic disorder			
Affective flattening	0.226 (0.276)	-0.006, 1.821	NS; > 0.05
Alogia	-0.039 (0.046)	-0.140, 0.035	NS; > 0.05
Avolition	**-0.250 (0.138)**	**-0.584, -0.046**	**Sig; p<0.05**
Anhedonia	-0.163 (0.189)	-0.553, 0.196	NS; > 0.05
Other psychotic disorders			
Affective flattening	0.194 (0.252)	-0.004, 1.857	NS; > 0.05
Alogia	-0.024 (0.035)	-0.126, 0.016	NS; > 0.05
Avolition	-0.194 (0.176)	-0.679, 0.018	NS; > 0.05
Anhedonia	-0.113 (0.141)	-0.469, 0.113	NS; > 0.05

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval.

Table 9-25. Indirect effects of the five diagnostic categories (compared with schizophrenia) on long-term symptom levels, via the starting point of the trajectory (i.e., intercept): unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects. Significant effects are presented in bolded text.

Specific indirect effect	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Baseline diagnosis → intercept of STT → long-term symptoms			
Schizophreniform			
Affective flattening	**-0.163 (0.106)**	**-0.457, -0.014**	**Sig; p<0.05**
Alogia	-0.087 (0.080)	-0.270, 0.050	NS; > 0.05
Avolition	-0.021, (0.055)	-0.216, 0.040	NS; > 0.05
Anhedonia	-0.169 (0.151)	-0.533, 0.078	NS; > 0.05
Schizoaffective			
Affective flattening	-0.015, (0.098)	-0.212, 0.183	NS; > 0.05
Alogia	-0.079, (0.088)	-0.275, 0.072	NS; > 0.05
Avolition	-0.033, (0.069)	-0.277, 0.040	NS; > 0.05
Anhedonia	0.059 (0.142)	-0.209, 0.369	NS; > 0.05
Depressive psychosis			
Affective flattening	-0.010 (0.102)	-0.216, 0.197	NS; > 0.05
Alogia	-0.098 (0.093)	-0.307, 0.063	NS; > 0.05
Avolition	-0.032 (0.067)	-0.280, 0.041	NS; > 0.05
Anhedonia	-0.025 (0.138)	-0.320, 0.235	NS; > 0.05
Bipolar psychotic disorder			
Affective flattening	**-0.168 (0.104)**	**-0.444, -0.014**	**Sig; p<0.05**
Alogia	**-0.200 (0.100)**	**-0.433, -0.039**	**Sig; p<0.05**
Avolition	-0.075 (0.109)	-0.353, 0.100	NS; > 0.05
Anhedonia	0.047 (0.157)	-0.237, 0.392	NS; > 0.05
Other psychotic disorders			
Affective flattening	-0.110 (0.145)	-0.423, 0.165	NS; > 0.05
Alogia	**-0.191 (0.104)**	**-0.424, -0.020**	**Sig; p<0.05**
Avolition	-0.038 (0.096	-0.371, 0.060	NS; > 0.05
Anhedonia	-0.005 (0.218)	-0.426, 0.454	NS; > 0.05

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval.

Table 9-26. Indirect effects of the five diagnostic categories (compared with schizophrenia) on long-term symptom levels, via the rate of change in the short-term trajectory (i.e., slope): unstandardised specific indirect effects (bias-corrected bootstrap standard errors) and asymmetric 95% confidence intervals, along with presence/absence of direct effects.

Specific indirect effect	Unstandardised coefficient ($SE_{bc\text{-}bootstrap}$)	95% CI	Statistical significance[1]
Baseline diagnosis → slope STT → long-term symptoms			
Schizophreniform			
Affective flattening	0.195 (0.409)	-0.017, 3.251	NS; > 0.05
Alogia	0.014 (0.093)	-0.147, 0.218	NS; > 0.05
Avolition	-0.232 (0.209)	-0.769, 0.077	NS; > 0.05
Anhedonia	-0.150 (0.142)	-0.547, 0.033	NS; > 0.05
Schizoaffective			
Affective flattening	0.276 (0.460)	-0.001, 3.825	NS; > 0.05
Alogia	0.003 (0.084)	-0.147, 0.190	NS; > 0.05
Avolition	0.014 (0.212)	-0.390, 0.470	NS; > 0.05
Anhedonia	**-0.180 (0.141)**	**-0.608, -0.001**	**Sig; p<0.05**
Depressive psychosis			
Affective flattening	**0.383 (0.603)**	**0.004, 4.957**	**Sig; p<0.05**
Alogia	-0.001 (0.095)	-0.186, 0.185	NS; > 0.05
Avolition	-0.043 (0.192)	-0.444, 0.342	NS; > 0.05
Anhedonia	**-0.222 (0.166)**	**-0.729, -0.018**	**Sig; p<0.05**
Bipolar psychotic disorder			
Affective flattening	0.159 (0.404)	-0.029, 2.887	NS; > 0.05
Alogia	0.061 (0.110)	-0.086, 0.333	NS; > 0.05
Avolition	0.077 (0.212)	-0.307, 0.575	NS; > 0.05
Anhedonia	-0.236 (0.198)	-0.817, 0.001	NS; > 0.05
Other psychotic disorders			
Affective flattening	0.154 (0.477)	-0.066, 3.578	NS; > 0.05
Alogia	0.085 (0.124)	-0.068, 0.414	NS; > 0.05
Avolition	-0.313 (0.333)	-1.173, 0.178	NS; > 0.05
Anhedonia	-0.314 (0.308)	-1.274, 0.001	NS; > 0.05

[1] Statistical significance is based on bias-corrected bootstrapped asymmetric 95% confidence intervals; effect is regarded as significant if zero is excluded from the interval.

9.4.4 Model 4 Summary

Prediction of long-term outcome

Baseline DSM-IV diagnosis failed to directly predict any long-term negative symptom outcomes, in contrast to its predictive utility in short-term outcomes. However, each baseline DSM-IV disorder (relative to schizophrenia) indirectly predicted one or more long-term negative symptom subscales via its effect(s) on either admission symptoms or on one of the latent variables comprising the short-term symptom trajectory. Compared with a diagnosis of schizophrenia, receiving a diagnosis of bipolar psychotic disorder was linked with less severe long-term affective flattening, alogia and avolition, via either admission symptoms or the intercept; depressive psychosis indirectly predicted less severe long-term anhedonia, but worse long-term affective flattening, via its effect on the slope of each of these symptoms; schizophreniform and other psychotic disorders indirectly predicted less severe long-term affective flattening and alogia respectively, via their intercepts; whilst schizoaffective disorder indirectly predicted less severe long-term anhedonia via decreasing changes on the slope.

Prediction of short-term outcome

Baseline DSM-IV psychotic diagnosis was linked with a range of short-term outcomes, both directly and indirectly. Symptom levels at admission continued to significantly predict the STTs when effects of diagnosis and baseline characteristics were considered, however the effects of the four participant presenting attributes on the trajectories were somewhat attenuated.

Firstly, with regard to prediction of symptom levels at admission, participants diagnosed with bipolar psychotic disorder exhibited significantly less severe negative symptoms on affective flattening, alogia, avolition and anhedonia; secondly, those with schizophreniform disorder exhibited significantly less severe alogia and anhedonia symptoms; and thirdly, participants with other psychotic disorders (comprising psychotic disorder NOS, delusional disorder and brief psychotic disorder) exhibited significantly less severe affective flattening and anhedonia.

As for the prediction of the short-term trajectories, four diagnostic categories were linked indirectly with lower symptom levels at the starting point of the trajectories,

and increasing severity of symptoms over the 1-year STTs as compared with the schizophrenia reference group , via their impact on level of symptoms at admission: (i) bipolar psychotic disorder indirectly conferred a protective effect on the starting points of all four symptom negative symptom trajectories via its impact on level of symptoms at admission, but interestingly, was also linked indirectly with increasing severity of symptoms on the affective flattening, avolition and anhedonia STTs; (ii) a diagnosis of other psychotic disorder similarly conferred a protective effect on the starting point of affective flattening and anhedonia, and was also linked with increased severity over their short-term trajectories; (iii) those diagnosed with schizophreniform disorder had lower symptom levels at the starting point of the alogia and affective flattening STTs, and, increasing severity of symptoms over short-term trajectory of anhedonia; and, (iv) individuals diagnosed with depressive psychosis exhibited a significant decrease in severity of anhedonia symptoms over the short-term trajectory.

9.5 Summary of Model Fitting Results for Negative Symptoms

As with the detailed description of modelling presented above, the summary below closely follows the evolution described for positive symptoms in Chapter 8 for each of the four negative symptom subscales. Except where noted, model specifications and technical details are identical. The unconditional models presented in **Section 9.1** demonstrated that the average short-term trajectory is essentially linear for each of the four negative symptom subscales over the 1-year interval subsequent to initial recovery from the first psychotic episode. Results established that the average change in severity of symptoms across the 1-year trajectory was below any threshold of clinical relevance for all scales except for affective flattening, which significantly and substantially decreased in severity over this period. Individuals varied significantly in their values at the beginning of the trajectory on the four negative symptom subscales, and in their rates of change over the short-term trajectory (STT) on alogia, avolition and anhedonia. As for affective flattening, it was shown that individual variability as captured by the fitted trajectories marginally failed to meet statistical significance ($p=0.059$). Residual variance (i.e., that around trajectories) was not significant.

Section 9.2 investigated the degree to which individual variability in the short-term negative symptom trajectories was predicted by severity of symptoms at admission,

and the extent to which long-term symptomatic outcome was accounted for by earlier course symptom predictors; specifically, admission symptoms, and the short-term trajectories.

Prediction of short-term trajectories: severity of symptoms at admission directly predicted (a) symptom levels at the starting point of the trajectory for each of the four subscales, and (b) the short-term change occurring in affective flattening and anhedonia over the subsequent 1-year interval.

Prediction of long-term outcome: results indicated that the STTs of avolition, alogia and anhedonia directly predicted their respective long-term symptomatic outcomes. Thus, elevated symptom levels at the starting point (intercept) and greater rates of change in symptoms (slope) over the 1-year interval subsequent to initial recovery directly predicted worse long-term negative symptom severity. For affective flattening, only the starting point (intercept) directly predicted long-term symptom levels. Furthermore, it was established that the respective STTs of anhedonia and alogia (intercept and slope) completely mediated the effects of symptoms at admission on their respective long-term symptom levels. Thus, the protective effects of lower anhedonia and alogia symptom levels at admission were transmitted to long-term outcome solely through their effects on their short-term symptom trajectories. As for affective flattening, the effect of admission symptom levels on long-term symptom levels was completely mediated by the starting point of its short-term trajectory. Hence, affective flattening at admission transmitted its effect on long-term outcome solely through its effect on level of symptoms at the starting point of the trajectory, which in turn impacted on long-term affective flattening symptoms. The effect of level of avolition symptoms at admission, on the other hand, was directly transmitted to long-term avolition symptoms, with no mediating effects apparent.

Section 9.3 examined the extent to which four presenting attributes of the participants differentiated individual short-term trajectories and long-term negative symptoms. Results are summarised below in two parts; (i) prediction of short-term negative symptom outcomes, and; (ii) prediction of long-term symptom outcomes.

Prediction of short-term outcomes

Regarding prediction of the STTs, poorer pre-morbid functioning and prolonged DUP were indirectly linked with more severe affective flattening, avolition and anhedonia at the starting point (intercept) and decreased rates of change (slope) in their 1-year trajectories, via their poor prognostic effect on admission symptoms. Additionally, poorer pre-morbid functioning directly predicted more severe alogia and anhedonia symptom levels at the start of their trajectories. Additionally, shorter DUP levels and better pre-morbid functioning each directly predicted lower levels of affective flattening, avolition and anhedonia at admission.

As for the other two presenting attributes, being older at the age at onset of the psychotic episode directly predicted less severe levels of affective flattening and alogia symptoms at the starting point, along with modest increases in rates of change in avolition symptoms over the subsequent 1-year trajectory. Male gender directly predicted greater severity of avolition symptoms at the starting point of the trajectory. Being male was also indirectly linked with decreased rates of change in the affective flattening trajectory, with its effects completely mediated by admission symptoms; males experienced higher symptom levels at admission compared with females, which led to decreased rates of change for males across the short-term affective flattening trajectory.

Elevated symptom levels at admission predicted worse symptom levels at the starting point of the trajectory (i.e., intercept), and decreased rates of change over the subsequent 1-year interval (i.e., slope) for each of the four negative symptom subscales. This finding strengthened results presented in Section 9.2.

Prediction of long-term outcome

STTs: The short-term negative symptom trajectories, represented by the intercept and slope latent variables, played a key role in the prediction of long-term symptom outcomes in this model. The STTs independently predicted long-term outcome, and also mediated effects of the presenting features of the study participants (comprising admission symptom severity, gender, age at onset of illness, DUP, and pre-morbid functioning) on long-term outcome. Specifically, both the alogia and anhedonia STTs (intercept and slope) independently predicted their respective long-term outcomes,

whilst the starting point (intercept) of affective flattening and the rate of change (slope) in the avolition trajectory predicted their outcomes. In each case, elevated symptom levels at the starting point and greater rates of change in the trajectories were associated with greater severity of long-term symptoms. Only one previously significant latent variable ceased to significantly predict long-term outcome once the presenting attributes were included; the starting point (intercept) of avolition.

The robustness of the growth trajectories as predictors of long-term outcomes when the effects of participant presenting features were taken into account, suggests that the STT may be a sentinel for long-term negative symptoms. In terms of their roles as mediators, either or both components of the STTs mediated the effects of: admission symptoms on all four negative symptom types; age at onset on long-term affective flattening, alogia and avolition; pre-morbid functioning on alogia and anhedonia; and DUP on anhedonia.

Presenting features: Pre-morbid functioning, DUP, age at onset of psychosis and gender predicted long-term negative symptoms. The majority of these effects were indirect. The only direct effect of note was that gender predicted long-term levels of avolition and anhedonia symptoms, with males experiencing worse symptomatic outcome on average, compared with females. Remaining effects were indirect in nature:

Pre-morbid functioning and DUP indirectly conferred their effects on long-term negative symptom outcomes through their impact on different components of short-term outcome (e.g., via symptom levels at admission or via the trajectory, i.e., the intercept or slope). The mechanism by which this occurred was that poorer pre-morbid functioning and prolonged DUP were each consistently linked with more severe short-term negative symptom levels, which in turn transmitted their effects to long-term negative symptoms. Specifically, poorer pre-morbid functioning and prolonged DUP were each linked with more severe levels of avolition symptoms at admission, the effects of which were transmitted to long-term symptom levels, resulting in greater severity of long-term avolition. Effects of pre-morbid functioning and DUP on long-term anhedonia symptoms were completely mediated by the starting point of the trajectory, which transmitted the effects of these baseline characteristics

to long-term anhedonia levels. The effects of pre-morbid functioning on long-term alogia symptom levels were also conferred indirectly via the trajectory starting point.

Similar to pre-morbid functioning and DUP, effects of age at onset of psychosis were transmitted indirectly to long-term symptoms. However unlike pre-morbid functioning and DUP, which were consistent in the direction of their effects on long-term severity levels across the four symptom types, age at onset impacted on long-term symptom levels in disparate ways. Being older at age of onset of psychosis indirectly predicted less severe long-term levels of affective flattening and alogia, with its effects mediated completely by symptom levels at the starting point of the trajectory. For example, older age at onset was linked with less severe affective flattening and alogia symptoms at the starting points of their trajectories, which in turn predicted less severe negative symptoms at long-term follow-up. Conversely, being older at the age at onset of the illness appeared to confer a harmful effect on long-term avolition symptom levels; in this instance, older age at onset of psychosis was linked with increased rates of change over the short-term avolition trajectory (i.e., the slope), which was linked with greater severity in avolition symptoms at long-term follow-up.

Section 9.4 introduced an additional predictor, baseline DSM-IV diagnosis of the first episode of psychosis. This has the potential to differentiate negative symptom trajectories and final long-term outcome, over and above the capacity of admission symptoms and presenting features of study participants. Despite this inclusion, the most notable finding was the central role played by the short-term trajectory (STT) both as an independent predictor of long-term symptom levels and as a mediator of diagnosis, admission symptoms and the baseline characteristics. The robustness of these findings over each incremental addition of candidate predictors to the latent growth curve models, suggests that the negative symptom STT is not simply a surrogate for other factors, such as severity of symptoms at service entry, the presenting features of the participants, nor their diagnoses.

Prediction of short-term outcome

Diagnosis: Particular diagnostic categories indirectly conferred favourable effects on the starting points of the negative symptom trajectories but were also linked with increasing severity of symptoms over the subsequent 1-year interval. The indirect

relationships were mediated by admission symptom levels. For example, those diagnosed with bipolar psychotic disorder had lower symptom levels at the starting point of all four symptom trajectories, but increasing severity on the subsequent 1-year trajectories of affective flattening, avolition and anhedonia. Similarly, the diagnostic group other psychotic disorders was indirectly linked with lower symptom levels at the starting point of affective flattening and anhedonia, but also with increasing severity over the trajectories of these symptoms. Schizophreniform disorder was indirectly linked with lower alogia and affective flattening at their starting points, and increased severity of anhedonia over its trajectory. Conversely, depressive psychosis and bipolar psychotic disorder each directly predicted decreasing severity in anhedonia symptoms over the STT.

Study participants diagnosed with bipolar psychotic disorder, schizophreniform or other psychotic disorders fared significantly better on symptom severity at admission compared with those diagnosed with schizophrenia. Bipolar psychotic disorder was associated with less severe symptoms on all four subscales; schizophreniform predicted less severe alogia and anhedonia; whilst other psychotic disorders predicted less severe affective flattening and anhedonia.

Presenting features: Prediction of the latent growth factors by the four presenting attributes were attenuated when baseline diagnosis was considered, with both direct and indirect effects impacted. The following effects remained: Most DUP levels continued to significantly predict the starting point of avolition, via admission symptoms. Likewise, very short to short $DUP_{0\text{-}28\ days}$ continued to directly predict the starting point of the anhedonia trajectory. Pre-morbid functioning remained a significant indirect predictor of the starting point of avolition, and the starting point and trajectory of anhedonia. Male gender continued to directly predict greater severity of avolition at the starting point. Age at onset of psychosis directly predicted less severe alogia at the starting point and increased rates of change in avolition. All other significant effects observed in the previous model, in which diagnosis was not considered, dropped out. Shorter DUP and better pre-morbid functioning each predicted lower avolition levels at admission, whilst good pre-morbid functioning additionally predicted lower anhedonia symptoms.

Admission symptoms: Increased severity of symptoms at admission was significantly linked with higher symptom levels at the starting point of the trajectory and decreased rates of change over the subsequent 1-year interval for each of the four negative symptom subscales (except the alogia slope), thus strengthening results from Section 9.2.

Prediction of long-term outcome

Diagnosis: In contrast to its predictive utility in short-term outcome, baseline diagnosis failed to directly predict any long-term negative symptom outcomes. Nonetheless, each baseline DSM-IV disorder (relative to schizophrenia) indirectly predicted one or more long-term negative symptoms via its effect(s) on either admission symptoms or on one of the latent variables comprising the short-term symptom trajectory. bipolar psychotic disorder was linked with less severe long-term affective flattening, alogia and avolition, via either admission symptoms or the intercept; depressive psychosis indirectly predicted less severe long-term anhedonia but worse long-term affective flattening via its effect on the slope of each of these symptoms; schizophreniform and other psychotic disorders indirectly predicted less severe long-term affective flattening and alogia respectively, via their intercepts; whilst schizoaffective disorder indirectly predicted less severe long-term anhedonia via decreasing changes on the slope.

STTs: Of note was the finding that the STT (or its components) for each of the negative symptom types directly predicted long-term symptom levels, and were not diminished by the inclusion of diagnosis or participant presenting features. Elevated levels of alogia and anhedonia at the starting point and increased rates of change on their trajectories predicted more severe long-term symptom levels, whilst elevated levels of affective flattening at its starting point and increased rates of change in the trajectory of avolition similarly predicted more severe symptom levels at long-term follow-up.

Furthermore, the STT (i.e., intercept and slope, or either of its components) continued to mediate the effects of admission symptom levels on long-term outcomes. For example, effects of affective flattening and anhedonia symptoms at admission on long-term symptom levels were completely mediated by their short-term trajectory latent variables (though their slope mediation mechanisms differed). Additionally, effects of

alogia at admission on long-term alogia were mediated by its intercept, whilst effects of avolition levels at admission on long-term avolition were mediated by its slope. As regards mediating mechanisms, higher levels of affective flattening, alogia and anhedonia at admission were linked with more severe symptoms at the starting points of their STTs, which subsequently led to worse symptomatic outcome at long-term follow-up. For avolition and anhedonia, higher symptom levels at admission were linked with decreased rates of change in their trajectories, which led to improved symptom levels at long-term follow-up. Conversely, higher levels of affective flattening at admission were linked with decreasing rates of change in its trajectory, which in turn was associated with worse affective flattening levels at long-term follow-up.

Presenting features: Gender was the only presenting attribute of study participants which directly predicted long-term outcome; males were rated with significantly more severe avolition and anhedonia at long-term follow-up. Being male was also indirectly linked with less severe long-term affective flattening via their increasing severity in affective flattening over the short-term trajectory, which in turn was linked with less severe affective flattening at long-term follow-up. This effect emerged only when diagnosis was included. Age at onset of psychosis continued to indirectly predict long-term affective flattening, alogia and avolition symptom levels. Being older at onset of the illness was linked with milder severity of affective flattening and alogia at the starting point of their trajectories, which in turn were linked with less severe symptoms at long-term follow-up. In contrast, being older was linked with a modest increase in the rate of change in avolition over its trajectory, which led to more severe long-term avolition symptoms.

Most DUP levels (except $DUP_{8\text{-}28\ days}$) were linked with less severe long-term avolition levels solely through their favourable impact on admission symptoms, whilst shorter $DUP_{0\text{-}28\ days}$ was linked with less severe anhedonia at long-term follow-up via its impact on the starting point of the anhedonia trajectory. These effects were robust to diagnostic inclusion. The effect of poorer pre-morbid functioning on long-term avolition symptoms was mediated by symptom levels at admission, whilst its effect on long-term anhedonia was mediated by level of symptoms at the trajectory starting point. In both instances, poorer pre-morbid functioning was linked with greater

severity of symptoms in the early course, which in turn predicted greater severity of symptoms at long-term follow-up.

9.6 General conclusion

There was little change in mean alogia, avolition, and anhedonia symptoms over the 1-year interval subsequent to initial recovery from the initial psychotic episode. However, individuals varied significantly in their starting values at the beginning of the trajectory on the four negative symptom subscales, and in their rates of change over the short-term trajectory on alogia, avolition and anhedonia. Individual variability in these trajectories accounted for long-term symptomatic outcome, even when effects of diagnostic, clinical, and demographic presenting attributes were considered. Additionally, the STTs mediated the effects of participant presenting attributes on long-term outcome, including age at onset, pre-morbid functioning, DUP, admission symptoms, and DSM-IV diagnosis.

The robustness of the growth trajectories as predictors of long-term outcomes when the effects of participant presenting features were taken into account, suggests that the STT may be a sentinel for long-term negative symptoms. Of the participant presenting attributes, only gender directly predicted long-term symptoms, with males experiencing more severe long-term avolition and anhedonia symptoms. Symptom levels at admission significantly predict the STTs when effects of diagnosis and baseline characteristics were considered, however the effects of the four participant presenting attributes on the trajectories were somewhat attenuated.

10 DISCUSSION

This concluding chapter comprises five sections. Firstly, a summary of the research findings is presented in section 10.1, followed by comparison with previous research in section 10.2. The implications of the findings are then discussed in section 10.3, and section 10.4 presents the limitations of the study. Section 10.5 considers future research directions, which covers broader issues to be covered in future work; specifically, the type and scope of work necessary to bring about general advancement in this area. Following on, section 10.6 briefly reviews the practical implications of the research. This chapter concludes with section 10.6, which contains a brief summary of what has been found in this study.

10.1 Summary of Research Findings

10.1.1 Shape and rate of change in short-term trajectories

The average shape of change in positive symptoms over the short-term course subsequent to initial remission conformed optimally to a non-linear trajectory, with a relatively steep and significant decline in severity of symptoms in the first six months, followed by a flat trajectory in the second part of the 1-year interval. The average starting point of the trajectory was equivalent to a rating of only 'very mild', which is consistent with the timing of the research assessment (conducted at remission or stabilisation of the initial episode), and which followed administration of antipsychotic medication soon after the young person entered the youth mental health service. There was strong evidence for significant individual variability around the starting point of the short-term trajectory, however individual variability in rates of change over the trajectory narrowly failed to be captured by the model ($p=0.065$).

In contrast to positive symptoms, each of the negative symptom trajectories over the 1-year interval were best described as linear in form. Similar to positive symptoms, the initial levels of the trajectories were relatively low, with average ratings of 'none' to 'questionable' for alogia and affective flattening, and average ratings of 'questionable' to 'mild' for avolition and anhedonia. Little change was detected in the average severity of alogia, avolition and anhedonia over the 1-year interval. Affective flattening, on the

other hand, decreased significantly over this period. Participants varied significantly in their starting points of all four negative symptom subscales and, in rates of change over the 1-year interval, on alogia, avolition and anhedonia. Individual variability in rates of change over the trajectory for affective flattening marginally escaped significance (p=0.054).

The failure of the positive and affective flattening symptom models to capture individual variability in rates of change over the trajectories demonstrates a typical scenario in growth models, where there is much higher variation in initial levels of growth trajectories than growth rate variation (B. Muthén, Khoo, Francis, & Boscardin, 2003).

10.1.2 Prediction of long-term symptomatic outcome

10.1.2.1 The STTs predict long-term outcome

The most notable finding of this thesis was that the short-term trajectory (STT) of all types of symptoms played a pivotal role in the prediction of long-term symptoms, both as an independent predictor of long-term symptomatic outcome and as a mediator of participant presenting features on long-term outcome. For positive symptoms, the starting point (intercept) of the STT consistently predicted long-term symptoms, across each stage of model development, with lower levels of positive symptoms directly predictive of less severe positive symptoms at long-term follow-up.

Even more compelling was the predictive utility of the negative symptom STTs on long-term negative symptoms. Both components of each of the alogia, avolition, and anhedonia STTs (intercept and slope) independently predicted their respective long-term outcomes, whilst the intercept of affective flattening trajectory predicted its long-term outcome. Higher initial trajectory levels, and increasing rates of change over the 1-year interval subsequent to initial recovery, predicted worse long-term symptomatic outcomes. When presenting attributes and diagnosis were controlled, the only change was that the intercept of the avolition trajectory ceased to significantly predict long-term avolition symptoms. These results suggest that the STT may be a sentinel for long-term negative symptoms, given the robustness of the growth trajectories as independent predictors of long-term outcome, when initial admission symptoms,

gender, age at onset, DUP, premorbid functioning, and DSM-IV diagnosis were considered.

10.1.2.2 Effects of most participant presenting attributes on long-term outcome were mediated by the short-term trajectories

The finding that the one or both components of the STTs played a mediating role in the effects of presenting attributes on long-term outcome, underscores its significance in the prediction of long-term symptoms. For example, the prognostically favourable effects of shorter levels of DUP were indirectly transmitted to long-term positive symptoms, anhedonia, and affective flattening symptoms, solely via their effect on the starting point of the respective STTs. For positive symptoms, shorter DUP categories of less than 90 days were linked with lower levels of psychotic symptoms at the starting point, which were linked with less severe long-term symptoms. This mechanism was similar for anhedonia and affective flattening, although with a more limited range of statistically significant DUP categories (28 days or less for anhedonia, and eight to 28 days for affective flattening). Effects of DUP on long-term avolition levels, on the other hand, were mediated by admission symptom levels; shorter DUP categories of one year or less were linked with lower levels of avolition symptoms at admission, the effects of which were transmitted to long-term avolition, resulting in less severe symptom levels. DUP did not predict either short-term or long-term alogia symptom levels.

Like DUP, the effects of better premorbid functioning were indirectly transmitted to long-term positive symptoms, anhedonia, and alogia symptoms via the starting point of their trajectories. For positive symptoms, the indirect effect of premorbid functioning was supplemented by a direct effect, where better premorbid functioning directly predicted less severe symptoms at long-term follow-up. These results imply that it is not prolonged DUP or premorbid functioning per se that are important in determining long-term positive and negative symptom severity, but the young person's symptom levels at stabilisation of illness (or in the case of avolition, symptom levels at initial admission), which is impacted by these factors. The partial mediation of premorbid functioning by the starting point of the positive symptom trajectory, on the other hand, suggests that premorbid functioning exerts an effect on long-term positive

symptom levels over and above the effect mediated by the starting point of the trajectory.

As for the other participant presenting attributes, being older at the onset of psychosis also appeared to confer a protective effect on long-term affective flattening and alogia via the starting point of their STTs, but conversely, was also linked with more severe long-term avolition symptoms via increased rates of change on the avolition trajectory. Whilst most effects of participant presenting attributes on long-term symptoms were indirect in nature, there was one exception: male gender directly predicted poorer long-term avolition and anhedonia symptoms.

Effects of the participant presenting attributes on long-term outcomes were generally not greatly impacted by the inclusion of diagnosis, in contrast to the attenuation observed of their effects on the STTs, which will be discussed later.

10.1.2.3 Effects of admission symptoms on long-term symptoms were mediated by the short-term trajectories

The effects of initial admission symptoms on long-term affective flattening and anhedonia were mediated by their trajectories (i.e., intercept and slope), when participant presenting attributes and DSM-IV diagnosis were accounted for. As for alogia and avolition, the starting point of the alogia trajectory, and the rate of change in avolition, mediated the effects of admission symptom severity on their respective long-term symptom levels. The only long-term symptom directly predicted by symptom levels at admission, was avolition, which remained robust when DSM-IV diagnosis was introduced. Regarding positive symptoms, there was no compelling evidence to suggest that the STT reliably mediated effects of admission symptoms on long-term symptom levels.

10.1.2.4 Diagnosis indirectly predicted long-term outcome

DSM-IV diagnosis indirectly predicted long-term positive and negative symptoms via its impact on early course symptoms (either admission symptom levels, the intercept, or slope of the STT). There was no evidence of any direct effect of psychotic diagnosis

on long-term outcome. Diagnostic effects were transmitted to long-term positive symptoms solely through their impact on the starting point of the trajectory. Diagnoses which indirectly resulted in reduced severity in long-term positive symptoms, as compared with schizophrenia disorder via this mechanism were: schizophreniform disorder, bipolar psychotic disorder, depressive psychosis, and other psychotic disorder. Schizoaffective disorder showed no differential effect from schizophrenia disorder in impacting long-term positive symptoms.

Each diagnostic disorder indirectly predicted one or more types of negative symptoms via early course symptoms. Bipolar psychotic disorder was linked with less severe long-term affective flattening, alogia and avolition, via either initial admission symptoms or the intercept; depressive psychosis indirectly predicted less severe long-term anhedonia, but worse long-term affective flattening via its effect on the slope of each of these symptoms; schizophreniform and other psychotic disorders indirectly predicted less severe long-term affective flattening and alogia respectively, via their intercepts; whilst schizoaffective disorder indirectly predicted less severe long-term anhedonia via decreasing changes on the slope.

10.1.3 Prediction of the short-term trajectories

10.1.3.1 Initial admission symptoms consistently predict the four negative symptom trajectories but not positive symptoms

Quite different factors predicted the short-term course of symptoms for positive and negative symptoms. For negative symptoms, symptom levels at admission predicted both the starting points and change trajectories of all four symptom subscales. Elevated symptom levels at admission predicted more severe symptoms at the starting point of the trajectory, and significant decreases in change over time. These findings remained convincingly robust when participant presenting attributes and DSM-IV diagnosis were controlled. Conversely, for positive symptoms, there was little evidence that admission symptom levels predicted the short-term trajectory; admission symptom levels only marginally predicted the positive symptoms starting point when no other presenting attributes were considered, and dropped out as a predictor in

subsequent models. Not having been examined in this way in previous research, these may be considered to be novel findings.

10.1.3.2 Participant presenting attributes predict the short-term trajectories in different ways for different symptom types

Of the four presenting attributes, DUP and premorbid functioning each predicted the short-term trajectories at a substantive level, although mechanisms differed for positive and negative symptoms. Effects on short-term positive symptoms were direct, with no mediation occurring. Shorter DUP categories of 90 days or less, and better premorbid functioning directly predicted less severe positive symptoms at the starting point of the trajectory. Gender and age at onset of psychosis were not linked with the short-term positive symptom trajectory.

In contrast, prediction of short-term negative symptoms was a mix of direct and indirect effects. For instance, shorter DUP levels and better premorbid functioning indirectly led to less severe affective flattening, avolition, and anhedonia at the starting point of the STT, and modest increases in rates of change over their 1-year trajectories, via their effect on admission symptoms. Additionally, better premorbid functioning directly predicted less severe alogia and anhedonia symptom levels at the start of their trajectories, with a similar effect for shorter DUP on anhedonia.

Being older at the age at onset of the psychotic episode conferred a protective effect on affective flattening and alogia symptoms at their starting points, and modest increases in rates of change in avolition symptoms over the subsequent 1-year trajectory. Male gender directly predicted greater severity of avolition symptoms at the starting point of the trajectory, and was also indirectly linked with decreased rates of change in the affective flattening trajectory via admission symptoms.

10.1.3.3 DSM-IV psychotic diagnosis directly predicts the starting point of positive symptom trajectory, and indirectly predicts the STTs of negative symptoms via initial admission symptoms

Unsurprisingly, the introduction of diagnosis at baseline led to the attenuated effects of the participant presenting attributes on the STTs for both positive and negative

symptoms, however did not greatly impact effects of the presenting attributes on long-term symptom outcomes. Baseline DSM-IV diagnosis directly predicted the starting point of the positive symptoms trajectory. Those with schizophreniform, bipolar psychotic disorder, depressive psychosis, and other psychotic disorders, exhibited significantly less severe positive symptoms at the starting point, compared with participants diagnosed with schizophrenia, whilst the other psychotic disorders group additionally exhibited increasing change over the trajectory.

The predictive mechanism for diagnosis differed for negative symptoms. Bipolar psychotic disorder indirectly conferred protective effects at the starting point of all four negative symptom trajectories, via admission symptoms, but also was linked with increasing severity on rates of change of affective flattening, avolition and anhedonia. In the same way, the diagnosis of other psychotic disorders was indirectly linked with lower symptom levels at the starting point of affective flattening and anhedonia, but also with increasing severity over the trajectories of these symptoms. For bipolar psychotic disorder, there was an additional direct effect on the starting point of affective flattening, alogia, and avolition, with decreased symptom levels relative to schizophrenia, and on the slope of anhedonia, with decreased rates of change compared to schizophrenia.

10.1.3.4 Other points

Consistently throughout this research, intercept effects far outweighed slope effects, both as direct predictors and as mediators. This situation seems to be ubiquitous in growth curve modelling (B. Muthén et al., 2003). Given the relative rarity of slope effects in this type of research, the detection of several such effects in the negative symptom models is notable. The slopes of the alogia, avolition, and anhedonia trajectories each directly predicted their long-term symptom levels, and remained robust when the presenting attributes of participants and their diagnoses were controlled.

Furthermore, the slopes of the four types of negative symptoms mediated the effects of various baseline factors on long-term symptom levels: (i) the slope of the anhedonia trajectory mediated the effect of initial admission symptom levels, schizoaffective disorder, and depressive psychosis on long-term anhedonia levels; (ii) the slope of the

affective flattening trajectory mediated the effect of depressive psychosis on long-term affective flattening; the slope of the avolition trajectory mediated the effect of age at onset of psychosis on long-term avolition; and, the slope of alogia mediated the effects of initial admission symptom levels on long-term alogia.

10.2 Comparison with Previous Research

10.2.1 Short-term trajectory: Positive and negative symptoms

The finding that positive symptom severity declined in the first six months of the 1-year interval after symptom remission, followed by a period of relative stability, is consistent with the findings of the Madras longitudinal study (Eaton et al., 1995) and others (Addington & Addington, 1991) . This contrasts with the relatively flat average trajectories of change observed in each of the negative symptom subscales, except for affective flattening which decreased significantly over the 1-year interval. Negative symptoms were thus generally characterised by stability, and in the case of affective flattening, improvement. Each of these scenarios is contrary to the earliest conceptions of schizophreniform that posited negative symptoms as following a path of progressive deterioration (Bleuler, 1950; Kraepelin, 1919).

The findings for negative symptoms therefore provide broad support for those studies that have reported relative stability in negative symptoms over time (Arndt et al., 1995; Dollfus & Petit, 1995; Fenton & McGlashan, 1991; Mueser et al., 1991; Pogue-Geile & Harrow, 1985; Ventura et al., 2015), but only partial support for other studies which reported improvement in symptoms. For instance, Addington and colleagues (Addington & Addington, 1991) found that all types of negative symptoms, with the exception of avolition, significantly improved over a six-month course; Eaton et.al. (Eaton et al., 1995) reported a marked decline in severity of negative symptoms in the first six months, Quinlan et.al. (Quinlan et al., 1995) reported that all negative symptoms except for avolition decreased over a two-year course, and a large meta-analytic study concluded that negative symptoms do not tend to follow a stable or deteriorating course, but are likely to improve over time, based on symptom change between two time points ranging in duration from 10 weeks to three years (Savill et al., 2015). Another study of interest found that positive symptom exacerbations, which

occurred in 77% of patients over a mean three -year period, were more common than negative symptom exacerbations, which occurred in only 42% of patients (Ventura et al., 2004). Their study, although small (N=48), was characterised by very frequent assessments, made every two weeks over the study period, a distinct advantage when modelling symptom change.

It is possible that the inconsistencies with studies which have found improvement in individual negative symptoms could be at least partly accounted for by differences in study design or stage of illness factors. For instance, Eaton et.al. (Eaton et al., 1995), and Addington (Addington & Addington, 1991) began following patients from hospitalisation, at which point patients might reasonably be expected to exhibit more severe symptoms, with greater scope for improvement over time.

In contrast, the present study defined the starting point of the short-term change trajectory as the point of remission or stabilisation of positive and negative symptoms, and thus was likely to leave less room for improvement. This aspect will be further addressed in section 10.5 in this chapter. In other studies, for instance, Quinlan et.al. (Quinlan et al., 1995), the significant improvement in negative symptoms may have been accounted for by the longer (two-year) period of follow-up, whilst the meta-analytic study of Savill et. al. (Savill et al., 2015) included studies with widely heterogeneous timeframes, ranging from 10 weeks to 3 years. However, these may be moot points, as pointed out in a recent meta-analytic study (Fusar-Poli et al., 2015), because whilst most pharmacological and psychological treatments reduced negative symptoms relative to placebo, no change met the threshold for clinically meaningful improvement.

10.2.2 Change in individual negative symptoms

Affective flattening

The significant improvement observed in affective flattening over the 1-year interval, although consistent with the findings of the abovementioned studies, runs counter to the finding of Kelley et.al. (Kelley et al., 1999) that affective flattening showed a lack of change over the course of one year, with the author explaining that in the literature, this symptom is generally regarded as the most stable over time, as it is considered less

responsive to medication. Change in affective flattening was also inconsistent with the work of Galderisi et.al. (Galderisi et al., 2013), who found that affective flattening was the most persistent negative symptom over the one-year course of the study. It is possible that this inconsistency may be due to diagnostic differences; the study samples used by Kelley et.al., and Galderisi et.al., each of which included participants with schizophrenia-spectrum disorders only, rather than the full diagnostic spectrum of psychotic disorders.

It has been pointed out (Menezes et al., 2006) that these restrictive samples may have worse outcomes than those studies inclusive of the broader diagnostic spectrum. The affective flattening results also provide an interesting contrast to the Madras 10-year longitudinal study, which demonstrated that the enduring influence of flat affect after the first episode has subsided, was predictive of poor outcome (Eaton, Thara, Federman, & Tien, 1998). The effect of the affective flattening STT on long-term affective flattening symptom levels in this thesis would appear to belie this, at least in part. Firstly, affective flattening was the only negative symptom to demonstrate significant improvement over the course of the 1-year interval subsequent to initial recovery from the psychotic episode, and; secondly, only the initial levels of the affective flattening trajectory were predictive of long-term symptom levels, and not the change over the 1-year trajectory.

Avolition

The finding that avolition symptoms did not change significantly over the 1-year course of the short-term trajectory, was at odds with Kelley et.al., (Kelley et al., 2008), who found that only avolition was the only negative symptom that changed significantly over the course of one year, along with anhedonia, when it was analysed as a linear rather than a categorical variable. The authors acknowledged the possibility that levels of affective flattening and alogia were too low to detect reasonable change over time, but also noted that the literature regards these symptoms as more stable. Others have noted the central role played by avolition in dictating the changes characterising the 'dementia praecox' decline (Foussias & Remington, 2010). The lack of change detected in the average avolition short-term trajectory would appear to contradict this. Predictors of the short-term avolition trajectory and long-term outcome common to

both were: admission symptom levels, DUP, premorbid functioning, male gender, and age at onset of psychosis.

10.2.3 Prognostic significance of admission symptoms on short-term and long-term outcomes

The finding that affective flattening and anhedonia symptom levels at service admission independently predicted their respective long-term symptom levels, supports the findings of Fenton et.al. (Fenton & McGlashan, 1991), who found that affective flattening and anhedonia were independent predictors of long-term outcome irrespective of pre-morbid functioning. However, Fenton et.al. also noted that negative symptoms showed less prognostic significance when assessed early in the course of illness than when assessed several years after the illness had been established. This was further emphasised by Carpenter and Strauss (W. T. Carpenter & Strauss, 1991), who pointed out that blunted affect may not bode well for long-term course, as it may signify a compromised integrity of the affect system, but that affect was difficult to ascertain during the psychotic episode given that it is distorted by the psychosis, and may be imprecise as a predictor of long-term outcome. The findings presented in this thesis would suggest otherwise; the effects of affective flattening and anhedonia at admission predicted long-term symptoms via their effects on the intercept and slope of their respective trajectories.

As for prediction of short-term outcomes, Addington et al. (Addington & Addington, 1991) found that negative symptom levels at hospitalisation were highly predictive of negative symptoms at 6-month follow-up, whereas positive symptoms yielded little predictive information. The results of my study support these findings; symptom levels of affective flattening, alogia, avolition, and anhedonia, directly predicted initial levels of trajectories, and change in symptoms over the subsequent 1-year interval, whilst positive symptom levels at admission had no prognostic effect on the short-term positive symptom trajectory.

10.2.4 Prediction of long-term outcome

10.2.4.1 The short-term trajectories as predictors

One of the key questions in this thesis concerns what role, if any, is played by heterogeneity in the short-term symptom trajectories in determining long-term symptomatic outcome; whether it directly predicts long-term outcome, or alternatively, is a mediator of the effects of the clinical presenting factors, or a combination of the two. The finding that the short-term symptom trajectories played a dual role as independent predictors of long-term symptom levels, and as mediators of the effects of participant presenting attributes (including DUP, premorbid functioning, gender, and age at onset of psychosis), admission symptoms, and DSM-IV diagnosis, on long-term symptom levels, may be considered a novel finding, as it has not been examined this way in previous research.

These results confirm and extend results obtained in a recent study (Ventura et al., 2015), which reported that negative symptom severity in the first year subsequent to medication stabilisation, predicted negative symptom severity eight years later. Ventura et.al. claimed that this demonstrates the moderate stability in negative symptoms even over long time periods, despite the fact that during the intervening years the patients may have experienced intervals of psychotic remission, exacerbation, relapse, or hospitalisation. The authors cautioned that the apparent relationship could be a spurious one, as third variables, such as premorbid functioning and DUP were not taken into account, and pointed out that the sample size for the 8-year follow-up was modest, with 53 research participants included in the analysis. By controlling for the effects of these and other factors using a robust sample size, the results of the models in my thesis suggest that the association is unlikely to be confounded by these third variable candidates.

10.2.4.2 DUP

The majority of studies to date have considered only the temporal stability of effects of DUP on outcome over relatively short time frames, for instance, Addington et.al. (Addington et al., 2004) , however there have been recent exceptions (Austin et al., 2015) . The longitudinal assessment of this cohort over multiple time points has

provided an opportunity to examine the mechanism of the DUP effect on both long-term and short-term symptomatic outcomes.

Investigations revealed that DUP significantly predicted short-term and long-term positive and negative symptomatic outcome independently of other factors. These effects were mostly indirect in nature, which contrasts with the direct effects reported in most studies of DUP and outcome. The difference in the mechanism of the predictive relationship is of particular interest, since the preponderance of indirect effects of DUP on long-term outcomes, where there were no direct effects present, implies that it is not prolonged DUP per se that is important in determining long-term severity, but the young person's symptom levels at illness stabilisation (or, in the case of avolition, symptom levels at admission). This contrasts with the interpretation of direct effects of DUP on outcome reported in other research, the core of which is essentially that DUP is of direct importance (without necessarily attributing causality to the relationship). Given the relative rarity of DUP and outcome studies which utilise mediation analysis, it is possible that the inability of some studies to detect an association between DUP and outcome (for example, (Barnes et al., 2000; Craig et al., 2000; B. Ho & Andreasen, 2001; B. C. Ho et al., 2000)), might be due in part to restricting their focus on the detection of direct effects.

10.2.4.2.1 DUP as a predictor of short-term outcomes

The finding that prolonged DUP was significantly associated with higher levels of positive symptoms at the initial point of the trajectory, supports the findings of other studies of DUP and short-term symptoms which also controlled for the effects of other factors (e.g., (Addington et al., 2004; T. K. Larsen et al., 2000; Malla et al., 2002)). The effect of DUP categories of 90 days or less on short-term positive symptoms was direct, impacting on the starting point of the STT. This supports the finding of Marshall et.al. (Marshall et al., 2005) that the association between DUP and positive symptoms during the first episode of psychosis was particularly robust, although the modelling in my thesis failed to detect a relationship between DUP and change in positive symptoms over the subsequent 1-year interval.

On the other hand, the finding that DUP predicted negative symptoms at initial recovery and over the subsequent 1-year interval did not accord with the findings of

the majority of those short-term studies (Addington et al., 2004; T. K. Larsen et al., 2000; Malla et al., 2002). In contrast to the findings presented in this thesis, Malla et.al. (Malla et al., 2002) reported that negative symptoms were influenced not by DUP, but by longer term characteristics such as premorbid functioning, earlier age at onset, gender, and prodromal duration. The conclusion by Malla et.al. that negative symptoms may therefore not be as responsive to effects of early intervention as positive symptoms, is therefore not supported by the present research.

The association between DUP and short-term outcome also concurs with evidence from a large systematic review of a moderately strong association between DUP and a range of short-term outcomes at 6 and 12 months of follow-up (Marshall et al., 2005). The authors observed that the association was usually not present at the time of presentation, but emerged after administration of treatment. However, the findings in this thesis are partly at odds with this; prolonged DUP independently predicted affective flattening, avolition, and anhedonia symptom levels at admission to the service, but not positive symptoms.

As for prediction of the negative symptom trajectories, indirect effects were predominant; DUP indirectly predicted the starting point and rates of change in the affective flattening, avolition, and anhedonia trajectories, via its effects on admission symptom levels. The additional direct effects of DUP on the starting point of these types of negative symptoms were more moderate, with fewer statistically significant DUP categories, compared to those of the indirect effects.

10.2.4.2.2 DUP and long-term outcome

The findings that DUP independently predicted long-term outcome partly concurred with those of two separate long-term research studies conducted over eight and 10-year follow-ups respectively. These two studies found that DUP independently predicted positive symptoms, but did not predict negative symptoms (Austin et al., 2015; Crumlish et al., 2009). The prognostically favourable effects of shorter levels of DUP of less than 90 days on long-term positive symptoms were broadly consistent with Austin et.al (Austin et al., 2015), who reported that prolonged DUP was associated with increased risk of a worse positive symptom prognosis for each of four positive symptom latent class trajectories compared to the reference trajectory (positive

symptom response group), when other baseline variables were controlled. The nature of the association between DUP and positive symptoms was the main point of difference; Austin et.al. reported that prolonged DUP directly predicted worse positive symptom outcomes, whilst the present study found that the effect of DUP on long-term positive symptom levels was completely mediated by initial levels of the positive symptom trajectory, with shorter DUP categories of 90 days or less leading to lower symptom levels at the beginning of the trajectory, which led to lower levels of long-term positive symptoms.

As for DUP and negative symptoms, (Austin et al., 2015) reported that there was no evidence that the four negative symptom trajectory groups were differentiated by DUP. This may be a result of their use of a composite score to measure overall negative symptom severity, rather than assessing each type of negative symptom. This thesis has presented evidence of variability in the relationship between DUP and each type of negative symptoms, hence it is possible that the decision of Austin et.al. to collapse over individual negative symptoms to form a measure of overall negative symptom severity may have resulted in non-detection of DUP effects and less nuanced findings. Additionally, my decision to model both direct and indirect effects provided the opportunity to detect alternative modes of prediction. Indeed, the effects of DUP on long-term negative symptoms were mediated by initial levels of the short-term trajectories (anhedonia, and affective flattening), or by admission symptom levels (avolition), rather by direct prediction of long-term negative symptoms.

On the other hand, the current study's finding concurred with the work of Bottlender et.al. (Bottlender et al., 2003), which showed support for a relationship between DUP and positive and negative symptoms at 15-year follow-up.

10.2.4.3 Premorbid functioning

The significant association between premorbid functioning and each of the long-term positive and negative symptomatic outcomes (with the exception of affective flattening), appeared to be consistent with much of the research on this topic (Haas et al., 1998; Johnstone et al., 1990; T. K. Larsen et al., 2000). However, the results did not provide unequivocal support for all studies. For example, Austin et.al. (Austin et al., 2015) found that although premorbid functioning was independently associated with

poorer negative symptom trajectory groups over the course of 10 years, it did not differentiate between positive symptom trajectory groups. As for the prediction of short-term outcome, the finding that premorbid functioning predicted the short-term trajectories of positive symptoms and each of the four negative symptom types is consistent with two short-term follow-up studies. Addington et.al. (Addington & Addington, 2005) found that individuals with poorer premorbid functioning had significantly higher levels of positive and negative symptoms at one-year follow-up, whilst Chang et.al. (Chang et al., 2011) reported that participants with poorer premorbid functioning had significantly higher levels of negative symptoms at two and three-year follow-up.

10.2.4.4 Gender

Results indicated that male study participants exhibited more severe avolition and anhedonia symptoms at long-term follow-up. These effects were direct in nature. Although early research had been inconsistent with regard to the effect of gender on negative symptoms, McGlashan et.al. (T. H. McGlashan & Fenton, 1992) pointed out that when present, gender effects were invariably in the direction of males having more negative symptoms, with no discernible effect for gender on positive symptoms, which is supported by my results. My findings for the effects on gender on long-term symptoms appear to variously support some later research studies (Chang et al., 2011), and contradict others (Eaton et al., 1995). For example, the work of Chang et.al. demonstrated that being male was associated with persistent negative symptoms over the course of three-year follow-up (Chang et al., 2011), whilst Eaton et.al. found that males were more likely to have positive symptoms than females over the course of 10-year follow-up, with no effect on negative symptoms (Eaton et al., 1995). More recently, Austin et.al. (Austin et al., 2015) demonstrated that male gender was not associated with positive symptom trajectory groups, but did predict poorer negative symptoms trajectory outcomes, which aligned with my research findings.

10.2.4.5 Age at onset of psychosis

Age at onset of psychosis impacted on long-term symptom levels in disparate ways. Being older at the onset of the initial psychotic episode indirectly predicted less severe long-term levels of affective flattening and alogia, and conversely, predicted more

severe long-term levels of avolition. The protective effects of being older at onset on affective flattening and alogia, concorded with the findings of the Madras longitudinal study (Eaton et al., 1995), which found that individuals aged less than 20 years at onset of psychosis were significantly more likely to experience negative symptoms than those aged more than 25 years at onset. Conversely, other papers based on the Madras longitudinal study found that being older at onset predicted poorer prognosis (Eaton et al., 1998), and greater risk of poor course (Thara et al., 1994), respectively. This is consistent with my finding that being older was linked with more severe long-term avolition symptom levels, but is seemingly incompatible with my finding that being older at age of onset was linked with less severe affective flattening and alogia symptoms at long-term follow-up. The inability of my study to detect any association between age at onset and positive symptoms was inconsistent with the earlier Eaton et.al. study, which found that those aged 20-24 years at onset were half as likely to experience positive symptoms than the older group (Eaton et al., 1995).

10.2.4.6 DSM-IV psychotic diagnosis

Most diagnostic categories, compared to the reference diagnosis of schizophrenia, were indirectly linked with less severe long-term positive symptoms. This supports the findings of Austin and colleagues, who ascertained that a diagnosis of schizophrenia predicted an increased risk of a worse positive symptom prognosis for each of four positive symptom trajectories assessed over the course of 10 years (Austin et al., 2015). The results for negative symptoms also broadly support the finding of Austin et.al. that schizophrenia diagnosis discriminated between different negative symptom trajectory groups. Our results also support the findings of an international long-term follow-up study; Harrison et.al. (Harrison et al., 2001) found that study participants with a diagnosis of schizophrenia did more poorly at 15-year follow-up, compared to those with schizoaffective disorder, acute schizophrenia, bipolar and depressive disorders, and other psychoses.

The negative symptom results are inconsistent with the findings from the Chicago study (Herbener & Harrow, 2001), which reported finding no diagnostic differences in severity of negative symptoms at any follow-up point over the course of 10 years. In contrast, the present study found an effect for bipolar psychotic disorder, with lower

long-term levels of affective flattening, alogia, and avolition symptoms compared with the reference diagnosis, schizophrenia. This thesis also found that depressive psychosis was linked with less severe long-term anhedonia, but worse long-term affective flattening symptom levels, that schizophreniform and other psychotic disorders were linked with less severe long-term affective flattening and alogia symptoms, and that schizoaffective disorder was linked with less severe anhedonia. It is notable that all diagnostic effects on long-term outcome were indirect, being mediated by either the short-term trajectories, or by admission symptoms. A possible reason that Herbener and colleagues failed to find any diagnostic effects for negative symptoms was their focus on direct effects only. However, their conclusion, in the light of their investigations into persistence of negative symptoms, that diagnosis appears to add additional vulnerability to later negative symptoms, even after the effects of early negative symptoms are considered, is relevant to the findings of the current study.

10.3 Implications of the Findings

Psychosocial treatments have, in the main, set their sights on positive symptoms as the primary focus of treatment and outcome (Tarrier, 2006), as have drug trials. The notion that negative symptoms are secondary to positive symptoms in first-episode psychosis is not necessarily supported by the findings of this thesis. Results suggest that there may be more capacity to intervene in negative symptoms than previously thought, given the role played by the alogia and anhedonia symptom short-term trajectories, and, to a lesser extent, affective flattening and avolition, as independent predictors of long-term symptom levels.

It has been noted that any advances made in the treatments for schizophrenia have been of limited benefit to negative symptoms (Savill et al., 2015). However, improvement in negative symptoms over the medium-term has been observed in patients randomised to cognitive-behavioural treatments (CBT) for positive symptoms in addition to treatment as usual (TAU), compared with TAU alone (Haddock et al., 2003; Tarrier, 2006; Tarrier et al., 2000). If negative symptom trajectories can be influenced by such treatments, the possibility of improving long-term negative symptoms may be enhanced. The potential importance of optimising the short-term trajectory is also underlined by the work of Harrison et.al., who, in their 15-year follow-

up, concluded that if the course of psychotic disorders depends upon short-term outcome and sociocultural settings, then early intervention programmes and intensive engagement strategies may have a favourable impact on the evolution of symptoms over the longer-term (Harrison et al., 2001). Whilst the results of this study suggest that the short-term trajectory may be considered a sentinel for long-term symptomatic outcome, causality can only be ascribed via the most methodologically rigorous means; that of the randomised controlled trial (RCT).

The mediational analyses have provided valuable information about the mechanisms by which predictors impact on various short-term and long-term outcomes. For example, the prognostically favourable effects of shorter levels of DUP were indirectly transmitted to long-term positive symptoms, anhedonia, and affective flattening, solely through their impact on initial levels of the short-term trajectories. Hence, it appears that what is important when it comes to prediction of long-term severity of positive and negative symptoms, is not prolonged DUP per se, given the absence of direct effects of DUP on long-term outcome, but the young person's symptom levels at initial recovery/stabilisation of the psychotic episode, which were impacted by DUP. As one of the few malleable predictors of outcome in first-episode psychosis, its prognostic influence has been shown to extend to both short-term and long-term outcomes, via indirect means. Knowledge of the mechanisms by which DUP impacts long-term outcome has implications for service delivery, which will be discussed shortly. The story was similar for premorbid functioning, which was associated with long-term positive and negative symptom levels, solely via its impact on initial levels of the short-term trajectory, save for an additional direct effect on long-term positive symptoms. The effects of age at onset of psychosis were also transmitted indirectly to long-term negative symptom levels.

Of particular interest, was the pivotal role played by the STTs in predicting long-term symptoms levels, independently of the effects of the admission symptoms, gender, age at onset, DUP, premorbid functioning, and baseline DSM-IV diagnosis. The association between the STT and long-term negative symptoms, in particular, was striking. Higher initial trajectory levels, and increasing rates of change over the 1-year interval subsequent to initial recovery, predicted worse symptomatic outcomes. This finding implies that what occurs after admission to the service is critical to how a young

person's symptoms continue to evolve, and suggest that the STT may be a sentinel for long-term negative symptoms. The importance of the STT is underlined, particularly when taken in conjunction with its role as a causal pathway for the effects of DUP, premorbid functioning, and, to a lesser extent, age at onset of psychosis, on long-term symptomatic outcome.

The central role played by the STT in predicting long-term outcome is particularly relevant clinically. The critical period for vulnerability to symptomatic deterioration, relapse, and the development of disability, is thought to occur during the early phase of psychosis, with relative stability in symptoms thereafter (Birchwood et al., 1998). It is hypothesised that intervention in the early years after the onset of psychosis is likely to have a much greater impact compared with interventions later in the course of illness. Following the critical period, it is thought that progression of symptoms and disability slow or stop, and the level of recovery attained by the end of the critical period endures into the long-term (Crumlish et al., 2009). In this context, the role of the STT as a predictor of long-term symptom severity, and as a mediator of effects of presenting attributes, DSM-IV diagnosis, and admission symptoms, highlight the value of early recognition of psychosis, and the nature and quality of subsequent treatment. This provides support for the critical period hypothesis, which proposes that interventions that shorten DUP, and, hopefully, arrest the "progressive deterioration" suggested in earlier conceptions of schizophrenia (Bleuler, 1950; Kraepelin, 1919) may have long-term benefits (Crumlish et al., 2009).

The role of the STT in predicting long-term symptomatic outcomes highlight the necessity for a continued focus on the delivery of well-designed, enhanced service delivery programmes to optimise recovery for young people experiencing their first psychotic episode, and to prevent long-term disability. The importance of developing targeted interventions to reduce negative symptoms has been emphasised by Ventura and colleagues (Ventura et al., 2015), however it has been acknowledged (Fusar-Poli et al., 2015; Savill et al., 2015) that to date, advances in the treatment of schizophrenia have provided only limited remediation for negative symptoms. A primary factor underlying the dearth of effective treatments for negative symptoms, is thought to be that their underlying pathophysiological and cognitive processes remain unknown. This contrasts with well-established models for positive symptoms, which underpin

the range of pharmacological and psychological treatments (Fusar-Poli et al., 2015). It has been pointed out that an in-depth understanding of the definition, course, and interaction of negative symptoms is necessary, by conducting further experimental and longitudinal studies (Tarrier, 2006).

Although the results of this study emphasise the longer term clinical implications of DUP, the design of the study does not allow a causal link with poor positive and negative symptom outcomes to be established. Therefore, it is not possible to make a definitive statement regarding the causality of effects of DUP on outcome. However, the potential significance of DUP as a malleable and prognostically important target is emphasised by the results. DUP consistently predicts outcome, and does not appear to be a proxy for the effects of other variables, as suggested by Verdoux et.al. (Verdoux, 2001; Verdoux et al., 1998; Verdoux et al., 2001). The models suggest that any gains from reducing DUP, assuming a causal relationship, are likely to occur relatively early in the course of psychosis. The window of opportunity for treatment to be sought and initiated appeared to differ for positive and negative symptoms. DUP levels of 90 days or less were indirectly linked with better long-term positive symptom levels, after which significant decline in positive symptoms occurred. For negative symptoms, there generally appeared to be more limited opportunity for intervention; 28 days or less for anhedonia, and 8-28 days for affective flattening, after which long-term symptom levels worsened. The exception was for avolition symptoms, with relatively long DUP levels of 1 year or less indirectly associated with more optimal long-term symptom levels. Coupled with evidence that the negative effects of DUP manifest early in this phase of illness, the merits of early intervention strategies would appear to be a "best bet" for optimising patient outcomes (Harrigan et al., 2003).

10.4 Limitations of the Study

The outcomes of this research need to be evaluated taking into consideration several methodological issues arising from the nature of the EPPIC study and dataset. These are presented as follows:

10.4.1 Retrospective assessment of duration of untreated psychosis

Firstly, by necessity, the research assessments were retrospective in nature. This is not an issue for some measures such as the BPRS and SANS, the time period under assessment of which respectively covers the two weeks and four weeks immediately prior to the interview. However, there is much potential for measurement error in DUP, not least because of the inevitable difficulties in accurately dating the onset of psychosis due to the retrospective nature of the ratings. Furthermore, the tipping point from the prodromal part of the illness to psychosis can be arbitrary, particularly for those more insidious onsets of psychosis. The more remote the tipping point, the more difficult it is for raters to accurately determine the onset. With some individuals experiencing extremely prolonged duration of untreated psychosis intervals, ratings are often only made possible by a considerable reduction in the precision of the estimate.

The EPPIC study minimised the measurement error in ascertaining DUP in several ways. Firstly, we used a standardised instrument, the RP-MIP which features meticulous measurement of DUP and prodromal phases of illness according to carefully operationalised criteria. Onset of psychosis was defined as the emergence of the first sustained psychotic symptom of any type at threshold level, and dated as precisely as possible to the nearest day, week or month (refer Section 4.5 in Method chapter). Secondly, information was obtained from multiple sources by interviewing patients and close relatives and then the accounts merged to produce an accurate record of the onset and duration of the illness. Thirdly, sample bias was minimised by using the full spectrum of functional psychotic disorders including affective psychosis. Furthermore, all psychotic individuals were included, even those with psychotic illnesses at a less acute level, hence individuals entering the service as outpatients were included, in addition to inpatients.

10.4.2 Disentangling primary and secondary negative symptoms

A second consideration to bear in mind is that part of the heterogeneity in negative symptoms is likely to be attributable to a range of factors, including neuroleptic side effects, unrelieved positive symptoms, depression, and hospitalisation (N. C. Andreasen et al., 1994; W. Carpenter, DW, & Alphs, 1985; Savill et al., 2015). These are

known as secondary negative symptoms, and are expressed in clinically similar ways to primary negative symptoms. Secondary negative symptoms, however, are fundamentally different from primary negative symptoms; the former are transient, and temporally related to these factors, whereas the latter are regarded as a core feature of schizophrenia (Möller, 2007). Like many psychosis research studies, the data in the current study were not collected with the intention of classification into primary and negative symptoms. The SANS measure used to assess negative symptoms is not designed to separate out secondary negative symptoms. It is therefore difficult to know to what extent the negative symptom severity scores across the five assessment points reflect primary or secondary negative symptoms. However, as Savill et.al. (Savill et al., 2015) point out, these difficulties are not new. Further research examining the longitudinal course of negative symptoms should include clearly defined criteria for discriminating primary and secondary symptoms in order to refine and confirm the findings in this thesis, and to clarify whether fluctuations in negative symptoms are best conceptualised as primary or secondary negative symptoms.

10.4.3 Structural data issues

Thirdly, there are a number of structural issues arising from the design of the EPPIC study that are inherent in the data. The assessment schedule was not designed with latent growth curve analysis, as undertaken in this thesis, in mind; rather the study data were originally intended to examine a different set of research questions to those currently under investigation. One of those original aims was to examine patterns of delay to treatment and its impact on short-term outcome up to 12 months after the initial psychotic episode had remitted or stabilised (P. D. McGorry et al., 1996). The timing of the assessment points at service admission (T1), initial recovery/symptom stabilisation (T2), 6-month follow-up (T3), and 12-month follow-up (T4), were framed around this broad objective. It was subsequently decided to add a fifth assessment point (T5), with participants followed up several years after their initial diagnosis and treatment. Whilst the aims of this thesis have facilitated additional and sophisticated analysis beyond that which the original investigators had planned, the study design and data generated by it presented specific challenges that required development and operationalization of a specific approach to growth curve modelling.

The scope of the latent growth curve analyses and depth of consequent insights gained in this thesis were somewhat curtailed by two features of the original study design; firstly, the limited number of assessments, and secondly, the timing of the second assessment (T2) at initial recovery or stabilisation. Regarding the first point, although the number of assessments was technically sufficient to perform latent growth curve analyses, there were too few assessment points across the study period to more flexibly model positive and negative symptomatology. For example, only three assessments were conducted across the 1-year short-term trajectory; remission (T2), six-month follow-up (T3), and 12-month follow-up (T4). The collection of additional waves of data between T1-T4 may have provided the opportunity to more accurately identify trajectories of change. This includes the possibility of fitting alternative curves to the data, which were not mathematically possible with only four time points. For example, the fitting of splines to capture the dramatic decrease in symptoms between T1 (service admission) and T2 (initial recovery/stabilisation), and the subsequent change thereafter, may have been an optimal model fitting approach, however this was simply not possible with only four waves of data.

Furthermore, additional assessments between the 12-month (T4) and long-term (T5) assessments would have permitted questions regarding long-term trajectories to be posed. Due to the distal nature of the T5 assessment relative to preceding time points, and the highly influential effect of the T5 data on the analyses given the distance from the T2-T4 scores, it was not possible to model long-term symptom trajectories to T5 in a way that accurately captured both short and long term change.

As for the timing of the second assessment (T2), whilst well-suited to the original study aims of investigating course and outcome following resolution of the initial psychotic episode, this held significant implications for the fitting of the T2-T4 growth curves. My research has focused on a time trajectory which is designed around the starting point being low, perhaps lower than usual. This weaves into the limitations and design issues of applying growth curve methodology to data that were not originally designed to be analysed in this way. In the case of positive symptoms, for instance, individuals initially presented with florid psychotic symptoms at T1, and were administered neuroleptic medication, which resulted in a dramatic decrease in symptom severity at T2. Thus, the research raters would wait for patients to get to a

certain point (symptom stabilisation, if not complete remission of symptoms) and then interview them when they were likely to be below average severity. Hence, any 'blip' in severity of symptoms at T3 is possibly an artefact of the low score at T2 assessment, a type of regression to the mean effect. This adds to the design issues which characterise this study, such as the matter of the timing of the T2 assessment being determined almost solely by how long it took patients to reach a certain point of wellness; if there was a 'perfect' treatment, the timing of T2 would simply be determined by the length of time taken for the treatment to produce a score of zero on the positive symptom and negative symptom measures. The timing of the T2 assessment, along with the highly influential effect of T5 on the analyses, given the distance of T5 from the T1-T4 assessments, is another example of the structural issues which hampered intentions to model the T1-T5 data using latent growth curve techniques.

10.4.4 Existence of possible 'floor' effect

Due to the necessity of starting the growth curve analyses on the second assessment, timed around the stabilisation or remission point of the young person's psychotic episode, the positive and negative symptom ratings were rated only as questionable to mild, hence there was a floor effect in operation where any downward change was limited by the fact that symptom decrease had already occurred in an earlier phase (service admission (T1) to initial recovery/stabilisation (T2)). Hence, the possibility of further change, except upward, was limited.

10.5 Future Research

The ability of researchers to think laterally is essential in advancing understanding of the evolution of positive and negative symptoms. Greater focus on the treatment of negative symptoms in psychotic disorders is overdue, in contrast to the range of relatively established treatments for positive symptoms. Detailed study of the development, course and interaction amongst negative symptoms is therefore necessary to develop an appreciation of the underlying pathophysiological and cognitive processes that might inform new treatment strategies. (Fusar-Poli et al., 2015). Well-designed longitudinal studies, with frequent assessment points, are emerging as the requisite basis for such investigations. To date, the majority of the all too few longitudinal research studies undertaken have included too few assessment

points, too widely separated in time to model these processes adequately. This applies even to those few studies with relatively frequent assessments (for instance, (Arndt et al., 1995; Austin et al., 2015; Marengo et al., 2000).

On the other hand, there exist rare studies that have the potential to support analytic investigations such as latent growth curve methods. For instance, studies undertaken by researchers such as Eaton et.al., and Ventura et.al., (Eaton et al., 1995; Ventura et al., 2004) were characterised by very frequent assessments, albeit of relatively modest sized samples. Eaton and colleagues collected monthly symptom data on 90 first-onset patients over the course of 10 years from first onset, whilst Ventura and colleagues assessed 48 recent-onset participants with the BPRS each fortnight for up to three years. Innovative analyses of such available data and addition studies of this kind are likely to hold the key to advancing knowledge about the aetiological processes underlying negative symptoms, and potentially lead to the development of effective treatments. Indeed, the model of research conducted by Ventura and colleagues, using very frequent assessments and smaller sample sizes, may be a be a viable alternative to designing and undertaking traditional follow-up studies with fewer assessments, and larger samples, the fruits of which are unlikely to be realised for many years, if not decades.

There is growing interest in employing experience sampling methodologies (ESM) in psychosis research. Experience sampling methods are designed to ascertain momentary ratings of experiences and cognitions of individuals multiple times each day, which makes them particularly useful for capturing dynamic psychological processes such as symptoms, moods, thoughts, and behaviours in everyday life. ESM relies on the collection of self-reports of these attributes from participants in real time, ideally using time-stamped electronic devices, to ensure that ratings are completed as per the times specified in the study design (Trull & Ebner-Priemer, 2009). This enables symptoms to be graphed along a temporal dimension. ESM is a repeated self-assessment technique, and is, by necessity, subjective, unlike interviewer-administered scales such as the BPRS and SANS. The use of these types of scales do not always accurately reflect patient behaviour in their usual environment (Möller, 2007), nor do they reflect the perspective of the individual.

Experience sampling is also known as ecological momentary assessment; "ecological", in the sense that processes are studied in participants' natural habitats. This is especially useful in psychosis research, since we are primarily interested in the individual's thoughts and symptoms in the context in which they occur, rather than as retrospective reports (either self-report, or by clinical interview) that are subject to recall bias. This may be particularly important in psychosis research, because of the possibility of decreased cognitive capacities in patients with psychotic disorders (Oorschot, Kwapil, Delespaul, & Myin-Germeys, 2009; Reichenberg & Harvey, 2007) which may hamper their ability to provide accurate retrospective accounts. ESM has been demonstrated as useful in the study the phenomenology of symptomatology in psychosis in the flow of daily life. It can be applied not only to psychotic phenomena, but also to negative symptoms It can be regarded as "…a powerful rationale for investigating experiences of symptoms in the context in which they are occurring…" (Oorschot et al., 2009), since the essence of psychotic experiences can be found in the interaction between the individual and their environment. Furthermore, the application of ESM in psychiatric populations has been demonstrated to be feasible, reliable, and valid (DeVries, 1992), despite the disquiet of those who question whether individuals with psychosis have sufficient insight for self-report methods to work. Experience sampling may hold the key to questions about fluctuations in negative symptoms over time, their impact on daily functioning, and their contextual basis. It may lead to an increased understanding about the phenomenology of symptoms and their underlying processes, which may assist in the development of new treatment strategies.

10.6 Conclusion

This thesis modelled the short-term trajectories (STT) of positive and negative symptoms of 413 young people over the 12-month interval following recovery from their initial psychotic episode, to better understand the mechanisms underlying course of recovery, and its role in prediction of long-term symptom levels at 7.3 year follow-up. The change in mean positive symptoms conformed optimally to a non-linear trajectory, whilst changes in affective flattening, alogia, avolition, and anhedonia, were linear. Individuals varied significantly in their starting values at the beginning of the trajectory on the four negative symptom subscales, and positive symptoms, and in

their rates of change over the short-term trajectory on alogia, avolition and anhedonia. The only symptoms which exhibited statistically significant change over the one-year trajectory were positive symptoms and affective flattening.

The most notable finding of the thesis was the pivotal role played by the short-term trajectories in predicting long-term symptoms levels, independently of the effects of DUP, premorbid functioning, gender, age at onset of psychosis, admission symptom levels, and baseline DSM-IV diagnosis. The association between the STTs and long-term negative symptoms, in particular, was striking. Higher initial trajectory levels, and increasing change over the 1-year interval subsequent to initial recovery, predicted worse symptomatic outcomes. This finding implies that what occurs after admission to the service is critical to how a young person's symptoms continue to evolve, and suggests that the STT may be a sentinel for long-term negative symptoms. The importance of the STT is underlined, particularly when taken in conjunction with its role as a causal pathway for the effects of DUP, premorbid functioning, age at onset of psychosis, and baseline DSM-IV diagnosis, on long-term symptomatic outcome.

Longitudinal investigations of the course of psychosis are essential in understanding the evolution of the illness, and to the development of effective, well-timed interventions designed to optimise treatment outcomes. It is fundamentally important that such studies include representative, homogenous samples at a similar stage of illness, and that they are inclusive of the full-spectrum of functional psychotic disorders, so that the full dimensions of the unfolding symptomatology can be examined. Studies such as these provide the key to identifying change in psychopathology, particularly negative symptoms, where there is an unmet therapeutic need for many individuals experiencing psychotic illness. The potential to develop novel treatments designed to modify trajectories of change in negative symptoms, and improve long-term prognosis, hinges on the ability to understand the pathophysiological and cognitive processes underpinning negative symptoms. The conduct of well-designed longitudinal studies to investigate negative symptom development and underlying processes is crucial in identifying novel treatments to address the debilitating burden of negative symptoms in psychosis.

REFERENCES

Addington, J., & Addington, D. (1991). Positive and negative symptoms of schizophrenia: Their course and relationship over time. *Schizophrenia Research, 5*, 51-59.

Addington, J., & Addington, D. P. (2005). Patterns of premorbid functioning in first episode psychosis: relationship to 2-year outcome. *Acta Psychiatrica Scandinavica, 112*, 40-46.

Addington, J., Van Mastrigt, S., & Addington, D. (2004). Duration of untreated psychosis: impact on 2-year outcome. *Psychological Medicine, 34*(2), 277-284.

Aiken, L. S., & West, S. G. (1991). *Multiple regression: Testing and interpreting interactions*. Newbury Park, CA: Sage.

Andreasen, N. (1983). Schedule for the Assessment of Negative Symptoms. Iowa City: University of Iowa.

Andreasen, N. C., Carpenter, W. T., Jr., Kane, J. M., Lasser, R. A., Marder, S. R., & Weinberger, D. R. (2005). Remission in schizophrenia: proposed criteria and rationale for consensus. *American Journal of Psychiatry, 162*(3), 441.

Andreasen, N. C., Nopoulos, P., Schultz, S., Miller, D., Gupta, D., Swayze, V., & Flaum, M. (1994). Positive and negative symptoms of schizophrenia: past, present, and future. *Acta Psychiatrica Scandinavica, 90*(suppl. 384), 51-59.

Arndt, S., Andreasen, N. C., Flaum, M., Miller, D., & Nopoulos, P. (1995). A longitudinal study of symptom dimensions in schizophrenia. *Archives of General Psychiatry, 52*(5), 352-363.

Association, A. P. (1987). *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised.* Washington, D.C.: American Psychiatric Association.

Association, A. P. (1994). *Diagnostic and Statistical Manual for Mental Disorders, 4th edition* Washington, D.C.: American Psychiatric Association.

Austin, S. F., Mors, O., Budtz-Jørgensen, E., Secher, R. G., Hjorthøj, C. R., Bertelsen, M., . . . Nordentoft, M. (2015). Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10 year follow-up study in the OPUS cohort. *Schizophrenia Research, 168*, 84-91.

Barnes, T. R., Hutton, S. B., Chapman, M. J., Mutsatsa, S., Puri, B. K., & Joyce, E. M. (2000). West London first-episode study of schizophrenia: Clinical correlates of duration of untreated psychosis. *British Journal of Psychiatry, 177*, 207-211.

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*, 1173-1182.

Beiser, M., Erickson, D., Fleming, J. A. E., & Iacono, W. G. (1993). Establishing the onset of psychotic illness. *American Journal of Psychiatry, 150*(9), 1349-1354.

Birchwood, M., Todd, P., & Jackson, C. (1998). Early intervention in psychosis: The critical period hypothesis. *British Journal of Psychiatry, 172*(supp. 33), 53-57.

Bleuler, E. (1950). *Dementia Praecox or the Group of Schizophrenias*. New York: International Universities Press.

Bollen, K. A., & Curran, P. J. (2006). *Latent Growth Curve Models: A structural equation perspective*. Hoboken, New Jersey: John Wiley & Sons, Inc.

Bottlender, R., Sata, T., Jager, M., Wegener, U., Wittmann, J., Straub, A., & Moller, H.-J. (2003). The impact of the duration of untreated psychosis prior to first psychiatric admission on the 15-year outcome in schizophrenia. *Schizophrenia Research, 62*, 37-44.

Bottlender, R., Straub, A., & Moller, H. (2000). Impact of duration of symptoms prior to first hospitalization on acute outcome in 998 schizophrenic patients. *Schizophrenia Research, 44*, 145-150.

Browne, S., Clarke, M., Gervin, M., Waddington, J. L., Larkin, C., & O'Callaghan, E. (2000). Determinants of quality of life at first presentation with schizophrenia. *British Journal of Psychiatry, 176*, 173-176.

Cannon-Spoor, H. E., Potkin, S. G., & Wyatt, R. J. (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia Bulletin, 8*(3), 470-484.

Carbone, S., Harrigan, S., McGorry, P. D., Curry, C., & Elkins, K. (1999). Duration of untreated psychosis and 12-month outcome in first-episode psychosis: the impact of treatment approach. *Acta Psychiatrica Scandinavica, 100*, 96-104.

Carpenter, W., DW, H., & Alphs, L. (1985). Treatment of negative symptoms. *Schizophrenia Bulletin, 11*, 440-452.

Carpenter, W. T., & Strauss, G. P. (1991). The prediction of outcome in schizophrenia IV: Eleven-year follow-up of the Washington IPSS cohort. *Journal of Nervous and Mental Disease, 179*(9), 517-525.

Chang, W. C., Hui, C. L. M., Tang, J. Y. M., Wong, G. H. Y., & Lam, M. M. L. (2011). Persistent negative symptoms in first-episode schizophrenia: A prospective three-year follow-up study. *Schizophrenia Research, 133*, 22-28.

Chong, S., Mythily., Lum, A., Chan, Y. H., & McGorry, P. (2005). Determinants of duration of untreated psychosis and the pathway to care in Singapore. *International Journal of Social Psychiatry, 51*(1), 55-62.

Craig, T. J., Bromet, E. J., Fennig, S., Tanenberg-Karant, M., Lavelle, J., & Galambos, N. (2000). Is there an association between duration of untreated psychosis and 24-month clinical outcome in a first-admission series? *The American journal of psychiatry, 157*(1), 60-66.

Crumlish, N., Whitty, P., Clarke, M., Browne, S., Kamali, M., Gervin, M., . . . O'Callaghan, E. (2009). Beyond the critical period: longitudinal study of 8-year outcome in first-episode non-affective psychosis. *British Journal of Psychiatry, 194*, 18-24.

Curran, P. J., & Hussong, A. M. (2003). The use of latent trajectory models in psychopathology research. *Journal of Abnormal Psychology, 112*(4), 526-544.

Curran, P. J., Obeidat, K., & Losardo, D. (2010). Twelve Frequently Asked Questions About Growth Curve Modeling. *Journal of Cognitive Development, 11*(2), 121-136.

de Haan, L., Linszen, D. H., Lenior, M. E., de Win, E. D., & Gorsira, R. (2003). Duration of untreated psychosis and outcome of schizophrenia: Delay in intensive psychosocial treatment versus delay in treatment with antipsychotic medication. *Schizophrenia Bulletin, 29*(2), 341-348.

DeVries, M. W. (1992). *The experience of psychopathology: investigating mental disorders in their natural settings.*

. Cambridge: Cambridge University Press.

Dollfus, S., & Petit, M. (1995). Stability of positive and negative symptoms in schizophrenic patients: a 3-year follow-up study. *European Psychiatry, 10*, 228-236.

Drake, R. J., Haley, C. J., Akhtar, S., & Lewis, S. W. (2000). Causes and consequences of duration of untreated psychosis in schizophrenia. *British Journal of Psychiatry, 177*, 511-515.

Eaton, W., Thara, R., Federman, B., Melton, B., & Liang, K. (1995). Structure and course of positive and negative symptoms in schizophrenia. *Archives of General Psychiatry, 52*(2), 127-134.

Eaton, W., Thara, R., Federman, B., & Tien, A. (1998). Remission and relapse in schizphrenia: the Madras longitudinal study. *The Journal of Nervous and Mental Disease, 186*(6), 357-363.

Efron, B., & Tibshirani, R. J. (1993). *An introduction to the bootstrap*. New York: Chapman& Hall.

Evensen, J., Rossberg, J. I., Barder, H., Haahr, U., ten Velden Hegelstad, W., Joa, I., . . . Friis, S. (2012). Flat affect and social functioning: A 10 year follow-up study of first episode psychosis patients. *Schizophrenia Research, 139*, 99-104.

Fenton, W. S., & McGlashan, T. H. (1991). Natural history of schizophrenia subtypes. *Archives of General Psychiatry, 48*, 978-986.

Fleiss J., L. (1986). *The design and analysis of clinical experiments*: Wiley.

Foussias, G., & Remington, G. (2010). Negative Symptoms in Schizophrenia: Avolition and Occam's Razor. *Schizophrenia Bulletin, 36*(2).

Friis, S., Melle, I., Larsen, T. K., Haahr, U., Johannessen, J. O., Simonsen, E., . . . T.H., M. (2004). Does duration of untreated psychosis bias study samples of first-episode psychosis? *Acta Psychiatrica Scandinavica, 110*, 286-291.

Fusar-Poli, P., Cappucciati, M., Rutigliano, G., Heslin, M., Stahl, S., Brittenden, Z., . . . Carpenter, W. T. (2016). Diagnostic Stability of ICD/DSM First Episode Psychosis Diagnoses: Meta-analysis. *Schizophrenia Bulletin, 42*(6), 1395-1406.

Fusar-Poli, P., Papanastasiou, E., Stahl, D., Rocchetti, M., Carpenter, W., Shergill, S., & McGuire, P. (2015). Treatments of negative symptoms in schizophrenia: Meta-analysis of 168 randomized placebo-controlled trials. *Schizophrenia Bulletin, 41*(4), 892.

Galderisi, S., Mucci, A., Bitter, I., Libiger, J., Bucci, P., Fleischhacker, W., . . . Group., E. S. (2013). Persistent negative symptoms in first episode patients with schizophrenia:Results from the European First Episode SchizophreniaTrial. *European Neuropsychopharmacology, 23*, 196-204.

Gibbons, R. D., Hedeker, D., Elkin, I., Waternaux, C., Kraemer, H. C., Greenhouse, J. B., . . . Watkins, J. T. (1993). Some conceptual and statistical issues in analysis of longitudinal psychiatric data. *Archives of General Psychiatry, 50*, 739-750.

Grube, B. S., Bilder, R. M., & Goldman, R. S. (1998). Meta-analysis of symptom factors in schizophrenia. *Schizophrenia Research, 31*(2-3), 113-120.

Haas, G., Garratt, L., & Sweeney, J. (1998). Delay to antipsychotic medication in schizophrenia: impact on symptomatology and clinical course of illness. *Journal of Psychiatric Research, 32*, 151-159.

Haddock, G., Barrowclough, C., Tarrier, N., Moring, J., O'Brien, R., Schofield, N., . . . Lewis, S. (2003). Cognitive-behavioural therapy and motivational intervention for schizophrenia and substance use: 18 month outcomes of a randomised controlled trial. *British Journal of Psychiatry, 183*, 418-426.

Hafner, H., Maurer, K., Loffler, W., & Riecher-Rossler, A. (1993). The influence of age and sex on the onset and early course of schizophrenia. *British Journal of Psychiatry, 162*, 80-86.

Harrigan, S. M., McGorry, P. D., & Krstev, H. (2003). Does treatment delay in first-episode psychosis really matter? *Psychological Medicine., 33*(1), 97-110.

Harris, M., Henry, L., Harrigan, S., Purcell, R., Schwartz, O., Farrelly, S., . . . McGorry, P. (2005). The relationship between duration of untreated psychosis and outcome: An eight-year prospective study. *Schizophrenia Research, 79*(1), 85-93.

Harrison, G., Hopper, K., Craig, T., Laska, E., Siegel, C., Wanderling, J., . . . Wiersma, D. (2001). Recovery from psychotic illness: a 15- and 25-year international followup study. *British Journal of Psychiatry, 178*, 506-517.

Helgason, L. (1990). Twenty years' followup of first-presentation for schizophrenia: What could have been prevented? *Acta Psychiatrica Scandinavica, 81*, 231-235.

Henry, L. P., Harris, M. G., Amminger, G. P., Yuen, H. P., Harrigan, S. M., Lambert, M., . . . McGorry, P. D. (2007). Early Psychosis Prevention and Intervention Centre long-term follow-up study of first-episode psychosis: methodology and baseline characteristics. *Early Intervention in Psychiatry, 2007*(1), 49-60.

Herbener, E. S., & Harrow, M. (2001). Longitudinal assessment of negative symptoms in schizophrenia/schizoaffective patients, other psychotic patients, and depressed patients. *Schizophrenia Bulletin, 27*(3), 527-537.

Ho, B., & Andreasen, N. (2001). Long delays in seeking treatment for schizophrenia. *The Lancet, 357*, 898-900.

Ho, B. C., Andreasen, N. C., Flaum, M., Nopoulos, P., & Miller, D. (2000). Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *The American journal of psychiatry, 157*(5), 808-815. doi:10.1176/appi.ajp.157.5.808

Hoyle, R. H., & Kenny, D. A. (1999). Statistical power and tests of mediation. In R. H. Hoyle (Ed.), *Statisitical strategies for small sample research* (pp. 195-222). Newbury Park: Sage.

Johnstone, E., Macmillan, J., Frith, C., Benn, D., & Crow, T. (1990). Further investigation of the predictors of outcome following first schizophrenic episodes. *British Journal of Psychiatry, 157*, 182-189.

Joreskog, K. G., & Sorbom, D. (1993). LISREL (Version 8.12). Chicago: Science Software International.

Judd, C. M., & Kenny, D. A. (1981a). *Estimating the effects of social interventions*. Cambridge, U.K.: Cambridge University Press.

Judd, C. M., & Kenny, D. A. (1981b). Process analysis: estimating mediation in treatment evaluations. *Evaluation Review, 5*, 602-619.

Kelley, M. E., Haas, G. L., & van Kammen, D. P. (2008). Longitudinal progression of negative symptoms in schizophrenia: A new look at an old problem. *Schizophrenia Research, 105*, 188-196.

Kelley, M. E., van Kammen, D. P., & Allen, D. N. (1999). Empirical validation of primary negative symptoms: independence from effects of medication and psychosis. *American Journal of Psychiatry, 156*(3), 406-411.

Kenny, D. A. (2009). http://davidakenny.net/cm/mediate.htm#WIM.

Keshavan, M. S., & Schooler, N. R. (1992). First-episode studies in schizophrenia: criteria and characterization. *Schizophrenia Bulletin, 18*(3), 491-513.

Kraepelin, E. (1919). *Dementia praecox and paraphrenia* (R. M. Barclay, Trans.). Edinburgh: E. & S. Livingstone.

Krantz, D. H. (1999). The null hypothesis testing controversy in psychology. *Journal of the American Statistical Association, 44*, 1372-1381.

Larsen, T., McGlashan, T., Johannessen, J., & Vibe-Hanson, L. (1996). First-episode schizophrenia: II. Premorbid patterns by gender. *Schizophrenia Bulletin, 22*(2), 257-269.

Larsen, T. K., Moe, L. C., Vibe-Hansen, L., & Johannessen, J. O. (2000). Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first-episode psychosis. *Schizophrenia Research, 45*(1-2), 1-9.

Lenzenweger, M. F., Johnson, M. D., & Willett, J. B. (2004). Individual growth curve analysis illuminates stability and change in personality disorder features. *Archives of General Psychiatry, 61*.

Loebel, A. D., Lieberman, J. A., Alvir, J. M., Mayerhoff, D. I., Geisler, S. H., & Szymanski, S. R. (1992). Duration of psychosis and outcome in first-episode schizophrenia. *The American journal of psychiatry, 149*(9), 1183-1188.

Lukoff, D., Nuechterlein, K. H., & Ventura, J. (1986). Manual for the Expanded Brief Psychiatric Rating Scale. *Schizophrenia Bulletin, 12*, 578-602.

MacCallum, R. C., Roznowski, M., & Necowitz, L. B. (1992). Model Modifications in Covariance Structure Analysis: The Problem of Capitalization on Chance. *Psychological Bulletin, 111*(3), 490-504.

MacKinnon, D. P. (2004). Mediating variable. In N. J. Smelser & P. B. Baltes (Eds.), *International Encyclopedia of the Social and Behavioral Sciences* (pp. 9503-9507). Oxford, England: Pergamon.

MacKinnon, D. P. (2008). *Introduction to statistical mediation analysis*. New York: Erlbaum.

MacKinnon, D. P., & Dwyer, J. H. (1993). Estimating mediated effects in prevention studies. *Evaluation Review, 17*, 144-158.

MacKinnon, D. P., Fairchild, A., J., & Fritz, M. S. (2007). Mediation analysis. *Annual Review of Psychology, 58*, 593-614.

MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G., & Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods, 7*, 81-104.

MacKinnon, D. P., Lockwood, C. M., & Williams, J. (2004). Confidence limits for the indirect effect: Distribution of the product and resampling methods. *Multivariate Behavioral Research, 39*(1), 99-128.

MacKinnon, D. P., Warsi, G., & Dwyer, J. H. (1995). A simulation study of mediated effect measures. *Multivariate Behavioral Research, 30*, 41-62.

Malla, A. K., Norman, R. M. G., Manchanda, R., Ahmed, M. R., Scholten, D., Harricharan, R., . . . Takhar, J. (2002). One year outcome in first-episode psychosis: influence of DUP and other predictors. *Schizophrenia Research, 54*, 231-242.

Marengo, J., Harrow, M., Herbener, E. S., & Sands, J. (2000). A prospective longitudinal 10-year study of schizophrenia's three major factors and depression. *Psychiatry Research, 97*, 61-77.

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of General Psychiatry, 62*(9), 975-983.

Maurer, K., & Hafner, H. (1995). Methodological aspects of onset assessment in schizophrenia. *Schizophrenia Research, 15*, 265-276.

McArdle, J. J. (1988). Dynamic but structural equation modeling of repeated measures data. In J. R. Nesselroade & R. B. Cattell (Eds.), *The Handbook of Multivariate Experimental Psychology* (2nd ed. ed.). New York: Plenum Press.

McDonald, R. P. (1997). Haldane's lungs: a case study in path analysis. *Multivariate Behavioral Research, 32*, 1-38.

McGlashan, T. (1999). Duration of untreated psychosis in first-episode schizophrenia: Marker or determinant of course? *Biological Psychiatry, 46*, 899-907.

McGlashan, T. H., & Fenton, W. S. (1992). The positive negative distinction in schizophrenia: Review of natural history validators. *Archives of General Psychiatry, 49*, 63-72.

McGorry, P., Krstev, H., & Harrigan, S. (2000). Early detection and treatment delay: implications for outcome in early psychosis. *Current Opinion in Psychiatry, 13*, 37-43.

McGorry, P. D. (2006, 18 June, 2006).

McGorry, P. D., Bell, R. C., Dudgeon, P. L., & Jackson, H. J. (1998). The dimensional structure of first episode psychosis: an exploratory factor analysis. *Psychological Medicine., 28*(4), 935-947.

McGorry, P. D., Copolov, D., & Singh, B. (1990). Royal Park Multidiagnostic Instrument for Psychosis: Part 1. Rationale and review. *Schizophrenia Bulletin, 16*, 501-515.

McGorry, P. D., Edwards, J., Mlhalopoulos, C., Harrlgan, S. M., & Jackson, H. J. (1996). EPPIC: An evolving system of early detection and optimal management. *Schizophrenia Bulletin, 22*(2), 305-326.

McGorry, P. D., Goodwin, R., & Stuart, G. (1988). The development, use and reliability of the Brief Psychiatric Rating Scale (Nursing modification) - An assessment procedure for the nursing team in clinical and research settings. *Comprehensive Psychiatry, 29*(6), 575-587.

McGorry, P. D., Singh, B. S., Copolov, D. L., Kaplan, I., Dossetor, C. R., & van Riel, R. J. (1990). The Royal Park Multidiagnostic Instrument for Psychosis: Part II. Development, reliability and validity. *Schizophria Bulletin, 16*(3), 517-536.

Melle, I., Larsen, T. K., Haahr, U., Friis, S., Johannessen, J. O., Opjordsmoen, S., . . . McGlashan, T. (2004). Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. *Archives of General Psychiatry, 61*(2), 143-150.

Menezes, N. M., Arenovich, T., & Zipursky, R. B. (2006). A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychological Medicine, 36*, 1349-1362

Meredith, W., & Tisak, J. (1984). *On "Tuckerizing" curves*. Paper presented at the Annual meeting of the Psychometric Society, Santa Barbara, California.

Meredith, W., & Tisak, J. (1990). Latent curve analysis. *Psychometrika, 55*(1), 107-122.

Merrill, R. (1994). *Treatment effect evaluation in nonadditive mediation models.* Tempe: Arizona State University.

Möller, H. J. (2007). Clinical evaluation of negative symptoms in schizophrenia. *European Psychiatry, 22*, 380-386.

Mueser, K. T., Douglas, M. S., Bellack, A. S., & Morrison, R. L. (1991). Assessment of enduring deficit and negative symptom subtypes in schizophrenia. *Schizophrenia Bulletin, 17*(4), 565-582.

Muthén, B., Khoo, S. T., Francis, D. J., & Boscardin, C. K. (2003). Analysis of reading skills development from Kindergarten through first grade: An application of growth mixture modeling to sequential processes. In S. R. Reise & N. Duan (Eds.), *Multilevel Modeling: Methodological Advances, Issues, and Applications* (pp. 71-89). Mahaw, NJ: Lawrence Erlbaum Associates.

Muthén, L. K., & Muthén, B. O. (1998-2011). Mplus User's Guide Los Angeles, CA: Muthén & Muthén.

Neuchterlein, K. H., Miklowitz, D. J., Ventura, J., Gitlin, M. J., Stoddard, M., & Lukoff, D. (2006). Classifying episodes in schizophrenia and bipolar disorder: Criteria for relapse and remission applied to recent-onset samples. *Psychiatry Research, 144*, 153-166.

Norman, R., & Malla, A. (2001). Duration of untreated psychosis: a critical examination of the concept and its importance. *Psychological Medicine, 31*(3), 381-400.

Norman, R. M., Townsend, L., & Malla, A. K. (2001). Duration of untreated psychosis and cognitive functioning in first-episode patients. *British Journal of Psychiatry, 179*, 340-345.

Oorschot, M., Kwapil, T., Delespaul, P., & Myin-Germeys, I. (2009). Momentary assessment research in psychosis. *Psychological Assessment, 21*(4), 498-505.

Overall, J. E., & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports, 10*, 799-812.

Peer, J. E., & Spaulding, W. D. (2007). Heterogeneity in recovery of psychosocial functioning during psychiatric rehabilitation: an exploratory study using latent growth mixture modeling. *Schizophrenia Research, 93*(1-3), 186-193. doi:10.1016/j.schres.2007.03.002

Perkins, D. O., Gu, H., Boteva, K., & Lieberman, J. A. (2005). Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *American Journal of Psychiatry, 162*(10), 1785-1804.

Pogue-Geile, M. F., & Harrow, M. (1985). Negative symptoms in schizophrenia: Their longitudinal course and prognostic importance. *Schizophrenia Bulletin, 11*(3), 427-439.

Quinlan, D. M., Schuldberg, D., Morgenstern, H., & Glazer, W. (1995). Positive and negative symptom course in chronic community-based patients: A two-year prospective study. *British Journal of Psychiatry, 166*, 634-641.

Reichenberg, A., & Harvey, P. D. (2007). Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychological Bulletin, 133*(5), 833-858.

Robinson, D., Woerner, M. G., Alvir, J. M., Bilder, R., Goldman, R., Geisler, S., . . . Lieberman, J. A. (1999). Predictors of relapse following response from a first-episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry, 56*(3), 241-247.

Robinson, D. G., Woerner, M. G., Alvir, J. M., Geisler, S., Koreen, A., Sheitman, B., . . . Lieberman, J. A. (1999). Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *American Journal of Psychiatry, 156*(4), 544-549.

Salthouse, T. A. (1984). Effects of age and skill in typing. *Journal of Experimental Psychology, 113*, 345-371.

Satorra, A. (2000). Scaled and adjusted restricted tests in multi-sample analysis of moment structures. In R. D. H. Heijmans, D. S. G. Pollock, & A. Satorra (Eds.), *Innovations in multivariate statistical analysis. A Festschrift for Heinz Neudecker.* (pp. 233-247). London: Kluwer Academic Publishers.

Satorra, A., & Bentler, P. A. (1999). *A scaled difference Chi-square test statistic for moment structure analysis*. UCLA Statistics Series. Department of Statistics. University of California (UCLA).

Savill, M., Banks, C., Khanom, H., & Priebe, S. (2015). Do negative symtoms of schizophrenia change over time? A meta-analysis of longitudinal data. *Psychological Medicine, 45*, 1613-1627.

Schafer, J. L., & Graham, J. W. (2002). Missing data: our view of the state of the art. *Psychological Methods, 7*(2), 147-177.

Scully, P., Coakley, G., Kinsella, A., & Waddington, J. (1997). Psychopathology, executive (frontal) and general cognitive impairment in relation to duration of initially untreated versus subsequently treated psychosis in chronic schizophrenia. *Psychological Medicine, 27*, 1303-1310.

Shrout, P. E., & Bolger, N. (2002). Mediation in experimental and nonexperimental studies: new procedures and recommendations. *Psychological Methods, 7*, 422-445.

Singh, S. P., Cooper, J. E., Fisher, H. L., Tarrant, J., Lloyd, T., Banjo, J., . . . Jones, P. (2005). Determining the chronology and components of psychosis onset: The Nottingham Onset Schedule (NOS). *Schizophrenia Research, 80*, 117-130.

Sobel, M. E. (1982). Asymptotic confidence intervalss for indirect effects in structural equation models. In S. Leinhardt (Ed.), *Sociological methodology*. Washington D.C.: American Sociological Association.

Stone, C. A., & Sobel, M. E. (1990). The robustness of estimates of total indirect effects in covariance structure models estimated by maximum likelihood. *Psychometrika, 55*, 337-352.

Tarrier, N. (2006). Negative Symptoms in Schizophrenia: Comments From a Clinical Psychology Perspective. *Schizophrenia Bulletin, 32*(2), 231-233.

Tarrier, N., Kinney, C., McCarthy, E., Humphreys, L., Wittkowski, A., & Morris, J. (2000). Two-year follow-up of cognitive--behavioral therapy and supportive counseling in the treatment of persistent symptoms in chronic schizophrenia. *Journal of Consulting and Clinical Psychology, 68*(5), 917-922.

Tein, J. Y., Sandler, I. N., MacKinnon, D. P., & Wolchik, S. A. (2004). How did it work? Who did it work for? Mediation in the context of a moderated prevention effect for children of divorce. *Journal of Consulting and Clinical Psychology, 72*, 617-624.

Thara, R., & Eaton, W. (1996). Outcome of schizophrenia: the Madras longitudinal study. *Australian & New Zealand Journal of Psychiatry, 30*(4), 516-522.

Thara, R., Henrietta, M., Joseph, A., Rajkumar, S., & Eaton, W. (1994). Ten-year course of schizophrenia - the Madras longitudinal study. *Acta Psychiatrica Scandinavica, 90*, 329-336.

Trull, T. J., & Ebner-Priemer, U. W. (2009). Using experience sampling methods/ecological momentary assessment (ESM/EMA) in clinical assessment

and clinical research: Introduction to the special section. *Psychological Assessment, 21*(4), 457-462.

Tschacher, W., Scheier, C., & Hashimoto, Y. (1997). Dynamical analysis of schizophrenia courses. *Biological Psychiatry, 41*, 428-437.

Ucok, A., Polat, A., Genc, A., Cakir, S., & Turan, N. (2004). Duration of untreated psychosis may predict acute treatment response in first-episode schizophrenia. *Journal of Psychiatric Research, 38*, 163-168.

Ventura, J., Nuechterlein, K. H., Green, M. F., Horan, W. P., Subotnik, K. L., & Mintz, J. (2004). The timing of negative symptom exacerbations in relationship to positive symptom exacerbations in the early course of schizophrenia. *Schizophrenia Research, 69*, 333-342.

Ventura, J., Subotnik, K. L., Gitlin, M. J., Gretchen-Doorly, D., Ered, A., Villa, K. F., . . . Neuchterlein, K. H. (2015). Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. *Schizophrenia Research, 161*, 407-413.

Verdoux, H. (2001). Have the times come for early intervention in psychosis? . *Acta Psychiatrica Scandinavica, 103*, 321-322.

Verdoux, H., Bergey, C., Assens, F., Abalan, F., Gonzales, B., Pauillac, P., . . . van Os, J. (1998). Prediction of duration of psychosis before first admission. *European Psychiatry, 13*, 346-352.

Verdoux, H., Liraud, F., Bergey, C., Assens, F., Abalan, F., & van Os, J. (2001). Is the association between duration of untreated psychosis and outcome confounded? A two year follow-up study of first-admitted patients. *Schizophrenia Research, 49*, 231-241.

Wiersma, D., Nienhuis, F. J., Giel, R., & Slooff, C. J. (1998). Stability and change in needs of patients with schizophrenic disorders: a 15- and 17-year follow-up from first onset of psychosis, and a comparison between 'objective' and 'subjective' assessments of needs for care. *Social Psychiatry and Psychiatric Epidemiology, 33*(2), 49-56.

Wunderink, A., Nienhuis, F. J., Sytema, S., & Wiersma, D. (2006). Treatment delay and response rate in first episode psychosis. *Acta Psychiatrica Scandinavica, 113*, 332-339.

Wyatt, R. (1991). Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin, 17*, 325-351.

APPENDICES

Appendix I: BRIEF PSYCHIATRIC RATING SCALE (Version 4.0)

N/A Not assessed	1 Not Present	2 Very Mild	3 Mild	4 Moderate	5 Moderately severe	6 Severe	7 Extremely severe

Rate items 1-14 on the basis of patient's self report during interview. Mark "N/A" for symptoms not assessed. Note items 7, 12, and 13 are also rated on observed behaviour during the interview. PROVIDE EXAMPLES.

1.	Somatic concern	N/A	1	2	3	4	5	6	7
2.	Anxiety	N/A	1	2	3	4	5	6	7
3.	Depression	N/A	1	2	3	4	5	6	7
4.	Suicidality	N/A	1	2	3	4	5	6	7
5.	Guilt	N/A	1	2	3	4	5	6	7
6.	Hostility	N/A	1	2	3	4	5	6	7
7.	Elevated mood	N/A	1	2	3	4	5	6	7
8.	Grandiosity	N/A	1	2	3	4	5	6	7
9.	Suspiciousness	N/A	1	2	3	4	5	6	7
10.	Hallucinations	N/A	1	2	3	4	5	6	7
11.	Unusual Thought Content	N/A	1	2	3	4	5	6	7
12.	Bizarre Behaviour	N/A	1	2	3	4	5	6	7
13.	Self-neglect	N/A	1	2	3	4	5	6	7
14.	Disorientation	N/A	1	2	3	4	5	6	7

Rate items 15-24 on the basis of observed behaviour or speech of the patient during the interview.

15.	Conceptual Disorganization	N/A	1	2	3	4	5	6	7
16.	Blunted affect	N/A	1	2	3	4	5	6	7
17.	Emotional withdrawal	N/A	1	2	3	4	5	6	7
18.	Motor Retardation	N/A	1	2	3	4	5	6	7
19.	Tension	N/A	1	2	3	4	5	6	7
20.	Unco-operativeness	N/A	1	2	3	4	5	6	7
21.	Excitement	N/A	1	2	3	4	5	6	7
22.	Distractibility	N/A	1	2	3	4	5	6	7
23.	Motor Hyperactivity	N/A	1	2	3	4	5	6	7
24.	Mannerisms and Posturing	N/A	1	2	3	4	5	6	7

Appendix II: SCALE FOR THE ASSESSMENT OF NEGATIVE SYMPTOMS (SANS)

0 = None 1= Questionable; 2 = Mild; 3 = Moderate; 4 = Marked 5 = Severe

AFFECTIVE FLATTENING OR BLUNTING

1.	Unchanging Facial Expression The patient's face appears wooden, changes less than expected as emotional content of discourse changes.	0	1	2	3	4	5
2.	Decreased Spontaneous Movements The patient shows few or no spontaneous movements, does not shift position, move extremities, etc.	0	1	2	3	4	5
3.	Paucity of Expressive Gestures The patient does not use hand gestures, body position etc, as an aid in expressing his ideas.	0	1	2	3	4	5
4.	Poor Eye Contact The patient avoids eye contact or "stares through" interviewer even when speaking.	0	1	2	3	4	5
5.	Affective Nonresponsivity The patient fails to smile or to laugh when prompted.	0	1	2	3	4	5
6.	Inappropriate Affect The patient's affect is inappropriate or incongruous, not simply flat or blunted.	0	1	2	3	4	5
7.	Lack of Vocal Inflections The patient fails to show normal vocal emphasis patterns, is often monotonic.	0	1	2	3	4	5
8.	**Global Rating of Affective Flattening** This rating should focus on overall severity of symptoms, especially unresponsiveness, eye contact, facial expression, and vocal inflections.	**0**	**1**	**2**	**3**	**4**	**5**

ALOGIA

9.	Poverty of Speech The patient's replies to questions are restricted in amount, tend to be brief, concrete and unelaborated.	0	1	2	3	4	5
10	Poverty of Content of Speech The patient's replies are adequate in amount but tend to be vague, overconcrete, or overgeneralised, and convey little information.	0	1	2	3	4	5
11	Blocking The patient indicates, either spontaneously or with prompting, that his train of thought was interrupted.	0	1	2	3	4	5
12	Increased Latency of Response The patient takes a long time to reply to questions; prompting indicates the patient is aware of the question.	0	1	2	3	4	5
13	**Global Rating of Alogia** The core features of alogia are poverty of speech and poverty of content.	**0**	**1**	**2**	**3**	**4**	**5**

AVOLITION - APATHY

14	Grooming and Hygiene The patient's clothes may be sloppy or soiled, and he may have greasy hair, body odour etc.	0	1	2	3	4	5
15	Impersistence at Work or School The patient has difficulty seeking of maintaining employment, completing school work, keeping house etc. If an inpatient, cannot persist at ward activities, such as OT, playing cards etc.	0	1	2	3	4	5
16	Physical Anergia The patient tends to be physically inert. He may sit for hours and not initiate spontaneous activity.	0	1	2	3	4	5
17	**Global Rating of Avolition-Apathy** Strong weight may be given to one or two prominent symptoms if particularly striking.	**0**	**1**	**2**	**3**	**4**	**5**

ANHEDONIA - ASOCIALITY

18	Recreational Interests and Activities The patient may have few or no interests. Both the quality and quantity of interests should be taken into account.	0	1	2	3	4	5
19	Sexual Activity The patient may show a decrease in sexual interest and activity, or enjoyment when active.	0	1	2	3	4	5
20	Ability to Feel Intimacy and Closeness The patient may display an inability to from close or intimate relationships, espec. with the opposite sex.	0	1	2	3	4	5
21	Relationships With Friends and Peers The patient may have few or no friends and may prefer to spend all his time isolated.	0	1	2	3	4	5
22	**Global Rating of Anhedonia-Asociality** This rating should reflect overall severity, taking into account the patient's age, family status, etc.	**0**	**1**	**2**	**3**	**4**	**5**

ATTENTION (this subscale not included in analyses)

23	Social Inattentiveness The patient appears uninvolved or unengaged. He may seem "spacey".	0	1	2	3	4	5
24	Inattentiveness During Mental Status Testing Tests of "serial 7s" (at least five subtractions) and spelling the word "world" backwards: Score 2 = 1 error, score 3 = 2 errors, score 4 = 3 errors.	0	1	2	3	4	5
25	**Global Rating of Attention** This rating should assess the patient's overall concentration, clinically and on tests.	**0**	**1**	**2**	**3**	**4**	**5**

Appendix III: Letter of approval to use the EPPIC dataset

ORYGEN Research Centre

ORYGEN Youth Health

Associate Professor Yoshi Kashima
Graduate Research Convener
Department of Psychology
The University of Melbourne
Grattan Street
Parkville 3052

May 9 2003

Dear Dr Kashima,

Susy Harrigan has worked with us at EPPIC (now Orygen Research Centre) for ten years in her capacity as statistician and research fellow. She is applying to undertake a PHD in the Department of Psychology and intends using data that we have collected over a number of years on 767 first-episode psychosis patients, termed the RP-MIP 767 cohort study. Susy has been involved in the organisation and maintenance of these databases and in the research emanating from the collection of these datasets.

I would like to make it clear that Susy has my full support to use these datasets to write her PHD thesis and to publish the research findings.

If you require further clarification I would be pleased to discuss this with you.

Yours sincerely,

Professor Patrick McGorry

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