Psychotic experiences and negative symptoms in the community from adolescence to emerging adulthood

Psychotic experiences and negative symptoms in the community from adolescence to emerging adulthood

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Declaration and statement of independent work

I, Laura Havers, declare that this Thesis is entirely my own work. This Thesis has not been submitted for any other degree at the University of London, or at any other academic institution.

This Thesis is based on secondary data, for which I was not involved with the data collection or the design of the assessment measures or procedures. For all studies conducted within this Thesis, the research aims, methods, analyses, and interpretations were all my own work.

I independently wrote all Chapters in this Thesis and I thank my supervisor for her advisory comments.

Signature: Laura Havers

Date: 29/06/22

Abstract

Psychotic experiences and negative symptoms (PENS) reported in non-clinical populations can be viewed as mild manifestations of clinical psychotic symptoms. PENS are reported across the lifespan. They are predictive of poor outcomes, particularly when they persist. Much of the literature has focussed on aggregated measures of psychotic experiences (PEs), and little is known about negative symptoms (NS). Given the known multidimensionality of PENS, this thesis investigates paranoia, hallucinations, and NS, as separate dimensions reported in the community. The focus is on the period from late adolescence to emerging adulthood, a stage of life when many mental health problems occur.

Chapter 2 presents analyses that test for longitudinal measurement invariance of the PENS dimensions across the study period. Chapter 3 assesses the optimal form of growth for the PENS dimensions and estimates the sample-wide latent trajectories. Chapter 4 investigates latent heterogeneity in the development of the PENS dimensions. In Chapter 5, the emergent trajectory classes are investigated in terms of the extent to which they associate with background factors reported in childhood/adulthood and with a range of polygenic scores. In Chapter 6, the latent structure of NS is investigated. Associations between polygenic scores and the subdomains of NS are reported.

This Thesis provides evidence that PENS dimensions show distinct characteristics, both in terms of development from adolescence to emerging adulthood, and in terms of the correlates that are associated with their development. Evidence is provided to suggest a multidimensional latent structure of NS, mirroring findings from clinical samples. The current findings highlight the value of taking a dimension-specific approach and using latent variable modelling to study PENS over time. Limitations and future research directions are

discussed. The findings of this Thesis have implications for future research that aims to test theories relating to the development and maintenance of specific PENS dimensions.

List of Contents

DECLARATION AND STATEMENT OF INDEPENDENT WORK 2
ABSTRACT 3
LIST OF TABLES 12
LIST OF FIGURES 13
LIST OF SUPPLEMENTARY TABLES 14
LIST OF SUPPLEMENTARY FIGURES 16
LIST OF SUPPLEMENTARY INFORMATION 17
LIST OF ABBREVIATIONS 18
ASSOCIATED PUBLICATIONS 20
ACKNOWLEDGEMENTS 21

Chapter 1 – Introduction 22

1.1 – PSYCHOTIC SYMPTOMS AND PSYCHOTIC EXPERIENCES 23
1.1.1 – Clinical psychotic symptoms 23
1.1.2 – Psychotic experiences in the community 23
1.1.3 – A continuum of psychosis 25
1.1.4 – Environmental and genetic continuity 27
1.1.5 – Psychotic experiences as a marker for later poor outcomes 29
1.2 – NEGATIVE SYMPTOMS 30
1.2.1 – Negative symptoms in psychosis 30
1.2.2 – Negative symptoms in the community 32
1.2.3 – A continuum of negative symptoms 33
1.2.4 – Etiological continuity between non-clinical and clinical negative symptoms 34
1.2.5 – Negative symptoms as a marker for later poor outcomes 35
1.3 – MULTIDIMENSIONALITY OF PSYCHOTIC EXPERIENCES AND NEGATIVE SYMPTOMS 36
1.3.1 – Dimensions of psychotic experiences and negative symptoms 36
1.3.2 – Dimensions of psychotic experiences 38
1.3.3 – Dimensions of negative symptoms 39
1.3.4 – Importance of a multidimensional approach 42
1.4 – PSYCHOTIC EXPERIENCES AND NEGATIVE SYMPTOMS ACROSS THE LIFESPAN 44
1.4.1 – Prevalence rates in childhood, adolescent, and adult samples 44
1.4.2 – Adolescence and emerging adulthood as a critical period 46
1.4.3 – Inferring change across the lifespan 46

1.5 – LONGITUDINAL DEVELOPMENT OF PSYCHOTIC EXPERIENCES AND NEGATIVE SYMPTOMS 47
1.5.1 – Repeated measures of psychotic experiences and negative symptoms 47
1.5.2 – Persistence of psychotic experiences and negative symptoms 49
1.5.3 – Proneness-persistence-impairment model 50
1.5.4 – Genetic influences on the development of psychotic experiences and negative symptoms 52
1.5.5 – Analysing change over time – methodological considerations 53
1.6 – SUMMARY, AND FUTURE DIRECTIONS FOR RESEARCH ON PSYCHOTIC EXPERIENCES AND NEGATIVE SYMPTOMS 56
1.7 – AIMS OF THESIS 57
Chapter 2 – Longitudinal measurement invariance analysis of paranoia, hallucinations, and negative symptoms 59
2.1 – INTRODUCTION 59
2.2 – METHODS 61
2.2.1 – Participants 61
2.2.1.1 – Twins Early Development Study sample 61
2.2.1.2 – TEDS sample for current Chapter 63
2.2.2 – Measures 64
2.2.3 – Statistical analyses 65
2.2.3.1 – Overview of analyses 65
2.2.3.2 – CFA and EFA 65
2.2.3.3 – CFA for base model 66
2.2.3.3.1 – Paranoia 67
2.2.3.3.2 – Hallucinations 67
2.2.3.3.3 – Negative symptoms 68
2.2.3.4 – Pseudo replication of EFA as a CFA model 69
2.2.3.5 – Model fit for CFA models 69
2.2.3.6 – Longitudinal measurement invariance 70
2.2.3.7 – Pseudo replication of longitudinal measurement model 71
2.2.3.8 – Data modelling 71
2.3 – RESULTS 71
2.3.1 – Paranoia 71
2.3.1.1 – EFA 71
2.3.1.2 – CFA 72
2.3.1.3 – Pseudo replication of EFA as a CFA model 72
2.3.1.4 – Longitudinal measurement invariance analyses 72
2.3.1.5 – Post hoc pseudo replication of longitudinal measurement model 73

2.3.1.6 – Post hoc longitudinal measurement invariance tests 73
2.3.2 – Hallucinations 74
2.3.2.1 – EFA 74
2.3.2.2 – CFA 74
2.3.2.3 – Pseudo replication of EFA as a CFA model 75
2.3.2.4 – Longitudinal measurement invariance analyses 75
2.3.2.5 – Post hoc pseudo replication of longitudinal measurement model 75
2.3.3 – Negative symptoms 76
2.3.3.1 – EFA 76
2.3.3.2 – CFA 76
2.3.3.3 – Pseudo replication of EFA as a CFA model 76
2.3.3.4 – Longitudinal measurement invariance analyses 76
2.3.3.5 – Planned pseudo replication of longitudinal measurement model 77
2.4 – DISCUSSION 84
2.5 – APPENDIX 88

Chapter 3 – Latent growth curve modelling of paranoia, hallucinations, and negative symptoms 106

3.1 – INTRODUCTION 106
3.2 – METHODS 108
3.2.1 – Participants 108
3.2.2 – Measures 108
3.2.3 – Statistical analyses 108
3.2.3.1 – Overview of analyses 108
3.2.3.2 – LGCM 109
3.2.3.3 – Model fit 110
3.2.3.4 – Data modelling 111
3.3 – RESULTS 111
3.3.1 – LGCM 111
3.3.1.1 – Paranoia 111
3.3.1.2 – Hallucinations 112
3.3.1.3 – Negative symptoms 113
3.4 – DISCUSSION 124
3.5 – APPENDIX 127

Chapter 4 – Growth mixture modelling of paranoia, hallucinations, and negative symptoms 135

4.1 – INTRODUCTION 135

4.2 – METHODS 136
4.2.1 – Participants 136
4.2.2 – Measures 137
4.2.3 – Statistical analyses 137
4.2.3.1 – Overview of analyses 137
4.2.3.2 – GMM 138
4.2.3.3 – Modelling of time 138
4.2.3.4 – Parameters 138
4.2.3.5 – Model fitting approach 138
4.2.3.5.1 – k-class models 138
4.2.3.5.2 – Constrained variance parameter models 139
4.2.3.6 – Model selection 139
4.2.3.7 – Post hoc sensitivity tests 140
4.2.3.8 – Complete data analyses 140
4.2.3.9 – Estimation 140
4.2.3.10 – Trajectory descriptors 141
4.2.3.11 – Data modelling 141
4.3 – RESULTS 141
4.3.1 – Paranoia 142
4.3.1.1 – Model fitting results 142
4.3.1.2 – Model selection 142
4.3.1.3 – Post hoc sensitivity tests 143
4.3.1.4 – Complete data analyses 144
4.3.2 – Hallucinations 144
4.3.2.1 – Model fitting results 144
4.3.2.2 – Model selection 145
4.3.2.3 – Post hoc sensitivity tests 146
4.3.2.4 – Complete data analyses 146
4.3.3 – Negative symptoms 147
4.3.3.1 – Model fitting results 147
4.3.3.2 – Model selection 147
4.3.3.4 – Post hoc sensitivity tests 148
4.3.3.5 – Complete data analysis 148
4.4 – DISCUSSION 157
4.5 – APPENDIX 160

Chapter 5 – Associations between the developmental trajectories of paranoia, hallucinations, and negative symptoms with polygenic scores, and with characteristics reported in childhood and adulthood 182

5.1 – INTRODUCTION 182
5.2 – METHODS 184
5.2.1 – Participants 184
5.2.2 – Measures 185
5.2.2.1 – PENS 185
5.2.2.2 – Additional measures 185
5.2.2.2.1 – Family background characteristics 185
5.2.2.2.2 – Age 7 characteristics 185
5.2.2.2.3 – Age 22 characteristics 186
5.2.2.3 – GPS 186
5.2.3 – Statistical analyses 187
5.2.3.1 – Overview of analyses 187
5.2.3.2 – Multinomial logistic regression analyses of family background, childhood characteristics, and GPSs 187
5.2.3.3 – Mean differences analyses 188
5.2.4 – Data modelling 189
5.3 – RESULTS 189
5.3.1 – Multinomial logistic regression analyses of family background, childhood characteristics, and GPSs 190
5.3.1.1 – Family background characteristics 190
5.3.1.2 – Age 7 characteristics 191
5.3.1.3 – GPS 192
5.3.2 – Mean differences analyses 193
5.3.2.1 – Family background characteristics 193
5.3.2.2 – Age 7 characteristics 194
5.3.2.3 – GPSs 194
5.3.2.4 – Age 22 characteristics 195
5.4 – DISCUSSION 208
5.5 – APPENDIX 212

Chapter 6 – The latent structure of negative symptoms in adolescence and emerging adulthood 228

6.1 – INTRODUCTION 228
6.2 – METHODS 230
6.2.1 – Participants 230
6.2.2 – Measures 231
6.2.2.1 – Negative symptoms 231
6.2.2.2 – GPS 231

6.2.3 – Statistical analyses 231
6.2.3.1 – Overview of analyses 231
6.2.3.2 – CFA models 232
6.2.3.3 – Model fit 233
6.2.3.4 – Measurement invariance 233
6.2.3.5 – Data modelling 234
6.2.3.6 – Association analyses 234
6.3 – RESULTS 235
6.3.1 – Descriptive statistics 235
6.3.2 – CFA 236
6.3.2.1 – Main subsample analyses 236
6.3.2.2 – Sensitivity analyses 236
6.3.2.3 – Cotwin subsample analyses 237
6.3.3 – Parameter estimates 237
6.3.4 – Measurement invariance 238
6.3.4.1 – Measurement invariance between the subsamples 238
6.3.4.2 – Longitudinal measurement invariance 238
6.3.5 – Associations between GPSs and subdomains 238
6.4 – DISCUSSION 245
6.5 – APPENDIX 248
Chapter 7 – Discussion 263
7.1 – AIMS AND FINDINGS OF EACH CHAPTER 263
7.2 – KEY FINDINGS AND EMERGING THEMES ACROSS CHAPTERS 265
7.2.1 – The measurement of paranoia, hallucinations, and negative symptoms shows (partial) invariance across adolescence and emerging adulthood 265
7.2.2 – Similar patterns of average latent change over time for paranoia and hallucinations, and an overall difference to negative symptoms 266
7.2.3 – Different patterns of latent heterogeneity underlie the trajectories of paranoia, hallucinations, and negative symptoms 267
7.2.4 – The most elevated trajectory classes show associations with suboptimal phenotypic and polygenic correlates 268
7.2.5 – Dimension-specific correlates, and the distinct pattern of correlates for persistent paranoia 269
7.2.6 – The latent structure of negative symptoms in the community mirrors the latent structure of negative symptoms in clinical samples – and the potential role of polygenic influences 270
7.3 – LIMITATIONS 272
7.3.1 – Sample/cohort effects 273
7.3.2 – Measures 274
7.3.3 – Specifications of latent growth 276

7.3.4 – Generalisability of the findings 276
7.3.5 – GPS selection....277
7.4 – FUTURE RESEARCH DIRECTIONS 279
7.4.1 – Embracing longitudinal noninvariance....279
7.4.2 – Paranoia-specific effects....279
7.4.3 – Gathering more data to infer change more accurately across the lifespan....280
7.4.4 – Co-developmental processes of latent growth....281
7.4.5 – Developmental associations for polygenic liability to schizophrenia 282
7.4.6 – Genetic influences on environmental effects....282
7.5 – CONCLUSIONS 283
REFERENCES....287

List of Tables

Table 2.1 *Descriptive Statistics for Paranoia*	78
Table 2.2 *Descriptive Statistics for Hallucinations*	79
Table 2.3 *Descriptive Statistics for Negative Symptoms*	80
Table 2.4 *Longitudinal Measurement Invariance Analysis of Paranoia in Main Subsample: Model Fit Results*	81
Table 2.5 *Longitudinal Measurement Invariance Analysis of Hallucinations in Main Subsample: Model Fit Results*	82
Table 2.6 *Longitudinal Measurement Invariance Analysis of Negative Symptoms in Main Subsample: Model Fit Results*	83
Table 3.1 *Latent Growth Curve Modelling of Paranoia for Different Functional Forms of Growth: Model Fit Results*	115
Table 3.2 *Parameter Estimates for Paranoia from Linear Growth Model*	116
Table 3.3 *Latent Growth Curve Modelling of Hallucinations for Different Functional Forms of Growth: Model Fit Results*	117
Table 3.4 *Parameter Estimates for Hallucinations from Linear Growth Model*	118
Table 3.5 *Latent Growth Curve Modelling of Negative Symptoms for Different Functional Forms of Growth: Model Fit Results*	119
Table 3.6 *Parameter Estimates for Negative Symptoms from Linear Growth Model*	120
Table 4.1 *Descriptive Statistics for Paranoia, Hallucinations, Negative Symptoms, and Age*	150
Table 4.2 *Growth Mixture Model Fit Results for Converged Models of Paranoia, Hallucinations, and Negative Symptoms*	151
Table 4.3 *Parameter Estimates for Each Best Fitting Growth Mixture Model for Paranoia, Hallucinations, and Negative Symptoms*	152
Table 5.1 *Multinomial Logistic Regression Results for Paranoia Latent Trajectory Class Regressed on Family Background Variables*	196
Table 5.2 *Multinomial Logistic Regression Results for Hallucinations Latent Trajectory Class Regressed on Family Background Variables*	198
Table 5.3 *Multinomial Logistic Regression Results for Negative Symptoms Latent Trajectory Class Regressed on Family Background Variables*	199
Table 5.4 *Multinomial Logistic Regression Results for Paranoia Latent Trajectory Class Regressed on Age 7 Variables*	200
Table 5.5 *Multinomial Logistic Regression Results for Hallucinations Latent Trajectory Class Regressed on Age 7 Variables*	201
Table 5.6 *Multinomial Logistic Regression Results for Negative Symptoms Latent Trajectory Class Regressed on Age 7 Variables*	202
Table 5.7 *Multinomial Logistic Regression Results for Paranoia Latent Trajectory Class Regressed on GPS Variables for Most Predictive f*	203
Table 5.8 *Multinomial Logistic Regression Results for Hallucinations Latent Trajectory Class Regressed on GPS Variables for Most Predictive f*	205
Table 5.9 *Multinomial Logistic Regression Results for Negative Symptoms Latent Trajectory Class Regressed on GPS Variables for Most Predictive f*	206
Table 5.10 *Characteristics of Latent Trajectory Classes for Paranoia, Hallucinations, and Negative Symptoms*	207
Table 6.1 *Measurement Invariance Analysis of 5-Factor Structure of Negative Symptoms at Age 16 Between Main and Cotwin Subsamples*	240
Table 6.2 *Measurement Invariance Analysis of 5-Factor Structure of Negative Symptoms at Age 17 Between Main and Cotwin Subsamples*	241
Table 6.3 *Measurement Invariance Analysis of 5-Factor Structure of Negative Symptoms at Age 22 Between Main and Cotwin Subsamples*	242
Table 6.4 *Single-Predictor Linear Regressions of Subdomain Mean Scores on Schizophrenia GPS and Major Depressive Disorder GPS for Most Predictive GPS f*	243

List of Figures

Figure 3.1 *Spaghetti Plot of Individual Trajectories for Observed Paranoia Scores*	121
Figure 3.2 *Spaghetti Plot of Individual Trajectories for Observed Hallucinations Scores*	122
Figure 3.3 *Spaghetti Plot of Individual Trajectories for Observed Negative Symptoms Scores*	123
Figure 4.1 *Linear Growth Mixture Model with Individual Time Scores*	153
Figure 4.2 *Plot of Estimated Trajectories from Best Fitting Growth Mixture Model of Paranoia*	154
Figure 4.3 *Plot of Estimated Trajectories from Best Fitting Growth Mixture Model of Hallucinations*	155
Figure 4.4 *Plot of Estimated Trajectories from Best Fitting Growth Mixture Model of Negative Symptoms*	156
Figure 6.1 *Five-Factor Model of Negative Symptoms at Ages 16, 17, and 22 in Main Subsample*	244

List of Supplementary Tables

Supplementary Table 2.1 *The Twins Early Development Study (TEDS) Sample*	91
Supplementary Table 2.2 *Correlations between Paranoia, Hallucinations, and Negative Symptoms*	92
Supplementary Table 2.3 *Exploratory Factor Analysis of Paranoia Items in Main Subsample*	93
Supplementary Table 2.4 *Confirmatory Factor Analysis of Paranoia in Main Subsample: Model Fit Results*	95
Supplementary Table 2.5 *Confirmatory Factor Analysis of Paranoia in Cotwin Subsample (of Model Suggested by EFA in Main Subsample)*	96
Supplementary Table 2.6 *Exploratory Factor Analysis of Hallucinations Items in Main Subsample*	97
Supplementary Table 2.7 *Confirmatory Factor Analysis of Hallucinations in Main Subsample: Model Fit Results*	98
Supplementary Table 2.8 *Confirmatory Factor Analysis of Hallucinations in Cotwin Subsample (of Model Suggested by EFA in Main Subsample)*	99
Supplementary Table 2.9 *Longitudinal Measurement Invariance Analysis of Hallucinations in Cotwin Subsample: Model Fit Results*	100
Supplementary Table 2.10 *Exploratory Factor Analysis of Negative Symptoms Items in Main Subsample*	101
Supplementary Table 2.11 *Confirmatory Factor Analysis of Negative Symptoms in Main Subsample: Model Fit Results*	103
Supplementary Table 2.12 *Confirmatory Factor Analysis of Negative Symptoms in Cotwin Subsample (of Model Suggested by EFA in Main Subsample)*	104
Supplementary Table 2.13 *Longitudinal Measurement Invariance Analysis of Negative Symptoms in Cotwin Subsample: Model Fit Results*	105
Supplementary Table 3.1 *Latent Growth Curve Modelling of Paranoia Using Alternative Modelling Techniques: Model Fit Results*	129
Supplementary Table 3.2 *Latent Growth Curve Modelling of Hallucinations Using Alternative Modelling Techniques: Model Fit Results*	130
Supplementary Table 3.3 *Latent Growth Curve Modelling of Negative Symptoms Using Alternative Modelling Techniques: Model Fit Results*	131
Supplementary Table 3.4 *Parameter Estimates for Paranoia derived from the Alternative Modelling Techniques*	132
Supplementary Table 3.5 *Parameter Estimates for Hallucinations derived from the Alternative Modelling Techniques*	133
Supplementary Table 3.6 *Parameter Estimates for Negative Symptoms derived from the Alternative Modelling Techniques*	134
Supplementary Table 4.1 *Paranoia Data Time-Point Characteristics*	162
Supplementary Table 4.2 *Hallucinations Data Time-Point Characteristics*	163
Supplementary Table 4.3 *Negative Symptoms Data Time-Point Characteristics*	164
Supplementary Table 4.4 *Full Growth Mixture Model Fit Results for Paranoia*	165
Supplementary Table 4.5 *Parameter Estimates for Each Best Fitting k-Class Model for Paranoia*	166
Supplementary Table 4.6 *Most Likely Class Classification Values for Each Best Fitting k-Class Model for Paranoia*	167
Supplementary Table 4.7 *Growth Mixture Model Fit Results for 2-Class Models of Paranoia (Sensitivity Analysis)*	168
Supplementary Table 4.8 *Growth Mixture Model Fit Results for Paranoia for Individuals with Complete Data*	169
Supplementary Table 4.9 *Parameter Estimates for Each Best Fitting k-Class Model for Paranoia for Individuals with Complete Data*	170
Supplementary Table 4.10 *Full Growth Mixture Model Fit Results for Hallucinations*	171
Supplementary Table 4.11 *Parameter Estimates for Each Best Fitting k-Class Model for Hallucinations*	172
Supplementary Table 4.12 *Most Likely Class Classification Values for Each Best Fitting k-Class Model for Hallucinations*	173

Supplementary Table 4.13 *Growth Mixture Model Fit Results for Hallucinations for Individuals with Complete Data*	174
Supplementary Table 4.14 *Parameter Estimates for Each Best Fitting k-Class Model for Hallucinations for Individuals with Complete Data*	175
Supplementary Table 4.15 *Full Growth Mixture Model Fit Results for Negative Symptoms*	176
Supplementary Table 4.16 *Parameter Estimates for Each Best Fitting k-Class Model for Negative Symptoms*	177
Supplementary Table 4.17 *Most Likely Class Classification Values for Each Best Fitting k-Class Model for Negative Symptoms*	178
Supplementary Table 4.18 *Growth Mixture Model Fit Results for Negative Symptoms for Individuals with Complete Data*	179
Supplementary Table 4.19 *Parameter Estimates for Each Best Fitting k-Class Model for Negative Symptoms for Individuals with Complete Data*	180
Supplementary Table 5.1 *Multinomial Logistic Regression Results for Paranoia Latent Trajectory Class Regressed on GPSs for all GPS f*	217
Supplementary Table 5.2 *Multinomial Logistic Regression Results for Hallucinations Latent Trajectory Class Regressed on GPSs for all GPS f*	222
Supplementary Table 5.3 *Multinomial Logistic Regression Results for Negative Symptoms Latent Trajectory Class Regressed on GPSs for all GPS f*	225
Supplementary Table 6.1 *Descriptive Statistics for Negative Symptoms Items, Subdomains, and Totals at Ages 16, 17, and 22 in Main and Cotwin Subsamples*	248
Supplementary Table 6.2 *Confirmatory Factor Analysis of Negative Symptoms in Main Subsample using Diagonally Weighted Least Squares Estimation: Model Fit Results*	249
Supplementary Table 6.3 *Confirmatory Factor Analysis of Negative Symptoms in Cotwin Subsample: Model Fit Results*	250
Supplementary Table 6.4 *Parameter Estimates from 5-Factor Model of Negative Symptoms at Age 16 in Main Subsample*	251
Supplementary Table 6.5 *Parameter Estimates from 5-Factor Model of Negative Symptoms at Age 17 in Main Subsample*	253
Supplementary Table 6.6 *Parameter Estimates from 5-Factor Model of Negative Symptoms at Age 22 in Main Subsample*	255
Supplementary Table 6.7 *Communality and Uniqueness Estimates from 5-Factor Model of Negative Symptoms at Ages 16, 17, and 22 in Main Subsample*	257
Supplementary Table 6.8 *Longitudinal Measurement Invariance of 5-Factor Structure of Negative Symptoms Between Ages 16, 17, and 22 in Cotwin Subsample*	258
Supplementary Table 6.9 *Single-predictor Linear Regressions of Subdomain Mean Scores on Schizophrenia GPS for All GPS f*	259
Supplementary Table 6.10 *Single-Predictor Linear Regressions of Subdomain Mean Scores on Major Depressive Disorder GPS for All GPS f*	260
Supplementary Table 6.11 *Pairwise Wald Test Results for Subdomain Mean Scores Regressed on Schizophrenia GPS And Major Depressive Disorder GPS*	261
Supplementary Table 6.12 *Multiple-Predictor Linear Regressions of Subdomain Mean Scores on Schizophrenia GPS and Major Depressive Disorder GPS*	262

List of Supplementary Figures

Supplementary Figure 4.1 *Decision-Making Flowchart for Growth Mixture Models* | 181

List of Supplementary Information

Supplementary Information 2.1 *Paranoia Subscale of the Specific Psychotic Experiences Questionnaire*	88
Supplementary Information 2.2 *Hallucinations Subscale of the Specific Psychotic Experiences Questionnaire*	89
Supplementary Information 2.3 *Negative Symptoms Subscale of the Specific Psychotic Experiences Questionnaire*	90
Supplementary Information 3.1 *Modelling the Nonindependence of Data*	127
Supplementary Information 4.1 *Preregistration of Hypotheses*	160
Supplementary Information 5.1 *Genotyping of TEDS Participants*	212
Supplementary Information 5.2 *Calculation of Genome-Wide Polygenic Scores*	214

List of Abbreviations

AIC	Akaike's Information Criterion
BIC	Bayesian Information Criterion
CAPE	Community Assessment of Psychic Experiences
CFA	Confirmatory factor analysis
CFI	Comparative fit index
EFA	Exploratory factor analysis
FDR	False Discovery Rate
FIML	Full information maximum likelihood
GMM	Growth mixture model/growth mixture modelling
GPS	Genome-wide polygenic score
GWAS	Genome-wide association study
k	Number of classes
LCGA	Latent class growth analysis
LD	Linkage disequilibrium
LGCM	Latent growth curve model/latent growth curve modelling
MLR	Robust maximum likelihood
NS	Negative symptoms
ONS	Office for National Statistics
PCs	Principal components
PCA	Principal components analysis
PENS	Psychotic experiences and negative symptoms
PEs	Psychotic experiences

RMSEA	Root mean square error of approximation
SES	Socioeconomic status
SNP	Single nucleotide polymorphism
SPEQ	Specific Psychotic Experiences Questionnaire
SRMR	Standardized root mean square residual
TEDS	Twins Early Development Study

Associated publications

Chapters 2-5

Havers, L., von Stumm, S., Cardno, A. G., Freeman, D., & Ronald, A. (2022). Psychotic experiences and negative symptoms from adolescence to emerging adulthood: developmental trajectories and associations with polygenic scores and childhood characteristics. *Psychological Medicine.* (In press). https://psyarxiv.com/a4guk/

Chapter 6

Havers, L., Cardno, A. G., Freeman, D., & Ronald, A. (2022). The latent structure of negative symptoms in the general population in adolescence and emerging adulthood. *Schizophrenia Bulletin Open*, sgac009. https://doi.org/10.1093/schizbullopen/sgac009

The studies reported in Chapters 2-5 were published as a preprint. The manuscript has been subsequently accepted for publication and is currently in press. The study reported in Chapter 6 was published as a peer reviewed article. Both manuscripts were published under a Creative Commons by Attribution licence. Under this licence (CC-BY), the material may be reused and reproduced without infringing copyright. Minor edits to the published versions were made for the purposes of this Thesis.

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As first author on the manuscripts, all reused and reproduced words, tables, and figures in this Thesis are my own work.

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Chapter 1 – Introduction

This Chapter will provide an overview of psychotic experiences (PEs) and negative symptoms (NS). The manifestation of psychotic experiences and negative symptoms (PENS) in the community will be described in the context of clinical psychotic symptoms and clinical negative symptoms. PEs will be discussed in terms of a spectrum of severity across a continuum (van Os et al., 2000). Evidence suggesting etiological continuity, and evidence suggesting that PEs may be a marker for later clinical outcomes will be outlined. It will be discussed that there are fewer findings regarding NS in the community, but evidence to suggest that NS represent a marker for later clinical outcomes will be set out, and evidence in support of a continuum model of NS will also be outlined (Kaiser et al., 2011). The multidimensionality of PENS will then be introduced as a theme, and the importance of taking a multidimensional approach to studying PENS will be discussed. An overview of PENS reported across the lifespan will be provided both in terms of cross-sectional measurement and longitudinal development. It will be discussed that persistence of PENS appears to be particularly indicative of later poor clinical and functional outcomes, which will be discussed in the context of a proneness-persistence-impairment model of psychosis (van Os et al., 2009). Evidence for genetic influences on the development of PENS over time will be described, and methodological considerations of delineating the longitudinal development of PENS will be discussed. The findings and limitations of prior research on PENS will be summarised, providing the platform for the aims of this Thesis.

1.1 – Psychotic symptoms and psychotic experiences

This Section will provide an outline of clinical psychotic symptoms and will describe the presentation of psychotic phenomena in non-clinical populations. The term 'psychotic experiences' will be introduced to refer to non-clinical psychotic phenomena. A continuum model of psychosis will be outlined and evidence suggesting etiological continuity will be discussed. Drawing on previous findings, PEs will be discussed both in terms of a precursor of psychiatric outcomes and as part of normal behavioural variation.

1.1.1 – Clinical psychotic symptoms

Thought and perceptual disturbances that manifest as delusions, hallucinations, and disorganised thinking (speech), constitute the key features pertaining to a diagnosis of schizophrenia (American Psychiatric Association, 2013). According to the American Psychiatric Association's most recent diagnostic manual (DSM-5), a diagnosis of schizophrenia is made where at least one of these 'key features' is accompanied by the presence of at least one other (including grossly disorganised or abnormal motor behaviour, and NS) – and where these symptoms persist and cause substantial impairment. Variations in the type or duration of these symptoms may give rise to the diagnosis of other types of psychotic disorder. The symptoms of delusions and hallucinations have been classically referred to as 'positive' psychotic symptoms – so called because they are thought to reflect an increase in or an excess of functions (Arndt et al., 1991).

1.1.2 – Psychotic experiences in the community

The symptoms of psychosis in the absence of clinical help-seeking or psychiatric diagnosis are reported in community samples (Healy et al., 2019; McGrath et al., 2015). Herein, the term 'psychotic experiences' (PEs) will be used to refer to psychotic symptoms

reported in non-clinical population studies, and 'psychotic symptoms' will be used to refer to symptoms reported in clinical samples. Discussed in terms of a continuum of psychosis in the following Section (1.1.3) – briefly here, there are two broad conceptualisations regarding the expression of psychotic phenomena (Johns & van Os, 2001). One is that PEs and psychotic symptoms differ in degree rather than in kind across a spectrum of severity. The other is that psychotic phenomena outside of psychosis reflect attenuated, trait-like expressions of psychotic symptoms (called schizotypal personality traits, or 'schizotypy'). This Thesis is generally positioned within the former ('degree rather than kind') framework, and it will be explicitly stated where previous findings are derived from measures of schizotypy.

The study of PEs has most often focussed on two out of the three key features of schizophrenia (as defined in Section 1.1.1) – delusions and hallucinations. Delusions refer to abnormal thought disturbances. These thought disturbances are measured, for example, using items such as, *"Do you ever feel as if people seem to drop hints about you or say things with a double meaning?"* (Peters et al., 1999). Paranoid or persecutory delusions represent a specific type of delusion, measured, for example, using items such as, *"Do you ever feel as if you are being persecuted in some way?"* (Peters et al., 1999). Findings derived from measures of delusions, broadly, and of paranoia/persecution, specifically, will be discussed interchangeably in this Thesis.

Hallucinations refer to abnormal perceptual disturbances. These perceptual disturbances can present via any of the sensory modalities (sight, hearing, smell, taste, touch, and sensed presence; Mitchell et al., 2017). Items such as, *"Do you ever hear sounds or music that people near you don't hear?"*, and, *"Do you ever experience smells or odours that people next to you seem unaware of?"*, can be used to measure auditory hallucinations, and olfactory hallucinations, respectively (Bell et al., 2006; Ronald et al., 2014).

Studies of PEs have assessed these experiences by interview (by either lay-person or clinician), or by self-report questionnaire. Assessment by interview has been found to yield lower prevalence rates than assessment by questionnaire (Healy et al., 2019; Linscott & van Os, 2013). The importance of studying PEs, whether self- or interviewer-reported, is supported by two lines of evidence. First, findings show that self-report measures of PEs predict interviewer-assessed PEs, albeit moderately and with greater agreement for certain items than others (Gundersen et al., 2019; Kelleher et al., 2011; Laurens et al., 2007). Second, like interviewer-assessed PEs (Carey et al., 2021; Poulton et al., 2000), self-reported PEs have been found to predict both concurrent (Hielscher et al., 2018) as well as later psychiatric outcomes (Healy et al., 2019).

1.1.3 – A continuum of psychosis

Whether differing in degree rather than in kind to clinical psychotic symptoms (PEs), or differing in degree and in kind (schizotypy) (as mentioned briefly in Section 1.1.2), the presence of psychotic phenomena outside of clinical populations may be considered as broad support for a hypothesised continuum of psychosis (Johns & van Os, 2001; van Os et al., 2000). As identified by Johns and van Os (2001), many lines of evidence converge to provide evidence in support of the continuum hypothesis, several of which are outlined in this Section because they are integral to the rationale underlying this Thesis.

The first relates to the estimated prevalence rates of PEs and of psychosis. One study that analysed data from the World Health Organization World Mental Health Surveys from more than 30,000 adults across 18 countries estimated the lifetime prevalence rate of non-clinical psychotic symptoms at 5.8% (McGrath et al., 2015). This estimate was broadly in line with median estimates of 5.3%-7.2% obtained through meta-analysis (Linscott & van Os, 2013; van Os et al., 2009). These findings suggest that PEs are more prevalent than

schizophrenia (< 1%) and psychotic disorders broadly (~ 3%-3.5%) (Perälä et al., 2007; Saha et al., 2005). Under a continuum model of psychosis, this can be considered as evidence to suggest that psychotic phenomena in and of themselves constitute only one element pertaining to the diagnosis of a psychotic disorder. That is, the manifest 'disorder' is due to a multitude of additional factors, both at the symptom-level (for example, frequency, intensity, other comorbid symptoms), and at a personal level, including impairment, coping, and social support (Johns & van Os, 2001; van Os et al., 2000).

This idea can be expanded further such that if extreme scores on a measure of psychotic phenomena do not necessarily indicate the need for clinical support – then quantitative variation from low to high scores solely within the distribution of PEs should be detectable. Such quantitative variation was found in a large-scale community sample, for example, in which the range of total paranoia scores was 0-72 (out of a maximum of 75), and the range of hallucinations scores was 0-45 (out of a maximum of 45) (Ronald et al., 2014).

Further in support of a continuum model and relevant to the current Thesis, are that i) the psychometric structure of psychotic phenomena appears to be similar in clinical and non-clinical populations (discussed in Section 1.3.1), ii) the environmental and genetic factors that are associated with clinical psychosis appear to be associated with PEs (discussed in Section 1.1.4), and iii) elevated levels of PEs appear to be associated with psychiatric outcomes (discussed in Section 1.1.5).

In sum, under the continuum hypothesis – PEs may be understood as representing an expression of liability to psychosis: the development of which may be contingent on the presence of genetic and environmental risk factors (van Os et al., 2009). This idea will be discussed further in Section 1.5.3 in the context of a 'proneness-persistence-impairment' model of psychosis.

1.1.4 – Environmental and genetic continuity

There are a range of findings that suggest that risk factors that are associated with psychotic disorders are also associated with PEs. Amongst the most documented factors found to confer risk for clinical psychotic outcomes include cannabis use (Hasan et al., 2020), childhood trauma (Bendall et al., 2008; Read et al., 2005), urban living environment (Abrahamyan Empson et al., 2020; Krabbendam & van Os, 2005), and migrant status (Dealberto, 2010). In the community, associations have been found for PEs with these factors (e.g., cannabis use (Jones et al., 2018; Shakoor, Zavos, et al., 2015), childhood trauma (Arseneault et al., 2011; Croft et al., 2019; Morgan et al., 2014), urban living (Polanczyk et al., 2010; van Os et al., 2001), and migrant status (Scott et al., 2006)). Notably, it has been shown that many of these 'environmental' risk factors, as well as their associations with PEs/psychotic disorders, are at least in part influenced by genetic factors (Maxwell et al., 2021; Shakoor, McGuire, et al., 2015a). This issue is considered further in Chapter 7.

It can also be tested whether genetic factors that influence the symptoms of psychosis, as well as the presence of psychotic disorder, are associated with non-clinical psychotic phenomena: Some important findings that suggest genetic continuity are for schizotypy (e.g., Debbané et al., 2015; A. Fanous et al., 2001; Mata et al., 2003). For example, one family study found that positive psychotic symptoms in probands with a diagnosis of schizophrenia predicted positive schizotypy, as well as social dysfunction and borderline personality disorder symptoms, in non-psychotic relatives (A. Fanous et al., 2001). Whilst these results are suggestive of genetic continuity across a spectrum of severity, family studies do not disentangle genetic and shared environment. Adoption studies have provided further evidence to suggest that familial associations are due to genetic and not (just) shared environmental influences (Kety et al., 1971, 1994). For example, in one adoption study – non-clinical/non-overt 'latent' schizophrenia was significantly more common in the biological relatives of

adopted-away individuals with a diagnosis of schizophrenia than it was in the biological relatives of adopted-away controls; and it was further absent in all adopted (non-biological) relatives (Kety et al., 1994).

Other studies that have leveraged individual-level genetic data have provided further, specific evidence for genetic continuity between PEs and psychotic disorders. The largest of these studies (N = 127,966) reported genetic overlap between schizophrenia (as well as other disorders) and PEs reported in adulthood (Legge et al., 2019). Genetic overlap, or continuity, can be inferred both by genetic correlation statistics, and by the regression coefficients of the associations between PEs and polygenic liability to schizophrenia (expressed as a genome-wide polygenic score (GPS); described in Supplementary Information 5.2). Findings have been mixed from studies in adolescence (Jones et al., 2016; Pain et al., 2018), but the largest of these studies also reported genetic overlap between schizophrenia GPS and PEs dimensions (Pain et al., 2018). Effect size estimates in these studies have been small (e.g., < 1% of the variance in PEs was explained by schizophrenia GPS in Pain et al., 2018). Small effect sizes such as this are expected in the context of findings that show that schizophrenia GPS predicts only up to ~ 18% of the variance in liability to schizophrenia in case-control samples of schizophrenia (Ripke et al., 2014), and ~ 9% of the variance in liability to a first episode of psychosis (Vassos et al., 2017).

Further to the previously discussed evidence for etiological continuity between clinical and non-clinical psychotic phenomena, findings from a large-scale twin study (N = 5,059 twin pairs) further suggest continuity of genetic and environmental influences across the distribution of PEs reported in the community (Zavos et al., 2014).

1.1.5 – Psychotic experiences as a marker for later poor outcomes

Importantly, a multitude of findings have shown that PEs are predictive of psychotic outcomes – as expected under a continuum model of psychosis. For example, one longitudinal study within the Dunedin Multidisciplinary Health and Development Study found that individuals with 'strong' PEs at age 11 (assessed by a psychiatrist) predicted a research-diagnosis of schizophreniform disorder at age 26 (OR 16.4, 95% CI 3.9-67.8) compared to individuals without PEs at age 11 (Poulton et al., 2000). Linear associations were non-significant between PEs and later diagnoses of mania and depression, and significant though smaller for anxiety – leading the authors to suggest specificity between PEs and psychotic outcomes. These and other results (e.g., Healy et al., 2019) that point to 'homotypic continuity' between PEs and psychosis offer clear support for a continuum model of psychosis.

PEs have also been found to predict non-psychotic clinical outcomes. For example, data collected at age 38 in the same sample as Poulton et al. (2000) showed that PEs at age 11 were associated with post-traumatic stress disorder and suicide attempts, in addition to schizophrenia (Fisher et al., 2013). Recent review findings support the notion that PEs appear to be an indicator of vulnerability to psychiatric outcomes *broadly* (Healy et al., 2019) – perhaps most accurately representing, "epiphenomenic flags of a broader vulnerability to a spectrum of mental disorders" (Raballo & Poletti, 2020, p.612). This is also supported by a meta-analytic estimate of the association between PEs and a family history of mental illness broadly (OR 3.06, 95% CI 1.58, 5.94; Linscott & van Os, 2013), as well as findings from the World Health Organization World Mental Health Surveys (McGrath et al., 2016) in which PEs were found to predict the onset of a range of non-psychotic psychiatric disorders (OR 1.3, 95% CI 1.2-1.5, to OR 2.0, 95% CI 1.5-2.6). An augmentation of the continuum model

of psychosis posits that PEs not only represent an 'extended' (psychosis-specific) phenotype, but also a 'transdiagnostic' phenotype (van Os & Reininghaus, 2016).

Importantly, PEs are often not associated with any psychiatric outcome, or even with any concurrent psychopathology or distress (e.g., Ronald et al., 2014; Yung et al., 2009): thus, some PEs may be considered part of typical behavioural variation (Kelleher & Cannon, 2011; Linscott & van Os, 2013; van Os et al., 2000, 2009). For example, a notable finding from the Poulton et al. (2000) study was that PEs at age 11 were not associated with later psychiatric diagnoses for approximately three quarters of individuals. Ascertaining the conditions that influence and indicate that PEs may be a marker for poor outcomes is an important goal: as will be discussed in Section 1.5.2 – persistence of PEs may be one such indication.

1.2 – Negative symptoms

This Section will provide an overview of NS. It will describe the presentation of NS in psychotic disorders and in non-clinical populations. A continuum model of NS will be discussed and evidence suggesting etiological continuity will be outlined. It will be discussed that whilst evidence is limited, NS in young people, like PEs, appear to represent a marker for later poor outcomes.

1.2.1 – Negative symptoms in psychosis

Up to this point in the Thesis, the focus has been on *positive* psychotic symptoms and experiences. However, as was seen in Section 1.1.1, *negative* symptoms are also a core component of a diagnosis of schizophrenia. The term 'negative symptoms' is used to describe a set of symptoms, so called because they are understood, figuratively, as reflecting a

diminution or lack of what are considered typical behaviours and emotions (Correll & Schooler, 2020).

NS reflect deficits in two overarching domains: expression, and motivation and pleasure (Kirkpatrick et al., 2006). Expressive deficits include flat or blunted affect, and alogia (poverty of speech). Motivational and pleasure deficits include avolition (lack of motivation), anhedonia (reduced derivation of pleasure), and asociality. In addition to being part of the diagnostic criteria for schizophrenia, NS are also symptomatic features of other specific psychotic disorders (e.g., schizophreniform disorder), other psychiatric disorders (such as major depressive disorder and bipolar disorder), and neurological disorders (such as Parkinson's disease and Huntington's disease), though they are not typically referred to as 'negative symptoms' outside of the schizophrenia spectrum of disorders (Strauss & Cohen, 2017).

Despite the transdiagnostic phenomenology of NS, they have classically and long been understood in terms of representing a core feature of schizophrenia (Bleuler, 1950; Kraeplin, in Kendler, 2020). As per the DSM-5 however, they are neither necessary nor sufficient for a diagnosis of schizophrenia. Nonetheless, a review estimated that between 50%-90% of individuals meeting criteria for a first episode of psychosis present in clinics with NS, and that 20%-40% of individuals diagnosed with schizophrenia have persisting NS (Mäkinen et al., 2008). Furthermore, NS are associated with poor prognostic features, and clinical and functional impairment (Ho et al., 1998; Patel et al., 2015; Rabinowitz et al., 2012, 2013). For example, one large-scale clinical study (N = 7,678) found that NS in schizophrenia predicted hospital admission, longer duration of hospitalisation, and readmission following discharge (Patel et al., 2015).

Whilst a review reported that the findings from several studies were suggestive of efficacy for the treatment of NS, the authors discussed these findings in the context of a range

of methodological issues that limit the certitude of the findings (Aleman et al., 2017). The review concluded that there is currently no consensus on how to effectively treat idiopathic NS, and it is widely acknowledged that research into clinical NS remains a priority (Correll & Schooler, 2020).

1.2.2 – Negative symptoms in the community

Much less has been documented and theorised about NS in the community than about PEs. Nonetheless, studies that have assessed NS in non-clinical populations have found that, like PEs, NS are also reported in non-clinical populations (e.g., Dominguez et al., 2010; Ronald et al., 2014; Stefanis et al., 2002). There are no reviews or meta-analyses assessing the prevalence of NS in the community to date, and prevalence rates vary substantially across studies. For example, a prevalence rate of 11% was estimated in a sample of 14-24-year-olds, based on the presence of at least one out of two interviewer-reported NS/disorganized items (Dominguez et al., 2010). In another study of 18-64-year-olds, a prevalence rate of 1% was estimated, based on the presence of at least one out of three interviewer-reported NS items.

The measurement of non-clinical NS is based on clinical measures of NS. These measures typically include items tapping the two domains of expression, and motivation and pleasure, and include items reflecting the five 'subdomains' of flat affect, alogia, avolition, anhedonia, and asociality (Section 1.2.1) – though a total score of NS has generally been used outside of clinical research. NS are understood to be *observable* through behaviour and have therefore typically been assessed through observer-report. There is also evidence to suggest that individuals are able to accurately report on their own symptoms in non-clinical populations (Engel & Lincoln, 2017), with mixed evidence for this in clinical populations (Liraud et al., 2004; Selten et al., 2000).

The current debate regarding the 'structure' of clinical NS will be outlined in Section 1.3.3 – though the five generally accepted, specific facets within the NS construct (Kirkpatrick et al., 2006) are described here: Within the expressive deficit domain (Section 1.2.1), flat affect refers to a blunting of emotion, either expressed verbally or by body language, including facial expressions and gestures. Flat affect is measured using items such as, *"(My child) often fails to smile or laugh at things others would find funny"* (Ronald et al., 2014). Alogia refers to limited speech production, often called 'poverty' of speech. Alogia is measured using items such as, *"Do you ever feel that you are not much of a talker when you are conversing with other people?"* (Stefanis et al., 2002).

Within the motivation-pleasure deficit domain (Section 1.2.1), avolition refers to a lack of motivation to engage with goal-oriented activities, measured, for example, using items such as, *"Do you ever feel that you are lacking in motivation to do things?"* (Stefanis et al., 2002). Anhedonia refers to a lack of pleasure derivation. There is interest in whether anhedonia in the context of NS (rather than in depression, for example, Section 1.2.1) specifically relates to the anticipation of future events (anticipatory anhedonia), instead of current events (consummatory anhedonia), though a recent meta-analysis found no evidence to support this view (Visser et al., 2020). Some scales specifically measure both anticipatory and consummatory anhedonia (e.g., Gard et al., 2006), and other scales measure anhedonia more broadly, for example, *"(My child) has very few interests or hobbies"* (Ronald et al., 2014). Asociality refers to a lack of motivation to engage in social activity. Asociality is measured using items such as, *"Do you ever feel that you have no interest to be with other people?"* (Stefanis et al., 2002).

1.2.3 – A continuum of negative symptoms

A dimensional approach to investigating NS has been advanced, in which NS exist across both a spectrum of psychotic and mood disorders and across a spectrum of severity

from non-clinical to clinical (Kaiser et al., 2011). Of note, the dimensional model of NS does not explicitly articulate that a spectrum of severity should exist *within* non-clinical populations. However, it is implicit within the hypothesis that a wide range of scores should be detectable in non-clinical populations (S. Kaiser, personal communication, 2022). The dimensional model of NS has, arguably, received much less attention than the continuum model of psychosis that delineates the continuity of positive psychotic phenomena (Section 1.1.3). Notwithstanding, the dimensional model aligns with the tenets of the psychosis continuum model in purporting that the study of NS in non-clinical populations is separable into two approaches: the first approach views NS as differing in quantity rather than kind to clinical NS, and the second views these symptoms as the attenuated, trait-like expression of clinical NS (Kaiser et al., 2011; Stefanis et al., 2002). This Thesis is positioned primarily within the former (quantity rather than kind) framework, though findings from studies of (negative) schizotypy will also be referred to. The term 'negative symptoms' will be used to refer to all NS, and it will be articulated whether the context is clinical or non-clinical. Findings of negative schizotypy will be explicitly stated as such.

1.2.4 – Etiological continuity between non-clinical and clinical negative symptoms

Whether expressed as differences in quantity rather than in kind, or as personality traits (Section 1.2.3), there is at least some evidence to suggest that NS reported in the community represent an extension of NS observed in schizophrenia. For example, in one study, NS were found to predict negative schizotypy, social dysfunction, and 'odd speech', as well as suspicious behaviour, in the non-psychotic relatives of individuals diagnosed with schizophrenia spectrum disorders (A. Fanous et al., 2001). In another study, elevated NS were observed in the non-psychotic relatives of individuals diagnosed with schizophrenia compared to individuals diagnosed with major depressive disorder (Tsuang, 1993). However,

other studies have reported evidence against etiological continuity between clinical and non-clinical NS (Craver & Pogue-Geile, 1999; Lataster et al., 2014), for example, by finding that NS were not elevated in the siblings of individuals diagnosed with schizophrenia compared to controls (Craver & Pogue-Geile, 1999).

Whilst the findings reported by Fanous et al. (2001), discussed above, are suggestive of familial continuity between clinical and non-clinical NS, the familial nature of the associations may reflect both environmental and genetic influences. Other studies that have leveraged individual-level genetic data have provided more specific evidence for genetic continuity. For example, at least two studies have reported associations between polygenic liability to schizophrenia and NS in the community (Jones et al., 2016; Pain et al., 2018).

There is also evidence to suggest that some of the same proxy environmental risk factors, or correlates, that are associated with clinical NS are found for NS reported in the community. For example, a large-scale study found that male sex, low level of education, and single marital status predicted an increased odds of NS in young people (Dominguez et al., 2010) – reflecting similar associations found for clinical NS (Leung & Chue, 2003; Mäkinen et al., 2010; Schultz et al., 1997). Of note, the finding of higher levels of NS in males than in females has been found in several community samples (e.g., Barragan et al., 2011; Maric et al., 2003; Ronald et al., 2014), and in a meta-analysis of clinical NS (Leung & Chue, 2003).

1.2.5 – Negative symptoms as a marker for later poor outcomes

As was discussed in Section 1.2.1, a wealth of evidence suggests that NS in clinical samples are predictive of poor clinical and functional outcomes. Similar associations have been found in individuals at clinical high risk for psychosis (Carrión et al., 2016; Corcoran et al., 2011). Whilst studies that have investigated the longitudinal outcomes of NS in the community are limited, the findings of these studies suggest that non-clinical NS appear to

represent a marker for later psychiatric outcomes. For example, in a population-cohort sample, NS reported at age 15-16 predicted later hospitalisation for a first episode of psychosis, with 94% of these hospitalised individuals having reported NS at baseline (Maki et al., 2008). In another longitudinal study, the presence of NS at age 25-34 was predictive of both schizophrenia and non-psychotic disorders 25 years later, though prediction of schizophrenia was contingent on the presence of frequent PEs (Werbeloff et al., 2015). A similar pattern of findings was reported in a study of NS measured at multiple time points, with persistent NS predicting PEs; and these symptoms jointly predicting later (researcher-defined) psychotic impairment (Dominguez et al., 2010). The findings from the Dominguez et al. (2010) study are discussed in more detail in the context of persistence in Section 1.5.2.

1.3 – Multidimensionality of psychotic experiences and negative symptoms

This Section will outline findings suggesting that PENS show a multidimensional structure when assessed together. It will be discussed that PEs, and NS may show further multidimensionality when assessed separately to each other, and that the findings are in line with those in clinical samples. The value of testing for multidimensionality and the importance of taking a multidimensional approach to both measuring and analysing PENS will be discussed.

1.3.1 – Dimensions of psychotic experiences and negative symptoms

Despite the close *diagnostic* relationship between positive psychotic symptoms and NS in schizophrenia (Section 1.1.1), psychometric associations between these symptoms appear to be modest (Andreasen et al., 1995). This is found similarly for PEs and NS reported in the community. For example, in the development study of the Specific Psychotic Experiences Questionnaire (SPEQ; Ronald et al., 2014), correlations of r = .13-.24 between

self-rated scales of paranoia, hallucinations, and cognitive disorganisation, with parent-reported NS were reported. Whilst the low levels of association may have been partly be explained by the different raters across the measures, similarly low correlations were reported for self-reported anhedonia with (self-reported) PEs, and the only significant yet modest association that was observed was between anhedonia and paranoia (r = .06).

Similarly, when the variance and covariance amongst PENS has been analysed, PEs and NS have been found to load onto separate factors/components (for factor analysis/principal components analysis (PCA), respectively). In factor analysis, within a latent variable modelling framework, this separation can be understood simplistically such that the observed scores of items of PEs share more variance amongst themselves than they do with the observed scores of NS items – because of an underlying (latent) factor reflecting positive psychotic experiences. Similarly, the observed scores of NS items share more variance amongst themselves than they do with the observed scores of items of PEs because of an underlying latent factor reflecting negative symptoms.

Separability between PEs and NS, as well as depressive symptoms, was demonstrated in the development of the Community Assessment of Psychic Experiences scale (CAPE; Stefanis et al., 2002). In this study, data were collected on PEs, NS, and depressive symptoms in a community sample of young men. Confirmatory factor analysis (CFA) was used to analyse the variance-covariance structure of these experiences and symptoms, and it was found that a 3-factor model (of PEs, NS, and depressive symptoms) was the best fitting model, compared to a 1-factor model and a 2-factor model. This was an important finding, because empirical support for the 2-factor model would have suggested that NS and depressive symptoms could be condensed to one factor, and similarly, support for the 1-factor model would have suggested no separability between PENS or depressive symptoms.

Similar granularity was reported for PENS analysed simultaneously using PCA. In a community sample of adolescents, a 6-component solution reflecting (self-reported) paranoia, hallucinations, cognitive disorganisation, grandiosity, and anhedonia, and parent-reported NS was found using the SPEQ (Ronald et al., 2014): These findings suggest psychometric separability not only between PEs and NS, but also between specific PEs – which is the topic of discussion for the following Section (1.3.2).

Importantly, the findings discussed in the current Section that suggest psychometric separability between PEs and NS in the community broadly reflect the findings from clinical samples – adding support to continuum models of psychotic phenomena (Sections 1.1.3 and 1.2.3). Many clinical studies have also reported separability with depressive symptoms and disorganised symptoms (Peralta et al., 1992; Peralta & Cuesta, 2001; Thompson & Meltzer, 1993; Tonna et al., 2019), often depending on the measures and methods used (Peralta & Cuesta, 2001).

1.3.2 – Dimensions of psychotic experiences

Studies that have investigated the latent structure of PEs in isolation have reported structural granularity beyond the distinction between PEs and NS (i.e., as above, Section 1.3.1). Whilst the exact configural structure of PEs differs between studies, most have reported a distinction between non-perceptual (paranoid/delusional) and perceptual (hallucinatory) experiences. For example, Stefanis et al. (2004) reported a 4-factor solution of the CAPE positive subscale, reflecting subdimensions of paranoia, first-rank (delusional) symptoms, hallucinations, and grandiosity, in a sample of 19-year-olds. In a sample of adolescents, four factors were also identified using the CAPE positive subscale (Yung et al., 2009): similar, though not identical, item-to-factor configurations were found to the Stefanis et al. (2004) findings – with the factors defined as reflecting magical thinking, persecutory

ideas, bizarre experiences, and perceptual abnormalities. These findings of multidimensionality *within* positive PEs in the community echo clinical findings of positive psychotic symptoms, at different stages of psychosis (e.g., Azis et al., 2021; Peralta & Cuesta, 1998).

Throughout, this Thesis focusses on the separable dimensions of paranoia and hallucinations, and NS. Multidimensionality *within* NS will further be considered in Chapter 6 because of the potential importance of this approach for the study of NS across a spectrum of severity (discussed in the following Section, 1.3.3). Of note, paranoia and hallucinations have also been found to show further multidimensionality when they are analysed individually (e.g., Bebbington et al., 2013; Freeman et al., 2005; Mitchell et al., 2017; Preti et al., 2014), though this will not be a focus of the current Thesis.

1.3.3 – Dimensions of negative symptoms

This Section will outline a brief historical overview regarding the structure of NS in schizophrenia spectrum disorders. It will outline findings that suggest a multidimensional structure of NS (Haguiara et al., 2021), and it will link these findings to investigations into the multidimensionality of NS in the community. There has been recent, renewed interest in establishing the best psychometric representation of clinical NS (Strauss, Ahmed, et al., 2019). This may be understood in the context that no effective treatments have been established for idiopathic NS (as discussed in Section 1.2.1), and in the context that therapeutic approaches have been designed according to the psychometric structure believed to represent these symptoms (Marder & Kirkpatrick, 2014). Targeted interventions for NS have historically, primarily, been based on unidimensional or 2-factor conceptualisations.

As has been discussed elsewhere, this focus is likely to have stemmed from the results of early exploratory factor analysis (EFA) of clinical NS (Strauss, Ahmed, et al., 2019).

Briefly, EFA is a data-driven method, used to extract an underlying, latent factor structure (though it can also be used solely as a data reduction technique). In contrast, CFA is a theory-driven method, used to specify a latent structure *a priori* to assess both standalone model fit, and to compare this fit with other specified models. Studies that employed EFA to analyse positive psychotic symptoms and NS jointly, yielded solutions showing separate positive and negative (as well as 'disorganised') factors (Andreasen et al., 1995; Arndt et al., 1991; Grube et al., 1998). As commented by Strauss et al., this joint analysis of positive and negative symptoms, "causes negative symptom items to artificially aggregate together, making the construct arbitrarily seem unidimensional" (Strauss et al., 2019, p.725). Competing models were not tested using a confirmatory framework, and so a unidimensional conceptualisation of NS was upheld until studies of NS in isolation were conducted.

Studies that looked at NS in isolation tended to yield 2-factor solutions, broadly reflecting deficits in expressivity, and in motivation and pleasure (e.g., Kelley et al., 1999; Kimhy et al., 2006; Kring et al., 2013; Nakaya & Ohmori, 2008): These collective findings made an impact in steering therapeutic research away from a unidimensional conceptualisation of NS, and towards searching for therapeutic targets concerned with the two deficit dimensions of expressivity and motivation-pleasure. Further, these dimensions were embedded in the descriptive criteria for schizophrenia in the DSM-5, which refers to NS as, "i.e., diminished emotional expression or avolition" (p.99, American Psychiatric Association, 2013).

The two dimensions of expressivity and motivation-pleasure appear to show some correspondence to current understandings of the neurobiology of NS (Galderisi et al., 2018). Nonetheless, the conceptualisation of a two dimensional structure and the description of NS in the DSM-5 have been empirically challenged, through the use of CFA (and network analysis, in Strauss, Esfahlani, et al., 2019), and by using measurement scales reflecting the

current conceptualisation of NS – encompassing the five subdomains of flat affect, alogia, avolition, anhedonia, and asociality (Kirkpatrick et al., 2006).

Recent studies have compared the model fit of 1-factor, 2-factor, 5-factor, and 5-factor hierarchical models (reflecting the five subdomains, and the two domains of expressivity and motivation-pleasure as higher order factors). These studies have consistently found a lack of empirical support for the unidimensional and 2-factor models and have found consistent support for the 5-factor and 5-factor hierarchical models: this has been found across different languages and cultures (China, USA, Italy, Spain, Switzerland; Ahmed et al., 2019), across rating scales (Brief Negative Symptom Scale, Scale for the Assessment of Negative symptoms, Clinical Assessment Interview for Negative Symptoms; Strauss et al., 2018), and at different stages of psychotic illness (clinical-high-risk, early psychosis, chronic schizophrenia; Chang et al., 2020; Strauss et al., 2018). Critically, these findings call into question not only the description of NS in the DSM-5, but arguably most importantly, the way in which targeted intervention research is conducted (Strauss, Ahmed, et al., 2019).

In the community, a handful of studies have used exploratory methods to analyse NS in isolation. These studies reported a multifactorial (3-factor) structure of NS measured in adolescents (Barragan et al., 2011) and in individuals aged 12-35 (Ziermans, 2013) using the negative subscale of the CAPE. Prior to the study that is presented in Chapter 6 of this thesis (published as Havers et al., 2022), only one study that used CFA to analyse NS in isolation (and none on negative schizotypy in isolation) had been published: This study (Rodríguez-Testal et al., 2019) did not specify a model reflecting the two NS dimensions of expressivity and motivation-pleasure as described in the DSM-5, so it was unable to directly test the appropriateness of the DSM-5 conceptualisation of NS in the community. Nonetheless, lack of empirical support was found for the unidimensional model, and for a 2-factor model (with one factor reflecting alogia, avolition, anhedonia, and asociality, and the other factor

reflecting flat affect). A hierarchical model that reflected the five subdomains of flat affect, alogia, avolition, anhedonia, and asociality, and total NS as a higher order factor, was found to best fit the data (Rodríguez-Testal et al., 2019). Importantly, like with the previously described clinical studies, these findings suggest granularity of NS beyond either one or two dimensions.

1.3.4 – Importance of a multidimensional approach

There are three pertinent points to consider from the prior Sections, 1.3.1-1.3.3. Respectively, first – PEs and NS are psychometrically related, though distinct, constructs. Second, PEs show a multifactorial structure, with evidence suggesting that paranoia and hallucinations are psychometrically separable constructs. Third, NS show a multifactorial structure, with evidence suggesting that up to five subdomains underlie the NS construct. The relative of importance of investigating PENS through a multidimensional lens may be judged by considering the extent to which a multidimensional approach adds to our understanding beyond using aggregated measures, which in turn may advance more effective interventions (discussed later in this Section). A starting point in such a dialogue is whether there are findings that validate the psychometric separability of PENS.

Findings that appear to validate the psychometric separability of PEs are discussed in the following paragraphs: Much less has been documented regarding the validity of the NS subdomains, which is in part the rationale for the study conducted in Chapter 6 of this Thesis.

In a twin study of 16-year-olds in the community (Zavos et al., 2014), genetic overlap between paranoia and hallucinations was high ($rA = .61$). This suggests substantial overlap in genetic influences between the two dimensions. However, the genetic correlation statistic also reflects that some of the genetic influences contributing to the variance in paranoia are distinct from the genetic influences contributing to the variance in hallucinations. Similarly,

the non-shared environmental correlation that was estimated (*r*E = .33) reflects that most of the non-shared environmental influences contributing to (the variance in) paranoia are distinct from those contributing to hallucinations (though it is noted that non-shared environmental influences also include measurement error).

Several other studies have found distinct associations between specific PENS and specific proxy environmental exposures (e.g., Bentall et al., 2012; Cosgrave et al., 2021; Shakoor, McGuire, et al., 2015a), other measures of psychopathology (e.g., Armando et al., 2010; Ronald et al., 2014; Wigman, Vollebergh, et al., 2011; Yung et al., 2009), and sleep disturbances (Sheaves et al., 2016). One area of the literature that demonstrates the potential importance of a multidimensional approach to PENS is the study of childhood trauma and later psychotic outcomes (Varese et al., 2012). An interesting picture has emerged by considering not only specific PEs, but also by considering specific types of childhood trauma. For example, cumulative findings suggest specificity between chronic victimisation in childhood and later paranoia, and between sexual abuse in childhood and later hallucinations – both in general population samples (Bentall et al., 2012; Janssen et al., 2003; Shevlin et al., 2007), and in clinical samples (Read et al., 2003; Sheffield et al., 2013; Valmaggia et al., 2015). Importantly, an understanding of the pathways from specific traumatic experiences to specific psychotic experiences may be used to enhance cognitive models of psychotic phenomena (Bentall et al., 2014).

An exemplary, dimension-specific, theoretical model developed by Freeman and colleagues conceptualises persecutory delusions as 'threat beliefs', formed and maintained via a series of specific interacting and cascading cognitive processes (Freeman et al., 2002; Freeman, 2007; discussed in Section 1.3.2). By translating the model into tractable cognitive interventions, a reduction in symptoms (delusions) has been found in clinical samples (Freeman et al., 2016, 2021).

The results discussed in this Section highlight the value of measuring and analysing PENS through a multidimensional lens. Further, having an understanding of the most probable outcomes associated with *specific* PENS may make it easier to identify when individuals are more likely to be 'at risk' for poor outcomes, or whether they are more likely to be expressing more typical behavioural variation (e.g., Yung et al., 2007, 2009). Most importantly, perhaps, by better understanding specific pathways to and from specific PEs, the frequency and intensity of psychotic symptoms and experiences may be amenable to reduction by focussing on the cognitive mechanisms that are theorised to give rise to them (Brown et al., 2019), thus reducing distress, improving wellbeing, and facilitating better outcomes (e.g., Freeman et al., 2016, 2021).

1.4 – Psychotic experiences and negative symptoms across the lifespan

This Section will summarise findings from studies of PENS that have estimated prevalence rates in childhood, adolescence, and adulthood. It will highlight that adolescence and emerging adulthood may be a particularly important time window for studying PENS. The limitations of cross-sectional research will be discussed in the context of comparing prevalence rates across the lifespan.

1.4.1 – Prevalence rates in childhood, adolescent, and adult samples

As outlined in Sections 1.1.2 and 1.2.2, an extensive body of research converges to suggest that PENS are common in the general population. Section 1.4.1 considers prevalence rates of PENS that have been reported across studies or derived through meta-analysis.

PEs have been reported in childhood as young as 9 years (e.g., Laurens et al., 2012), in adolescence (e.g., Ronald et al., 2014; Wigman, Vollebergh, et al., 2011), and in adulthood (e.g., McGrath et al., 2015). Taken collectively, the results from two meta-analyses appear to

suggest that PEs become less prevalent as age increases. For instance, in childhood and adolescence, the median prevalence rate was estimated at 17% for 9-12 year olds and 7% for 13-18-year olds (Kelleher, Connor, et al., 2012) and in studies mainly comprised of adult samples, the median prevalence rate was estimated as 5.3% (van Os et al., 2009). A more conservative and updated review of the one conducted in 2009 (van Os et al., 2009) estimated the median prevalence rate as 7.2% (Linscott & van Os, 2013) – perhaps rendering the notion of 'decreasing prevalence with increasing age' less clear-cut beyond childhood and adolescence.

In a more recent meta-analysis of hallucinations in isolation, however, whilst the estimated prevalence rates did not differ between childhood (12.7%) and adolescence (12.4%), lower prevalences were found in adulthood (5.8%) and in late-adulthood (4.5%) compared to in childhood/adolescence (Maijer et al., 2018). Building on the limitations of comparing prevalence rates across studies, and also looking at hallucinations as a separate dimension – one recent study combined the results obtained from multiple cross-sectional assessments and found an age-related decrease in the prevalence of hallucinations assessed using the same measure for all assessments (Yates et al., 2021). The minimum age of the study was 16, so the findings cannot speak to the different results previously reported between childhood and adolescence (i.e., Kelleher, Connor, et al., 2012; Maijer et al., 2018) – but significant age-related decline in prevalence was estimated across the entire range of ages (categorised as 16-19, and up to 70 and above) (Yates et al., 2021).

To date, there have been no meta-analyses or reviews of NS in the population, though it could be inferred from data available from across different studies that NS become less prevalent with increasing age. For example, in one study of 13-17-year-olds (M = 13.4 years, SD = 0.59), 98% of the sample endorsed at least one self-reported NS item (Barragan et al., 2011). In another study of older adolescents (M = 16.32 years, SD = 0.68) individual

anhedonia items were reported by up to 37.6% of the sample, and NS items were parent-reported for up to 33.1% (Ronald et al., 2014). In young adulthood, reported prevalence rates range between 9.9% and 38.8% (Alemany et al., 2013; Dominguez et al., 2010; Werbeloff et al., 2015; Wigman et al., 2012), and in a study of older adults (*M* = 41.1 years, *SD* = 12.0), prevalence was estimated at 1.1% (Maric, Krabbendam, Vollebergh, de Graaf, & van Os, 2003).

1.4.2 – Adolescence and emerging adulthood as a critical period

Adolescence (the period spanning approximately 12-18-years of age) and emerging adulthood (spanning approximately 18-25-years of age) may be considered particularly important windows for studying PENS, for several reasons. First, findings suggest that PEs are more predictive of clinical outcomes in adolescence compared to in childhood (Kelleher, Keeley, et al., 2012). Second, it has been estimated that approximately three quarters of adult psychiatric diagnoses are present by the age of 18 (Kim-Cohen et al., 2003), and in another study, by the age of 25 (Kessler et al., 2007). Third, the typical age of onset for psychotic disorders is estimated to be in the early twenties (Kessler et al., 2007). Collectively, these findings highlight that better understanding PENS as they present and develop during adolescence and emerging adulthood may facilitate efforts to prevent the manifestation of poor outcomes associated with PENS, which may be achieved through theory development and translation into early intervention strategies (Trotman et al., 2013; Verdoux et al., 1998).

1.4.3 – Inferring change across the lifespan

For NS, the limited findings (Section 1.4.1) make age-related change difficult to infer. Further, whilst a general trend for decline with increasing age is *suggested* for PEs (Section 1.4.1), there is considerable variability in prevalence rates across studies. Variation in

measurement tools (e.g., dimensional versus categorical endorsement, range of dimensions and number of items assessed), methods of assessment (e.g., self-report, interview), and reporting prevalence (e.g., any item endorsed, individual items endorsed) further make it hard to determine whether the reporting of PENS varies as a function of age, or as a function of methodological factors. For example, more thorough measures tend to yield higher rates of prevalence compared to brief measures, and interview-assessment tends to yield lower estimates than self- report (Healy et al., 2019; Johns & van Os, 2001; van Os et al., 2009). These limitations are the point of departure for discussing the importance and advantages of using longitudinally collected data on PENS to infer change across the lifespan.

1.5 – Longitudinal development of psychotic experiences and negative symptoms

This Section will highlight the value of delineating the longitudinal development of PENS using repeated measures. It will outline findings suggesting that persistence over time is a particular risk factor, or marker, for later poor outcomes, which will be discussed in the context of a proneness-persistence-impairment model of psychosis. Methodological considerations for analysing change over time will be outlined, and a summary of factors that have been found to be associated with the development of PENS will be provided.

1.5.1 – Repeated measures of psychotic experiences and negative symptoms

Further to the cross-sectional measurement of PENS (Section 1.4.1), other studies have reported on PENS measured *repeatedly* over time in the same sample. These studies strengthen our ability to infer change over time, building on the previously discussed limitations of drawing inference by considering prevalence rates from across different studies. One study that measured PEs repeatedly across a period of eight years in a sample of

14-17-year-olds at baseline reported mean-level decline in PEs with increasing age (Dominguez et al., 2011).

The study discussed above (Dominguez et al., 2011) analysed PEs at an aggregate level, potentially masking dimension-specific variation (as discussed in Section 1.3.1). However, studies that have analysed repeated measures of delusions/paranoia and hallucinations separately have reported similar patterns of decline over time. For example, in a sample of 14-24-year-olds at baseline, the prevalence of delusions was estimated at approximately 21%, 2.5 years after baseline, and 11%, 8.5 years after baseline, and the prevalence of hallucinations was estimated at approximately 5% and 3% at these intervals, respectively (Smeets et al., 2012). Similar findings were reported in a study of 13/14-year-olds at baseline, with a decrease in the prevalence of delusions and hallucinations reported approximately two years after baseline (De Loore et al., 2011). Another study reported item-level prevalence rates for repeated assessments of 'paranoid ideation' and 'psychoticism', measured longitudinally across ages 20-40 (Rössler et al., 2007): most items showed a decline in prevalence with increasing age, with several exceptions for items that are not typically included in measures of PEs (e.g., *"Others not giving you proper credit", "Feeling that people take advantage of you"*).

In terms of NS, only three studies to my knowledge have reported on NS measured repeatedly over time in non-clinical samples (Dominguez et al., 2010; Janssens et al., 2016; Smeets et al., 2012). Findings from one of these studies (Dominguez et al., 2010) showed a general *increase* in the prevalence of NS with increasing age from 11% at baseline (age 14-24) to 12%, 8.5 years after baseline. The Smeets et al. (2012) study was based on the same sample as Dominguez et al. (2010). Similarly, prevalences/means were not reported in the Janssens at el. (2016) study.

Despite the use of repeated measures to estimate the prevalence of NS reported at multiple ages in the Dominguez et al. (2010) cohort study, there are limitations to these findings: At the first time point (age 14-24) and the third time point (approximately 8.5 years after baseline), NS were measured using one item reflecting NS and one item reflecting disorganised symptoms (age 14-24). At time point two (approximately 2.5 years after baseline), an additional five items were used to measure NS. This inconsistency of measurement interferes with the inference of change over time. In addition to the different measures and differing number of items that were used, the 7-item Likert response scale of the measures was re-coded for the purpose of analysis to reflect a dichotomous presence versus absence, thus potentially masking important variation in terms of symptom severity.

1.5.2 – Persistence of psychotic experiences and negative symptoms

Findings from studies of PENS measured repeatedly across development indicate that persistence compared to remittance or transience may be particularly predictive of poor clinical and functional outcomes (e.g., De Loore et al., 2011; Dominguez et al., 2010; Mackie et al., 2011; Wigman, van Winkel, Raaijmakers, et al., 2011). For example, in a study of 14-17-year-olds at baseline, persistence of (self-reported) PEs was associated with increased odds for (researcher-rated) psychotic impairment at the end of the study period. The odds of this association increased in a dose-response manner, with odds ratios of 1.5, 5, and 9.9 for presence of PEs at one, two, and three time points, respectively (Dominguez et al., 2011). Evidence for a dose-response relationship between the persistence of self-reported PEs and (researcher-rated) psychotic outcomes was also found through meta-analysis (Kaymaz et al., 2012). These findings suggest that persistence appears to be an important modifying factor for poor outcomes when PEs are measured and or analysed at an aggregate level. There is also evidence to suggest that persistence of specific PEs dimensions may be associated with

specific poor outcomes. For example, persistence of self-reported auditory hallucinations, but not other types of PEs, was found to be associated with increased odds for suicide attempts and non-suicidal self-injury in a sample of 12-17-year-olds at baseline (Hielscher et al., 2021).

Of the studies that have analysed repeated measures of NS (Section 1.5.1), persistence has been found to be an indicator of poor outcomes. For example, the previously discussed cohort study of 14-24-year olds followed for 10 years found that persistence of NS predicted presence and persistence of PEs, in-turn conferring increased risk for psychotic impairment, compared to persistence of PEs alone (Dominguez et al., 2010). In another study that measured NS twice over a period of three years in adulthood, persistence was associated with distress and functional impairment, both for individuals with high genetic risk for schizophrenia and for controls (Janssens et al., 2016).

The methodological and analytic limitations of some of these studies will provide a platform for the aims of this Thesis (Sections 1.6 and 1.7). The findings discussed in the current Section highlight not only the importance of measuring PENS across multiple time points, but further suggest that investigating the development of PEs as separate dimensions may contribute even more to unravelling the pathways and mechanisms associated with poor outcomes (De Loore et al., 2011).

1.5.3 – Proneness-persistence-impairment model

This Section will outline the proneness-persistence-impairment model of psychosis (Linscott & van Os, 2013; van Os et al., 2009), which augments the continuum model of psychosis (Section 1.1.3). As was discussed in Sections 1.1.3 and 1.1.5, despite being associated with concurrent distress and other psychopathology for *some* individuals (e.g., Ronald et al., 2014), PEs are typically transient (Linscott & van Os, 2013) and are not

associated with later poor outcomes for most individuals (e.g., Poulton et al., 2000; Section 1.1.5). Nonetheless, PEs *do* represent a marker for later impairment, and risk increases with persistence (and severity) of these experiences (Section 1.5.2): One prevailing theoretical model delineates the pathway from proneness to persistence of PEs and thus to associated impairment, via genetic and environmental load. Different components of the proneness-persistence-impairment model (Linscott & van Os, 2013; van Os et al., 2009) are supported by the findings of several different studies, as discussed below.

For example, one study that investigated the stage from proneness to persistence using two separate cohorts (14-24-year-olds and 18-64-year-olds), found not only that PEs at baseline were associated with PEs approximately 3 years later, but also that the probability of persistence was progressively stronger in individuals who (at baseline) reported cannabis use and trauma and who resided in an urban location, compared to individuals reporting an absence of these environmental exposures (Cougnard et al., 2007). The Dominguez et al. (2011) study that was outlined Section 1.5.2, provides support for the persistence to impairment stage of the proneness-persistence-impairment model, by showing a dose-response association between persistence of PEs and increased odds for psychotic impairment.

These two studies, above, conceptualised the *reporting of PEs* as reflecting 'proneness'. Other studies have used proxies of genetic risk for schizophrenia to infer proneness. One study that used sibling history of psychosis as a proxy for genetic risk found that higher genetic risk was associated with persistence of PEs, as well as persistence of NS, measured twice over three years in adulthood (Janssens et al., 2016). This persistence was in turn associated with impairment. Interestingly, it was found that the association between genetic risk and persistence remained significant for NS when controlling for PEs, but not the

other way around. As suggested by the authors, this could suggest that genetic risk for psychosis is particularly relevant in the context of the developmental course of NS.

The Dominguez et al. (2010) study (discussed in Sections 1.5.1 and 1.5.2) that measured NS as well as PEs at multiple time points found that persistence of NS predicted presence and persistence of PEs, in-turn conferring increased risk for psychotic impairment, compared to persistence of PEs alone: The findings of this study are included in the current Section because the theoretical model that was suggested by the authors is in accord with the proneness-persistence-impairment model. That is, Dominguez et al. (2010) postulated that NS reflect a broad genetic vulnerability to developmental impairment, which, when combined with environmental risk factors (i.e., cannabis use, trauma, urbanicity), predicts PEs and risk of clinical impairment.

1.5.4 – Genetic influences on the development of psychotic experiences and negative symptoms

Whilst there are a considerable number of studies that have investigated the influence of genetic factors on PENS reported at single time points (e.g., Jones et al., 2016; Pain et al., 2018; Selzam et al., 2019; Sieradzka et al., 2015), little has been documented regarding genetic influences on the persistence of PENS. However, findings from a handful of community twin studies suggest that genetic factors play a role in the development of PEs measured broadly in in adulthood (Wigman, van Winkel, Jacobs, et al., 2011), and of separate PEs and NS measured in adolescence (Havers et al., 2019). For example, in the Twins Early Development Study (TEDS) sample, a substantial proportion of the covariance in PEs (38-46%) and NS (54-62%) measured at two time points in mid-late adolescence was attributable to genetic factors (Havers et al., 2019). Another study reported that ~ 80% of the covariance in a latent schizotypy factor identified early (11-13-years) and later (14-16-years)

in adolescence was accounted for by genetic factors (Ericson et al., 2011). The importance of genetic factors in the persistence of PENS was also suggested by the results of a family study that used sibling history of psychosis as a proxy for genetic risk (Janssens et al., 2016): This study found that persistence of both PEs and NS was more likely in individuals at genetic risk of psychosis, compared to control subjects.

Only one study to my knowledge has leveraged individual-level genetic data to investigate the association between polygenic liability to schizophrenia and the development of PEs, in which a null association between schizophrenia GPS and the persistence of aggregated PEs was found (Rammos et al., 2021). Of note, these findings do not indicate that genetic factors do not play a role in the persistence of PEs, but rather they can be understood such that the aggregated effects of the measured common genetic variants that are associated with schizophrenia were not associated with the persistence of PEs in the study. Because PENS may reflect broad vulnerability for poor functional and clinical outcomes (Healy et al., 2019; van Os & Reininghaus, 2016; Yung et al., 2009), as discussed in Section 1.1.5, the extent to which the development of PENS dimensions is associated with polygenic liability across a *range* of phenotypes, including psychiatric disorders, clinical help-seeking, intelligence and educational attainment, is of further interest.

1.5.5 – Analysing change over time – methodological considerations

As was discussed in Section 1.5.1, repeated measures studies build on the limitations of cross-sectional studies of PENS to infer change over time. Studies that have repeatedly measured PENS over time have either used manual classification of observed data to specify trajectories of development, or they have used latent trajectory analysis to classify individuals according to similarities in their trajectories.

Studies that have used a manual classification approach have typically used presence versus absence (Cougnard et al., 2007; De Loore et al., 2011; Dhossche, Ferdinand, Ende, et al., 2002; Hielscher et al., 2021; Steenkamp et al., 2021; van Rossum et al., 2011) or a cut-off score (Dominguez et al., 2011; Havers et al., 2019; Janssens et al., 2016) to classify PENS as persistent or transient. The results from these studies that have used manual classification have made an important contribution to our understanding of PENS. For example, the continuum model and the proneness-persistence-impairment model are largely supported by the results of studies that have used observer-classified (i.e., non-latent) trajectories. Whilst these findings are unquestionably valuable, considering the points outlined in the following paragraph, findings from studies that have used latent trajectory modelling should be used, at the very least to triangulate these findings, and further hold potential for offering additional insights into the development of PENS.

A fundamental assumption of the latent growth modelling framework, broadly, is that an underlying, unobservable (latent) growth process gives rise to the repeated measures that are observed: because this latent growth process is statistically separable to random measurement error associated with static observations, the latent growth framework builds on the manual classification approach described above, which *only* uses the observed static observations to infer trajectories of change over time (Willett & Sayer, 1994). Latent growth can be estimated at a sample-wide level, as well as for a specified number of latent classes or subgroups that are characterised by distinct growth profiles (Herle et al., 2020). There are several advantages to using latent variable modelling to investigate trajectories of change compared to using manual classification – three of which are highlighted here. First, latent trajectory modelling facilitates a data-driven estimation of latent trajectory profiles. This contrasts the often arbitrary, researcher-led decisions regarding classification, and thus removes the reliance on researcher-imposed expectations and constraints regarding

development (though importantly, Chapter 4 will discuss how similar issues are a *potential* threat to the application of growth mixture models). Second, latent trajectory modelling can be used to formally test competing models that specify a different number of latent trajectory classes. Third, manual classification approaches are reliant on complete data (though Rammos et al., 2021 recently used imputation with missing data). In contrast, latent trajectory modelling can be conducted using full information maximum likelihood (FIML) estimation, which accommodates missing data and allows for data from all observations to contribute to the estimation of the model.

Of the studies that have used latent trajectory modelling, multiple latent trajectory classes including a persistent or increasing class have been identified for aggregated PEs measured across adolescence (Bourque et al., 2017; Lin et al., 2011; Mackie et al., 2011, 2013; Thapar et al., 2012; Wigman, van Winkel, Raaijmakers, et al., 2011), and adulthood (Wigman, van Winkel, Jacobs, et al., 2011). There are currently no published latent trajectory findings for paranoia/hallucinations separately, or for NS reported in the community.

Notwithstanding the inherent methodological advantages that latent variable modelling confers (as discussed in paragraph 3, above), it cannot be inferred from previous studies, above (nor from any of the other studies cited in this Chapter) whether the change in PEs over time that has been inferred reflects change at the *construct* level, or whether this change merely reflects recalibration at the measurement level. For instance, it is plausible that an item such as, *"Have you ever believed that you were being sent special messages through the television?"* (Laurens et al., 2007) could be measuring something markedly different in childhood compared to in adulthood. The ability to infer construct-level change over time is testable via an analysis of measurement invariance, which is the focus of Chapter 2.

1.6 – Summary, and future directions for research on psychotic experiences and negative symptoms

This Chapter outlined previous research that has shown that the symptoms that characterise psychotic disorders are also commonly reported in non-clinical populations in the community, and that these PENS show a multidimensional psychometric structure. The Chapter highlighted the importance of understanding PENS as separate dimensions, and the importance of understanding the development of PENS over time. Adolescence and emerging adulthood was described as a 'critical period' in the study of PENS.

Whilst a wealth of studies have found that PENS are associated with poor clinical outcomes, particularly when they persist, many of these studies have reported on aggregated PEs, rather than PEs analysed as separate dimensions. The development of separate dimensions has been investigated in a limited number of studies, however, the measures used have tended to be comprised of only a few items (with a few exceptions), potentially masking information that may be ascertained from probing a broader range of experiences. Furthermore, many longitudinal studies have manually classified individuals into trajectory groups, often, though not always, based simply on the presence or absence of PEs at each time point. Studies that have used latent variable modelling to explore the developmental trajectories of PEs have identified a 'persistent' class of individuals, though this has been for aggregated PEs, and no studies have investigated the latent developmental trajectories of NS in the community. Genetic continuity between psychotic disorders and the development of PENS has been suggested by the results of one family study (Janssens et al., 2016). However, another study that incorporated individual-level genetic data did not find evidence of genetic continuity between polygenic liability to schizophrenia and the persistence of PEs (Rammos et al., 2021).

Building on this foundation of previous research findings, future research should seek to delineate the development of separate PENS dimensions that capture a broad range of experiences, as well as variation in terms of frequency and or strength of these experiences. Latent variable modelling should be used to facilitate the use of data from individuals with incomplete as well as complete data, and to estimate sample-wide averages/variances for PENS dimensions, as well as investigate whether distinct trajectory subgroups can be identified: Ascertainment of the extent to which age-related change in PENS dimensions reflects 'true' change will be important for further interpreting these findings.

Moreover, this Chapter highlighted that there is a paucity of research into NS in the community in general. The extent to which the psychometric structure of non-clinical NS mirrors that of clinical NS is uncertain, which, in the context of the current clinical focus on NS – may be considered a research priority. As a starting point in moving this area of research forward, the latent structure of NS in the community should be investigated: measurement models that have been hypothesised to underlie the construct of NS should be tested, using scales that measure a broad range of behaviours and that further reflect the current conceptualisation of NS in schizophrenia. An augmentation of these findings would be to explore the extent to which genetic liability scores are associated with the identified subdomains.

1.7 – Aims of thesis

The points that were outlined in Section 1.6 (above) highlight what is needed to move research on PENS forward. Motivated by these points, this Thesis aimed broadly, first, to investigate the measurement invariance/noninvariance of paranoia, hallucinations, and NS, as separate dimensions across adolescence/emerging adulthood (Chapter 2). Second and third, it aimed to investigate the latent development of paranoia, hallucinations, and NS, separately,

across adolescence/emerging adulthood (Chapter 3), and to explore whether distinct latent trajectory groups underlie this development (Chapter 4). Fourth, explore whether membership in the latent trajectory groups shows associations with behaviours/characteristics previously found to be associated with persistence of aggregated PEs, and with polygenic liability for a range of outcomes (Chapter 5). Fifth, it aimed to investigate the structure of NS in the community and associations between the identified subdomains and polygenic liability scores (Chapter 6). Each of these aims will be expanded and addressed in the empirical Chapters that follow.

Chapter 2 – Longitudinal measurement invariance analysis of paranoia, hallucinations, and negative symptoms

2.1 – Introduction

The notion of measurement invariance was introduced briefly in Section 1.4.3. The current Section will describe the conceptual foundations of measurement invariance and will outline the existing findings on the measurement invariance of PENS.

Briefly, the concept of testing for measurement invariance can be understood such that, in comparing scores on a construct between different groups of individuals or across different time points, it is important to establish the extent to which measurement of the construct can ostensibly be considered invariant. In other words, to what extent do observed differences or changes in scores reflect 'true' differences or changes at the *construct* level, rather than at the level of the *measurement instrument*?

Before turning to findings of measurement invariance in PENS, it is first useful to consider some descriptive findings in the literature. For example, it has been shown in several studies that higher prevalence rates and average levels of PEs are found for females than males, and that higher prevalence rates and average levels of NS are found for males than females (e.g., Dominguez et al., 2010; Maric et al., 2003; Ronald et al., 2014). The extent to which these observed differences reflect 'true', or construct level differences is less researched. One study that, incidentally, reported no significant differences in PEs between females and males in a community sample, did however find measurement invariance of the instrument across sexes (using the Youth Psychosis At-Risk Questionnaire, brief version; Fonseca-Pedrero et al., 2016) – suggesting that the *measurement* of PEs was the same

between the groups. Other studies have reported varying degrees of invariance in the measurement of PEs between other 'groups' – for example, different cultures (e.g., Pignon et al., 2019; Vermeiden et al., 2019), self-identified gender categories, and ethnic minority/majority status (Lång et al., 2021).

As discussed in Section 1.5.1, results of previous longitudinal studies on PENS tend to suggest a decline in the prevalence rates/mean scores of PEs reported with increasing age, and there are mixed findings regarding NS (e.g., De Loore et al., 2011; Dhossche, Ferdinand, van der Ende, et al., 2002; Dominguez et al., 2010; Smeets et al., 2012). Several studies have further used latent trajectory modelling to identify multiple underlying subgroups of individuals, classified according to similarities in their latent trajectories of PEs reported over time, as is the topic of Chapter 4 (e.g., Thapar et al., 2012; Wigman, van Winkel, Jacobs, et al., 2011; Wigman, van Winkel, Raaijmakers, et al., 2011). All these studies that have harnessed data obtained at repeated measurement occasions provide valuable information about the developmental course of PENS, above and beyond what can be inferred from cross-sectional measurement (Section 1.4.3): nonetheless, the extent to which change occurred at the *construct* level cannot be inferred from these results.

The current Chapter aimed to investigate the extent to which the measurement of paranoia, hallucinations, and NS was invariant across ages 16, 17, and 22 in the TEDS sample. These analyses were conducted as a precursor for conducting subsequent latent growth modelling of the measures (Chapters 3 and 4). No specific hypotheses were made for paranoia and hallucinations. It was expected that a 5-factor measurement model of NS would be invariant across ages, based on recent findings for NS reported in clinical samples (Section 1.3.3).

2.2 – Methods

2.2.1 – Participants

All empirical Chapters in this Thesis conducted secondary analysis of data that was collected as part of the Twins Early Development Study (TEDS), described in Section 2.2.1.1, below. Ethical approval for secondary data analysis of the TEDS data was granted by the Birkbeck Psychology Department Ethics Committee (please note that the ethics request for secondary data analysis was classed as 'routine' and therefore was not assigned a reference number).

TEDS is a twin dataset, though none of the studies in this Thesis involved twin modelling analyses. It is explicitly stated whether the studies used data from only one (randomly selected) twin per pair, or where data from both twins per pair was used. In the latter case, the family unit was treated as a cluster variable and standard errors were adjusted for the nonindependence of observations.

An exclusion variable was precalculated by TEDS administrators and was used in all Chapters of this Thesis to exclude individuals if, i) their sex or zygosity was unknown, ii) they had a 'severe medical condition' that would impact on their ability to participate (this included severe cases of autism spectrum disorder), iii) they did not have any 1st contact study data, and or iv) they had experienced severe perinatal complications. Further details are listed on the TEDS data dictionary webpage https://www.teds.ac.uk/datadictionary/exclusions.htm

2.2.1.1 – Twins Early Development Study sample

TEDS is a longitudinal community sample, comprised of families that were recruited between 1995 and 1998. Ethical approval for the original TEDS protocol was granted by The Institute of Psychiatry, Psychology and Neuroscience ethics committee at Kings College, London (ref: 05/Q0706/228). Families with twins born between 1994 and 1996 in England

and Wales were identified and contacted by the Office for National Statistics (ONS) on behalf of TEDS and invited to participate. Sixteen thousand, eight hundred and ten (16,810) families responded to the ONS invitation and 16,302 were subsequently invited by TEDS to participate in the '1st contact' study. Reasons that families were not invited to participate in the 1st contact study (and subsequent studies) are detailed in Supplementary Table 2.1. Thirteen thousand, four hundred and eighty-eight (13,488) families returned data for the 1st contact study. Following the 1st contact study, families were invited to participate in subsequent studies as detailed on the TEDS data dictionary webpage https://www.teds.ac.uk/datadictionary/home.htm. See Rimfeld et al. (2019) for a recent overview of the TEDS sample.

The data that was used in this Thesis came primarily from data collections at ages 16 and 17 (as part of the Longitudinal Experiences and Perceptions (LEAP) study), and at age 22 (called the '21-year study' in TEDS). Contact of families and data returns for these studies are shown in Supplementary Table 2.1. Data for each of the studies was collected via questionnaire, either written or online (detailed below).

For the 16-year study, 10,874 families were contacted, and 5,123 (47.11%) families returned data. Families were invited to participate unless they, i) had previously withdrawn from TEDS, ii) could not be traced, iii) had not previously returned any data, and or iv) were identified as having severe medical conditions. Questionnaires were sent to each participating individual in a household, along with a letter, information sheet and consent form, via post, and were returned using a prepaid envelope. A reward in the form of a gift voucher and entry into a prize draw was offered for return of data (for individuals, not parents). Informed written consent was required for each family member returning data and was also required from parents of consenting individuals.

For the 17-year study, 1,773 families were contacted, and 1,475 families (83.19%) returned data. A subset of families who responded to the 16-year study were invited to take part in the 17-year study, which was conducted approximately 9 months after the 16-year study. Mailing, reward, and informed consent procedures were the same as for the 16-year study.

For the 22-year study, 10,451 parents were contacted, and 5,352 parents (51.21%) returned data. Eight thousand, six hundred and eleven (8,611) individuals were contacted, and 5,184 individuals (60.20%) returned data. Non-invitation was due to the same reasons as for the 16-year study, with the addition that if one or both individuals had withdrawn from TEDS, parents were not contacted. Invitation to participate in the 22-year study was made either by email or by post. Reward procedures were the same as for the 16-year study. Informed written consent was required for each family member returning data, though consent was not required from parents of consenting individuals.

2.2.1.2 – TEDS sample for current Chapter

For the study conducted in this Chapter, data from one (randomly selected) twin per pair was used for the main analyses. The cotwin data was used as a pseudo (non-independent) replication sample for the purpose of EFA (described in Section 2.2.3.2).

Individuals completed questions relating to paranoia and hallucinations at mean ages 16.32 years (*SD* 0.68; range 14.91-21.34), 17.06 years (*SD* 0.88; range 15.55-19.0), and 22.85 years (*SD* 0.88; range 21.16-25.19). Parents completed questions relating to their twins' NS at mean ages 16.32 years (*SD* 0.68; range 14.91-19.45), 17.06 years (*SD* 0.88; range 15.55-19.0), and 22.30 years (*SD* 0.93; range 20.56-25.59).

N for paranoia in the main subsample at ages 16, 17, and 22 were 4,943, 1,468, and 4,166, respectively. *N* for hallucinations at ages 16, 17, and 22 were 4,949, 1,471, and 4,164,

respectively. *N* for NS at ages 16, 17, and 22 were 4,971, 1,468, and 5,177, respectively (Table 2.1).

Note that the *N* reported above reflect the number of individuals with *total score data.* Deviations from these *N* in the current Chapter (and in subsequent Chapters) reflect the use of *item-level data* and the use of FIML estimation (Section 2.2.3.8).

2.2.2 – Measures

The SPEQ (Ronald et al., 2014) is a questionnaire that was designed to assess quantitative variation in a range of PEs and NS. Items were adapted from existing measures (detailed below) for use in an adolescent sample by clinical experts (Daniel Freeman, Alastair Cardno). In the development of the SPEQ in the TEDS sample, the subscales used in the current Thesis showed good test-retest reliability across ~ 9-months (r = .65-.68) and good item-scale reliability (α = .85-.93) (Ronald et al., 2014). Paranoia and hallucinations measured at age 16 were also assessed for their associations with positive psychotic experiences measured using the psychosis-like symptoms questionnaire (PLIKS-Q; Zammit et al., 2011) and showed moderate convergence (r = .48-.60) (Ronald et al., 2014).

Paranoia was measured by 15 items adapted from the Paranoia Checklist (Freeman et al., 2005). Individuals were asked how often they have thought, for example, *"I can detect coded messages about me in the press/TV/internet", and "People might be conspiring against me".* Ratings were on a 6-point scale ('not at all', 'rarely', 'once a month', 'once a week', 'several times a week', 'daily'). Paranoia items are listed in Supplementary Information 2.1.

Hallucinations were measured by nine items adapted from the Cardiff Anomalous Perceptions Scale (Bell et al., 2006). Individuals were asked to rate the frequency that they, for example, *"Hear sounds or music that people near you don't hear?",* and *"See shapes,*

lights, or colours even though there is nothing really there?". Ratings were on a 6-point scale ('not at all', 'rarely', 'once a month', 'once a week', 'several times a week', 'daily'). Hallucinations items are listed in Supplementary Information 2.2.

Negative symptoms were measured in the current Chapter by eight items adapted from the Scale for the Assessment of Negative Symptoms (Andreasen, 1982). Parents were asked to rate how strongly they agree or disagree with statements such as, *"My child often fails to smile or laugh at things others would find funny"*, and *"My child seems emotionally 'flat', for example, rarely changes the emotions he/she shows"*. Ratings were on a 4-point scale ('not at all', 'somewhat true', 'mainly true', 'definitely true'). The following items were not included in the current analyses, in line with current conceptualisations of the NS construct (see Havers et al., 2022): *"My child does not pay attention when being spoken to"*, and *"My child is often inattentive and appears distracted".* NS items are listed in Supplementary Information 2.3.

2.2.3 – Statistical analyses

2.2.3.1 – Overview of analyses

Prior to testing for longitudinal measurement invariance (described in Section 2.2.3.6), confirmatory factor analysis (CFA) was used to ascertain the 'base' model that would be used for this testing. Several CFA models were tested, including a model derived using EFA.

2.2.3.2 – CFA and EFA

Factor analysis explains variance and covariance in a set of items using a minimal number of factors (Flora & Flake, 2017): These methods are embedded within the framework of latent variable modelling, in which variance in each (observed) variable is partitioned into variance that is shared with other observed variables (and is thus attributable to an underlying, unobserved, 'latent' factor), and into that which is unique and is not shared with

other variables (this unique variance also includes measurement error). Despite the common principals that underly CFA and EFA, they differ in an important way – explained briefly below in the context of the current analyses.

EFA: EFA was used to suggest the factor structure underlying the set of observed items, with all items allowed to load onto all factors and factor rotation used to derive a structure with maximally distinct loadings. The EFA structure was then respecified as a more restricted (CFA) model in a subsample. This process of replication (testing across samples/subsamples) is necessary because EFA models are overfitted to sample data (Flora & Flake, 2017; Osborne & Fitzpatrick, 2019).

A variety of methods can be used to decide on the number of factors to extract using an EFA. In this Thesis, the method of parallel analysis was used. Briefly, parallel analysis generates a random set of data with the same number of variables and observations as the empirical dataset and then calculates eigenvalues of the randomly generated correlation matrix. Eigenvalues of the correlation matrix in the empirical dataset that exceed those from the randomly generated data determine the number of factors to retain.

CFA: CFA was used to test competing theory-based/hypothesised models, with each item loading onto one factor only. Because of the restrictions (zeros) that are placed on the parameters, the CFA framework allows for model comparison through the associated differences in degrees of freedom.

2.2.3.3 – CFA for base model

CFA was used to establish the base models to test for longitudinal measurement invariance. For paranoia and hallucinations, longitudinal measurement invariance analysis was conducted as a precursor for conducting latent growth curve modelling and therefore only a limited number of models were tested using CFA. For NS, the analysis of longitudinal measurement invariance was conducted as a precursor for latent growth curve modelling, and

as well, as part of a separate study that investigated the latent structure of NS (see Chapter 6) and therefore a greater number of models were tested using CFA.

2.2.3.3.1 – Paranoia

For paranoia, the models that were tested were as follows: Model 1) a 1-factor model, in which all items were assumed to share variance via a single latent factor. All parameters were freely estimated.

Model 2) a 3-factor model – based on the construct facets that were included in development of the paranoia subscale, reflecting mistrust, ideas of reference, and ideas of persecution (Freeman et al., 2005; Ronald et al., 2014). All parameters were freely estimated, and latent factors were allowed to correlate.

Model 3) a model suggested by principal axis EFA with oblique (Oblimin) rotation, using parallel analysis for factor retention. Parallel analysis suggested that seven, six, and five factors should be retained for the data at ages 16, 17, and 22, respectively. In the CFA, factors were specified according to which items had the highest factor loadings in the EFA. No cross-loadings were specified in the CFA. Factors were free to correlate, and all parameters were freely estimated. The only exceptions were for single-item indicators, where two constraints are required for model identification: here, factor loadings were fixed to one and residual variances fixed to zero.

2.2.3.3.2 – Hallucinations

For hallucinations, the models that were tested were as follows: Model 1) a 1-factor model, in which all items were assumed to share variance via a single latent factor. All parameters were freely estimated.

Model 2) a 4-factor model – based on the construct facets that were included in development of the hallucinations subscale, reflecting the modalities of audio, visual, smell,

and touch (Bell et al., 2006; Ronald et al., 2014). All parameters were freely estimated, and latent factors were allowed to correlate.

Model 3) a model suggested by principal axis EFA with oblique (Oblimin) rotation, using parallel analysis for factor retention. Parallel analysis suggested that three factors should be retained at each age. In the CFA, factors were specified according to which items had the highest factor loadings in the EFA. No cross-loadings were specified in the CFA. Factors were free to correlate, and all parameters were freely estimated. The only exceptions were for single-item indicators, where two constraints are required for model identification: here, factor loadings were fixed to one and residual variances fixed to zero.

2.2.3.3.3 – Negative symptoms

The models tested for NS are described in detail in Section 6.2.3.2. They are described here briefly, as follows: Model 1) a 1-factor model, in which all items were assumed to share variance via a single latent factor. All parameters were freely estimated.

Model 2) a 2-factor model, reflecting an expressive deficit, and motivational-pleasure deficit. The two latent factors were free to correlate, and all parameters were freely estimated.

Model 3) a model suggested by principal axis EFA with oblique (Oblimin) rotation, using parallel analysis for factor retention. Parallel analysis suggested retaining four factors at each age. In the CFA, factors were specified according to which items had the highest factor loadings in the EFA. No cross-loadings were specified in the CFA. Factors were free to correlate. All parameters were freely estimated, except for the single-item indicators, where factor loadings were fixed to one and residual variances were fixed to zero.

Model 4) a 5-factor model, reflecting flat affect, alogia, avolition, anhedonia, and asociality. Anhedonia and asociality were specified as single-item indictors. Factors were free to correlate. All parameters were freely estimated, except for the single-item indicators (as above).

Model 5) a 5-factor hierarchical model, reflecting the five factors specified in Model 4 as first order factors (flat affect, alogia, avolition, anhedonia, asociality), and the two factors specified in Model 2 as second order factors (expressive deficit, motivation-pleasure deficit). The second order factors were free to correlate, and the first order factors were specified as uncorrelated. All parameters were freely estimated, except for the single-item indicators (as above).

2.2.3.4 – Pseudo replication of EFA as a CFA model

To pseudo-replicate the EFA findings, the EFA model suggested in the main subsample was tested in the cotwin subsample as a CFA, and the absolute fit of the model was examined.

2.2.3.5 – Model fit for CFA models

A series of goodness of fit indices were used to assess standalone model fit of the base models: the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). Whilst the use of cut off values is debated (Marsh et al., 2004), CFI values > 0.95 (or > 0.90, less conservatively), RMSEA values < 0.06, and SRMR values < 0.08 were used to indicate generally acceptable fit (Hu & Bentler, 1999; Marsh et al., 2004; van de Schoot et al., 2012).

Bayesian Information Criterion (BIC) was primarily used to assess the relative fit between models, with lower values indicative of better fit. A difference between the values in excess of two was considered to reflect 'positive' evidence, and a difference between the values in excess of 10 was considered 'very strong' evidence (Neath & Cavanaugh, 2012). Akaike's Information Criterion (AIC) was referred to where the difference in BIC values was less than two, with lower values indicative of better fit. A difference between AIC values in excess of two was considered 'strong' evidence (Burnham & Anderson, 2004).

2.2.3.6 – Longitudinal measurement invariance

An analysis of measurement invariance was conducted to assess the extent to which the best fitting CFA model ('the base model') was invariant across ages 16, 17, and 22 for each measure.

A series of specific models were specified to test for incremental levels of measurement invariance. Each model tested the extent to which specific parameters could be considered equivalent across the time points. The models reflected different 'levels' of measurement invariance, which were, configural (testing the equivalence of the configuration of items to factors); metric (testing the equivalence of the factor loadings); scalar (testing the equivalence of the observed item scores when the latent factor is zero). A further level of 'strict' invariance tested for equivalence between residual variances, though it is not necessary to obtain invariance at this level to infer measurement invariance (Mackinnon et al., 2022; Putnick & Bornstein, 2016; Widaman & Reise, 1997).

In the current Chapter, the following measurement invariance models were tested: 1) no equality constraints (configural model), 2) equality constraints placed on factor loadings (metric model), 3) equality constraints placed on factor loadings in addition to item intercepts (scalar model), 4) equality constraints placed on factor loadings and item intercepts in addition to residual variances (strict model). To test for incremental levels of measurement invariance, acceptable standalone fit (Section 2.2.3.5) as well as negligible change in the fit indices between models was required: specifically, CFI < 0.010, RMSEA < 0.015, and SRMR < 0.030 (Chen, 2007).

Any non-negligible change in the fit indices would prompt inspection of the modification indices and a partial invariance model would be tested if appropriate. Testing for partial invariance is generally considered tenable (Putnick & Bornstein, 2016), though there is notable debate around this issue (Steinmetz, 2013; Widaman & Reise, 1997).

2.2.3.7 – Pseudo replication of longitudinal measurement model

For paranoia and hallucinations, a post hoc analysis of longitudinal measurement invariance was also conducted in the cotwin subsample because the measurement model that was assessed for longitudinal invariance in the main sample was derived using EFA. For NS, the best fitting model was not derived from EFA, but pseudo replication of the theoretical model was carried out as part of the planned analyses in Chapter 6. The results are reported in the current Chapter for consistency along with the paranoia and hallucinations analyses.

2.2.3.8 – Data modelling

Any data that was missing was assumed to be missing at random, and was accommodated using FIML estimation. A robust version of the FIML estimator was used (MLR) to correct for multivariate nonnormality of the residuals. MLR adjusts both the *SE* and the overall test statistic. EFA models were estimated using the psych package in R (version 2.5.2). Cross-sectional CFA models were run using the lavaan package (Rosseel, 2012) in R, and longitudinal measurement invariance models were run in Mplus (version 8.6).

2.3 – Results

Descriptive statistics for paranoia, hallucinations, and NS at each age are shown in Tables 2.1, 2.2, and 2.3, respectively. Cross-age correlation coefficients are shown in Supplementary Table 2.2.

2.3.1 – Paranoia

2.3.1.1 – EFA

The results of the parallel analysis suggested to retain seven factors at age 16, six at age 17, and five at age 22. Supplementary Table 2.3 shows the factor loadings derived from

the EFA fit to the data at each age. The EFA model results showed that the basic configuration of items to factors was largely consistent at ages 16 and 17, with only the item-to-factor configuration for item 4 differing across ages. The basic configuration of items to factors at age 22 differed to that of ages 16 and 17.

2.3.1.2 – CFA

Supplementary Table 2.4 shows the results of the CFA at each age. At each age, the model suggested by the EFA at the corresponding age provided the best fit to the data, both in terms of standalone fit and comparative fit.

Because the structure of the EFA models differed across ages, in the interest of parsimony, the 5-factor (age 22) model was also specified as a CFA at ages 16 and 17. At ages 16 and 17, the 5-factor model provided acceptable fit to the data and showed better fit than both the 1-factor and 3-factor models. The 5-factor model was taken forward as the base model.

2.3.1.3 – Pseudo replication of EFA as a CFA model

The 5-factor model showed acceptable standalone fit when run as a CFA in the cotwin subsample at age 16 (Supplementary Table 2.5). At age 17, the latent covariance matrix for the 5-factor model was associated with a nonpositive definite outcome (i.e., indicating either a correlation greater than or equal to one, a negative variance, or a linear dependency between factors). At age 22, the 5-factor model showed acceptable standalone fit in the cotwin subsample.

2.3.1.4 – Longitudinal measurement invariance analyses

Table 2.4 shows the results of the longitudinal measurement invariance analysis for paranoia. The initial models that tested for configural and metric invariance showed acceptable fit and negligible change. However, the initial scalar model had a non-plausible model-implied covariance matrix, so the models (configural, metric) were re-run with

correlated residual variances between items 2 and 8 at each age: This decision was based on inspection of the modification indices, and the similar item wording was considered theoretical grounds by which to make the modification (i.e., "*There might be negative comments being spread about me"*, and "*Bad things are being said about me behind my back"*). Specifying the residual correlation led to plausibility of the model-implied covariance matrix.

Further constraining the item-level intercepts in the scalar model resulted in a model with non-negligible change in CFI value (> 0.010). A partial scalar invariance model was run following inspection of the modification indices, in which the parameters for item 12 (*"People might be conspiring against me")* were free to vary across time points. The partial scalar invariance model (with parameters for item 12 free to vary) provided acceptable standalone fit and negligible change in fit indices. The subsequently run partial strict invariance model provided acceptable standalone fit but the CFI change was unacceptable (> 0.010), so partial scalar invariance was concluded.

2.3.1.5 – Post hoc pseudo replication of longitudinal measurement model

When the 5-factor EFA model suggested in the main sample was specified as a configural model in the cotwin subsample, an improper solution was obtained. Specifically, the latent factor specified at age 17 indicated by items 2 and 13 was associated with a nonpositive definite outcome i.e., indicating either a correlation greater than or equal to one, a negative variance, or a linear dependency between factors.

2.3.1.6 – Post hoc longitudinal measurement invariance tests

Considering the configural consistency between the EFA models at ages 16 and 17 (Table 2.3, discussed in Section 2.3.1.1), as a post hoc sensitivity check – the 6-factor and 7-factor models were also specified as base models. However, the configural model for both structures resulted in an improper solution, with at least one element of the latent variable

covariance matrix being non-positive definite (i.e., indicating either a correlation greater than or equal to one, a negative variance, or a linear dependency between factors). For both models, the issue concerned the latent factor specified at age 22 as indicated by items 3 and 5.

2.3.2 – Hallucinations

2.3.2.1 – EFA

The results of the parallel analysis suggested to retain three factors at each age. Supplementary Table 2.6 shows the factor loadings derived from the EFA fit to the data at each age. The EFA model results showed that the configuration of items to factors was consistent at ages 16 and 17. The configuration of items to factors at age 22 differed to that of ages 16 and 17, though with some notable consistency (e.g., the clustering of items 1-3, and items 4 and 9).

2.3.2.2 – CFA

Supplementary Table 2.7 shows the results of the CFA at each age. At ages 16 and 17, the 3-factor model suggested by the EFA provided the best fit to the data, both in terms of standalone fit and comparative fit. At age 22, the 4-factor theoretical model provided the best fit.

Because the best fitting models differed across ages, in the interest of parsimony (i.e., selecting the 3-factor EFA model over the 4-factor theoretical model), the 3-factor model that was suggested at ages 16 and 17 was also specified as a CFA at age 22. At age 22, this model showed good standalone fit and showed better fit than both the 1-factor model and the 3-factor model suggested by the EFA at 22. The (age 16/age 17) 3-factor model was taken forward as the base model.

2.3.2.3 – Pseudo replication of EFA as a CFA model

The EFA models that were suggested by the data also showed good standalone fit when run as CFA models in the cotwin subsample (Supplementary Table 2.8).

2.3.2.4 – Longitudinal measurement invariance analyses

Table 2.5 shows the results of the longitudinal measurement invariance analysis. The configural and metric invariance models showed acceptable fit and negligible change. Further constraining the item-level intercepts in the scalar model resulted in a model with non-negligible change in CFI value (> 0.010). A partial scalar invariance model was run following inspection of the modification indices, in which the parameters for item 1 (*"Hear sounds or music that people near you don't hear?")* were free to vary across time points. The partial scalar invariance model (with parameters for item 1 free to vary) provided acceptable standalone fit and negligible change in fit indices. The subsequently run partial strict invariance model resulted in at least one element of the latent variable covariance matrix being non-positive definite (i.e., indicating either a correlation greater than or equal to one, or a negative variance), and partial scalar invariance was concluded.

2.3.2.5 – Post hoc pseudo replication of longitudinal measurement model

When the 3-factor EFA model suggested in the main sample was assessed for longitudinal invariance in the cotwin subsample (Supplementary Table 2.9), the results were unchanged. That is, the configural and metric models were acceptable, but the scalar model resulted in a CFI change > 0.010. Item 1 parameters were freed, and the resulting fit was acceptable. The partial strict model resulted in an improper solution and partial scalar invariance was concluded.

2.3.3 – Negative symptoms

2.3.3.1 – EFA

The results of the parallel analysis suggested to retain four factors at each age. Supplementary Table 2.10 shows the factor loadings derived from the EFA fit to the data at each age. The EFA model results showed that the configuration of items to factors was consistent at ages 16 and 17. The configuration of items to factors at age 22 differed to that of ages 16 and 17, though with some notable consistency (e.g., the clustering of items 1 and 2, and items 3 and 4).

2.3.3.2 – CFA

Supplementary Table 2.11 shows the results of the CFA at each age. The 5-factor model showed the best fit to the data at each age, both in terms of standalone fit and comparative fit. The 5-factor model was taken forward as the base model.

2.3.3.3 – Pseudo replication of EFA as a CFA model

The EFA models that were suggested by the data also showed good standalone fit when run as CFA models in the cotwin subsample (Supplementary Table 2.12).

2.3.3.4 – Longitudinal measurement invariance analyses

Table 2.6 shows the results of the longitudinal measurement invariance analysis. The configural, metric and scalar invariance models showed acceptable fit and negligible change in fit indices. Further constraining the residual variances in the strict model resulted in a model with non-negligible change in CFI value (> 0.010). A partial strict invariance model was run following inspection of the modification indices, in which the parameters for item 2 (*"My child seems emotionally 'flat'"*) were free to vary across time points. The partial strict invariance model (with parameters for item 2 free to vary) provided acceptable standalone fit and negligible change in fit indices, and partial strict invariance was concluded.

2.3.3.5 – Planned pseudo replication of longitudinal measurement model

The same pattern of results was observed for the cotwin subsample as for the main subsample (Supplementary Table 2.13). That is, the configural, metric and scalar invariance models showed acceptable fit and negligible change in fit indices. Further constraining the residual variances in the strict model resulted in a model with non-negligible change in CFI value (> 0.010). A partial strict invariance model was run in which the parameters for item 2 were free to vary across time points. The partial strict invariance model provided acceptable standalone fit and negligible change in fit indices, and partial strict invariance was concluded.

Table 2.1

Descriptive Statistics for Paranoia

	Age 16	Age 17	Age 22
N	4,943	1,468	4,166
Range	0-75	0-70	0-74
Mean	12.20	14.64	10.13
95% CI	11.90, 12.50	13.95, 15.33	9.78, 10.47
Variance	113.86	183.69	130.35
SD	10.67	13.55	11.42
Median	10	11	6
Mode	0	0	0
N > 3 *SD*	61 (1.23%)	20 (1.36%)	69 (1.66%)
Skewness	1.57	1.43	1.85
Coefficient α	0.93	0.95	0.94

Note. Scale range 0-75.

Table 2.2

Descriptive Statistics for Hallucinations

	16 years	17 years	22 years
N	4,949	1,471	4,164
Range	0-45	0-42	0-41
Mean	4.81	6.76	1.75
95% CI	4.64, 4.98	6.38, 7.15	1.62, 1.87
Variance	38.20	56.94	17.83
SD	6.18	7.55	4.22
Median	2	4	0
Mode	0	0	0
N > 3 *SD*	70 (1.41%)	20 (1.36%)	81 (1.95%)
Skewness	2.08	1.56	4.50
Coefficient α	0.88	0.90	0.88

Note. Scale range 0-45.

Table 2.3

Descriptive Statistics for Negative Symptoms

	Age 16	Age 17	Age 22
N	4,971	1,468	5,177
Range	0-24	0-24	0-24
Mean (*SD)*	2.21 (3.21)	3.01 (4.07)	2.66 (3.64)
95% CI	2.13, 2.30	2.80, 3.21	2.56, 2.76
Variance	10.30	16.55	13.24
Median	1.00	2.00	1.00
Mode	0.00	0.00	0.00
Skewness	2.40	2.11	2.27
N > 3 *SD*	88 (1.77%)	26 (1.77%)	109 (2.11%)
Coefficient α	0.83	0.88	0.84

Note. Scale range 0-24.

Table 2.4

Longitudinal Measurement Invariance Analysis of Paranoia in Main Subsample: Model Fit Results

	Parameters	Fit indices			Comparison of fit indices between nested models		
		CFI	RMSEA [90% CI]	SRMR	Δ CFI	Δ RMSEA	Δ SRMR
Configural invariance model (no constraints) [a]	276	0.940	0.028 [0.027, 0.029]	0.035	-	-	-
Metric invariance model (factor loadings constrained) [a]	256	0.936	0.028 [0.028, 0.029]	0.041	0.004	0.000	-0.006
Scalar invariance model (factor loadings and intercepts constrained) [a]	237	0.922	0.031 [0.030, 0.032]	0.044	0.014	-0.003	-0.003
Partial scalar invariance model (factor loadings and intercepts constrained) [a, b]	241	0.926	0.030 [0.029, 0.031]	0.042	0.010[c]	-0.002 [c]	-0.001 [c]
Partial strict invariance model (factor loadings, intercepts and residual variances constrained) [a, b]	218	0.913	0.032 [0.032, 0.033]	0.053	0.013	-0.002	-0.009

Note. N = 6,032. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Δ denotes change value. [a] Correlated residual variance between item 2 and item 8. [b] Item 12 parameters free to vary. [c] Change values compared to metric invariance model. The measurement model was a 5-factor model.

Table 2.5

Longitudinal Measurement Invariance Analysis of Hallucinations in Main Subsample: Model Fit Results

	Parameters	Fit indices			Comparison of fit indices between nested models		
		CFI	RMSEA [90% CI]	SRMR	Δ CFI	Δ RMSEA	Δ SRMR
Configural invariance model (no constraints)	144	0.978	0.016 [0.015, 0.018]	0.025	-	-	-
Metric invariance model (factor loadings constrained)	132	0.978	0.016 [0.014, 0.017]	0.028	0.000	0.000	-0.003
Scalar invariance model (factor loadings and intercepts constrained)	120	0.965	0.020 [0.018, 0.021]	0.033	0.013	-0.004	-0.005
Partial scalar invariance model (factor loadings and intercepts constrained) [a]	122	0.974	0.017 [0.015, 0.018]	0.029	0.004 [b]	-0.001 [b]	-0.001 [b]

Note. N = 6,032. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Δ denotes change value. [a] Item 1 intercepts free to vary. [b] Change values compared to metric invariance model. The partial strict model resulted in non-positive definite latent variable matrix so the results are not reported. The measurement model was a 3-factor model.

Table 2.6

Longitudinal Measurement Invariance Analysis of Negative Symptoms in Main Subsample: Model Fit Results

	Parameters	Fit indices			Comparison of fit indices between nested models		
		CFI	RMSEA [90% CI]	SRMR	Δ CFI	Δ RMSEA	Δ SRMR
Configural invariance model (no constraints)	189	0.992	0.014 [0.012, 0.016]	0.016	-	-	-
Metric invariance model (factor loadings constrained)	183	0.991	0.014 [0.012, 0.016]	0.018	0.001	0.000	0.002
Scalar invariance model (factor loadings and intercepts constrained)	177	0.988	0.016 [0.014, 0.018]	0.020	0.003	-0.002	-0.002
Strict invariance model (factor loadings, intercepts and residual variances constrained)	165	0.968	0.025 [0.023, 0.027]	0.030	0.020	-0.009	-0.010
Partial strict invariance model (factor loadings, intercepts and residual variances constrained, excluding item 2) [a]	171	0.980	0.020 [0.019, 0.022]	0.026	0.008 [b]	-0.004 [b]	-0.006 [b]

Note. N = 6,330. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Δ denotes change value. [a] The change in CFI value from the scalar model to the strict model exceeded the acceptable limit (of 0.010). Consultation of the modification indices and subsequent free estimation of the item 2 parameters provided acceptable deterioration in model fit. [b] Change values compared to scalar invariance model. The measurement model was a 5-factor model.

2.4 – Discussion

This Chapter investigated the extent to which the measurement of paranoia, hallucinations, and NS in the community across ages 16, 17, and 22 could be considered invariant. Partial scalar invariance was found for paranoia and hallucinations, and partial strict invariance was found for NS.

The aim of this Chapter was to investigate longitudinal measurement invariance for the purposes of subsequent latent growth modelling (Chapters 3 and 4). For paranoia and hallucinations, to the extent that partial scalar level invariance was found, the results suggest that the longitudinal measurement of these constructs is partially invariant. Thus, any changes that may subsequently be observed across age can be considered *at least in part* to reflect 'true' change, and not merely a recalibration of the measures (Grimm et al., 2017). These findings are useful for proceeding to latent growth modelling of these PEs dimensions. They are also the first to my knowledge to demonstrate longitudinal measurement invariance for PEs dimensions in the community.

Notwithstanding, the results of the EFA suggested a different configuration of items to factors for both paranoia and hallucinations at age 22, compared to at ages 16 and 17 (with minor deviations observed between 16 and 17 for paranoia). Whilst seemingly contradictory to the findings of longitudinal measurement invariance, these results both reflect and highlight an important difference between EFA and CFA. That is, they suggest that when all items were allowed to load onto all factors in the EFA, the *unrestricted* factor structure shows some variation across ages, particularly at age 22 compared to at ages 16 and 17. However, when a more *restricted* structure was imposed on the data by specifying an EFA model with no cross-loadings (i.e., as a CFA), the factor structure was both adequately described at each age, as suggested by the cross-sectional CFA results, and was equivalent across ages, as suggested by the longitudinal invariance results. Of note however, when the factor structures

suggested by the EFA for paranoia at ages 16 (7-factor) and 17 (6-factor) were subjected to post hoc tests of longitudinal configural invariance, a proper solution could not be obtained. This may suggest that the configuration of items to factors at age 22 is less flexible than at ages 16 and 17. The improper solution that was obtained for the 5-factor longitudinal paranoia model in the cotwin subsample may further indicate that the (sub)sample variance/covariance involved with items 2 and 13 at age 17 may be less generalisable than the variance and covariance for the other items and at the other ages (Osborne & Fitzpatrick, 2019).

As hypothesised, longitudinal measurement invariance of NS was found for a 5-factor structure, similar to what best describes NS in clinical samples (Ahmed et al., 2019; Chang et al., 2020; Strauss et al., 2018). As discussed in more detail in Section 6.4, the results presented here add to clinical findings suggesting that a 5-factor model appears to be an empirically robust representation of the data. As was discussed for paranoia and hallucinations, above, the results suggest that the measurement of NS shows longitudinal invariance and thus any changes across age can be considered (at least in part) to reflect change at the construct level. Like for paranoia and hallucinations, the results of the EFA suggested that the configuration of items to factors at age 22 was slightly different compared to at ages 16 and 17.

Notably, one item for each of paranoia, hallucinations, and NS was *non*invariant. The noninvariance at the scalar level that was observed for the items, *"People might be conspiring against me"* (paranoia), and *"Hear sounds or music that people near you don't hear"* (hallucinations), should be considered as measuring something potentially different at the different ages, particularly in emerging adulthood (age 22) compared to in adolescence (ages 16 and 17). Specifically, at the scalar-level, this suggests that the specific noninvariant items differ across ages for reasons other than the underlying factor. For NS, noninvariance

was identified at the level of residual variance for the item, *"My child seems emotionally 'flat'"*. This noninvariance could reflect differences in the observed score variances, in the unique variances, and or in measurement error (Putnick & Bornstein, 2016).

It is noted that some methodologists regard that partial *scalar* invariance may be less acceptable for subsequent analysis of observed scores (as for the current thesis; Chapters 4 and 5) than of latent factors (Steinmetz, 2013): Whilst this should be considered when interpreting the latent growth modelling findings for paranoia and hallucinations that are subsequently reported in Chapters 3 and 4 – the simulations that informed this perspective (Steinmetz, 2013) were for noninvariance of either 50% or one third of a small number of items (either 4 or 6). It is a relative strength of the current study that noninvariance was only found for ~ 7% of 15 items (paranoia) and ~ 11% of nine items (hallucinations).

A potential limitation is that an *extensive* comparison of theory-based models was not conducted for paranoia and hallucinations as it was for NS (i.e., owing to the potential clinical relevance of this testing for NS, discussed in Sections 1.2.1 and 1.6, and in Chapter 6). It is therefore possible that different, better fitting representations of the data would give rise to different properties of invariance across age. Nonetheless, in the current context of conducting longitudinal measurement invariance analysis prior to conducting growth modelling of *observed total scores* – invariance of *any* measurement model is informative, reflecting that measurement of the items that underlie the observed total scores can be considered equivalent across time.

In summary, this Chapter found that a 5-factor structure of paranoia, a 3-factor structure of hallucinations, and a 5-factor structure of NS were invariant across ages 16, 17, and 22 in the community. The partial nature of this invariance and the observed configural differences suggested by the EFA notwithstanding, these results suggested that any stability or change that is subsequently observed across age can be understood at least in part as

reflecting stability or change at the construct level, rather than at the level of the measurement instrument.

2.5 – Appendix

Supplementary Information 2.1

Paranoia Subscale of the Specific Psychotic Experiences Questionnaire

1. I need to be on my guard against others

2. There might be negative comments being spread about me

3. People are deliberately trying to irritate me

4. I might be being observed or followed

5. People are trying to upset me

6. People are looking at me in an unfriendly way

7. People are being hostile towards me

8. Bad things are being said about me behind my back

9. Someone has bad intentions towards me

10. Someone has it in for me

11. People would harm me if given an opportunity

12. People might be conspiring against me

13. People are laughing at me

14. I am under threat from others

15. I can detect coded messages about me in the press/TV/internet

Supplementary Information 2.2

Hallucinations Subscale of the Specific Psychotic Experiences Questionnaire

1. Hear sounds or music that people near you don't hear?

2. See things that other people cannot?

3. Feel that someone is touching you, but when you look nobody is there?

4. Hear noises or sounds when there is nothing about to explain them?

5. Detect smells which don't seem to come from your surroundings?

6. See shapes, lights, or colours even though there is nothing really there?

7. Notice smells or odours that people next to you seem unaware of?

8. Experience unusual burning sensations or other strange feelings in or on your body that can't be explained?

9. Hear voices commenting on what you're thinking or doing?

Supplementary Information 2.3

Negative Symptoms Subscale of the Specific Psychotic Experiences Questionnaire

1. My child often fails to smile or laugh at things others would find funny

2. My child seems emotionally 'flat', for example, rarely changes the emotions he/she shows

3. My child usually gives brief, one word replies to questions, even if encouraged to say more

4. My child often does not have much to say for himself/herself

5. My child often sits around for a long time doing nothing

6. My child has a lack of energy and motivation

7. My child has very few interests or hobbies

8. My child has few or no friends

The following items were not included in the current analyses:

9. My child does not pay attention when being spoken to

10. My child is often inattentive and appears distracted

Supplementary Table 2.1

The Twins Early Development Study (TEDS) Sample

	N families contacted	*N* families returned data	% return rate	*N* (approximate) not contacted from ONS sample owing to exclusions [1]
N families that responded to initial ONS invitation, *N* = 16,810 ('ONS sample')				
1st contact study	16,302	13,488	82.74%	500
16-year study	10,874	5,123	47.11%	5,900
17-year study	1,773	1,475	83.19%	See [2] below
22-year study [a,b]	10,451	5,352	51.21%	6,250
22-year study [a,c]	8,611	5,184	60.20%	8,210

Note. [a] '22-year study' is the called the 21-year study on the TEDS website. [b] Parent-rated data. [c] Twin self-rated data. [1] Exclusions were due to families withdrawing from the study, address problems, severe medical conditions, families being inactive, families with no recent data, and for 'other reasons', which are detailed in full on the TEDS data dictionary (https://www.teds.ac.uk/datadictionary/studies/returns/samples.htm). [2] The sample at 17 was a selected subset of 1,773 of the families who had returned data at 16.

Supplementary Table 2.2

Correlations between Paranoia, Hallucinations, and Negative Symptoms

	Para age 16	Para age 17	Para age 22	Halls age 16	Halls age 17	Halls age 22	NS age 16	NS age 17
Para age 17	**0.68 [0.65, 0.71]**							
Para age 22	**0.42 [0.39, 0.45]**	**0.55 [0.50, 0.59]**						
Halls age 16	0.47 [0.45, 0.49]	0.49 [0.45, 0.53]	0.26 [0.23, 0.29]					
Halls age 17	0.40 [0.35 0.44]	0.55 [0.52, 0.59]	0.29 [0.23, 0.34]	**0.66 [0.63, 0.68]**				
Halls age 22	0.20 [0.16, 0.23]	0.33 [0.28, 0.39]	0.36 [0.33, 0.38]	**0.33 [0.26, 0.36]**	**0.42 [0.37, 0.47]**			
NS age 16	0.13 [0.10, 0.15]	0.16 [0.10, 0.20]	0.11 [0.07, 0.14]	0.11 [0.08, 0.14]	0.13 [0.08, 0.18]	0.11 [0.08, 0.15]		
NS age 17	0.19 [0.14, 0.24]	0.19 [0.13, 0.23]	0.16 [0.10, 0.22]	0.15 [0.10, 0.20]	0.15 [0.10, 0.20]	0.08 [0.02, 0.14]	**0.69 [0.66, 0.72]**	
NS age 22	0.07 [0.04, 0.10]	0.11 [0.05, 0.16]	0.12 [0.09, 0.16]	0.08 [0.05, 0.11]	0.11 [0.06, 0.17]	0.12 [0.09, 0.15]	**0.51 [0.48, 0.53]**	**0.57 [0.53, 0.61]**

Note. *N* = 989-5,177. Data from one randomly selected twin per pair was used, with phenotypic pairwise deletion. Para = paranoia. Halls = hallucinations. NS = negative symptoms. Spearman's rank correlation coefficient [95% confidence intervals]. Bold typeset indicates within-trait correlations.

Supplementary Table 2.3

Exploratory Factor Analysis of Paranoia Items in Main Subsample

	Age 16 (63%)							Age 17 (70%)						Age 22 (65%)				
	F1 (14%)	F2 (14%)	F3 (11%)	F4 (9%)	F5 (6%)	F6 (5%)	F7 (4%)	F1 (19%)	F2 (16%)	F3 (14%)	F4 (9%)	F5 (8%)	F6 (4%)	F1 (20%)	F2 (19%)	F3 (12%)	F4 (10%)	F5 (5%)
1. I need to be on my guard against others	0.09	0.06	0.05	0.04	0.06	0.02	**0.61**	0.16	0.16	0.08	-0.03	0.06	**0.54**	**0.74**	0.16	0.00	-0.03	0.01
2. There might be negative comments being spread about me	-0.04	**0.69**	0.01	0.08	0.10	-0.05	0.16	-0.03	**0.76**	0.11	0.06	-0.08	0.16	**0.66**	-0.01	0.00	0.33	-0.02
3. People are deliberately trying to irritate me	-0.01	0.00	0.01	**0.85**	-0.01	-0.02	0.02	-0.03	0.00	**0.83**	0.01	-0.03	0.07	**0.74**	0.02	0.09	0.01	0.08
4. I might be being observed or followed	0.02	-0.03	0.03	0.01	**0.68**	-0.01	0.04	**0.44**	0.19	0.20	-0.10	0.04	0.06	**0.42**	-0.03	0.41	-0.04	0.26
5. People are trying to upset me	0.12	0.11	0.07	**0.39**	0.18	0.20	-0.09	0.06	0.05	**0.66**	0.09	0.16	-0.06	0.24	0.24	0.18	0.05	**0.40**
6. People are looking at me in an unfriendly way	-0.04	0.24	0.12	0.05	0.17	**0.41**	0.06	0.07	0.27	0.13	0.01	**0.51**	0.05	**0.36**	0.11	0.23	0.25	0.01
7. People are being hostile towards me	0.13	0.02	0.21	0.12	0.01	**0.44**	0.11	0.10	-0.01	0.24	0.16	**0.46**	0.13	0.24	0.06	0.07	**0.57**	0.14
8. Bad things are being said about me behind my back	0.04	**0.81**	0.10	0.00	-0.03	0.06	-0.02	0.04	**0.78**	-0.02	0.09	0.15	-0.04	-0.04	**0.43**	0.05	0.27	0.36
9. Someone has bad	-0.01	0.10	**0.66**	0.06	0.04	0.09	0.05	0.09	0.18	0.12	**0.55**	0.14	0.06	0.10	**0.79**	-0.07	-0.3	0.07

intentions towards me																		
10. Someone has it in for me	0.11	0.00	**0.72**	0.02	0.03	-0.01	0.02	0.26	0.11	0.12	**0.58**	-0.01	-0.03	0.07	0.13	0.33	**0.46**	-0.07
11. People would harm me if given an opportunity	**0.68**	0.00	0.07	0.10	-0.03	-0.01	0.07	**0.60**	-0.02	0.06	0.22	0.06	0.04	-0.01	**0.77**	0.08	-0.02	0.02
12. People might be conspiring against me	**0.61**	0.10	0.01	0.01	-0.06	0.15	-0.05	**0.73**	0.10	-0.04	0.12	0.03	-0.01	0.00	0.05	**0.72**	0.05	0.03
13. People are laughing at me	0.27	**0.47**	-0.14	0.09	0.08	0.14	-0.01	0.24	**0.45**	0.11	-0.06	0.15	0.05	0.15	**0.40**	0.31	0.10	-0.12
14. I am under threat from others	**0.72**	-0.01	-0.01	-0.03	0.06	0.08	0.08	**0.82**	-0.06	0.02	0.02	0.04	0.09	0.01	**0.61**	0.07	0.09	-0.13
15. I can detect coded messages about me in the press / TV / internet	**0.20**	0.10	0.16	0.01	0.16	-0.10	-0.11	**0.43**	0.15	0.18	-0.15	-0.10	-0.19	-0.08	**0.47**	-0.03	0.00	0.03

Supplementary Table 2.3.a

Factor Correlations

	Age 16						Age 17[a]					Age 22[a]			
	F1	F2	F3	F4	F5	F6	F1	F2	F3	F4	F5	F1	F2	F3	F4
F2	0.53	1.00	-	-	-	-	0.57	1.00	-	-	-	0.58	1.00	-	-
F3	0.73	0.65	1.00	-	-	-	0.59	0.73	1.00	-	-	0.70	0.56	1.00	-
F4	0.52	0.65	0.59	1.00	-	-	0.68	0.50	0.50	1.00	-	0.63	0.47	0.52	1.00
F5	0.60	0.60	0.58	0.57	1.00	-	0.52	0.58	0.60	0.48	1.00	0.48	0.45	0.38	0.23
F6	0.42	0.57	0.48	0.47	0.42	1.00	0.36	0.45	0.52	0.20	0.28	-	-	-	-
F7	0.42	0.44	0.42	0.51	0.56	0.25	-	-	-	-	-	-	-	-	-

Note. N age 16 = 4,953. *N* age 17 = 1,472. *N* age 22 = 4,225. F = factor. Principal axis factoring with oblique (Oblimin) rotation. Bold typeset indicates strongest factor loading for each item at each age. Mean item complexity at 16 = 1.7. Mean item complexity at 17 = 1.5. Mean item complexity at 22 = 1.8.

Supplementary Table 2.4

Confirmatory Factor Analysis of Paranoia in Main Subsample: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Age 16								
1-factor model	45	-82,654.065	165,398.130	165,690.952	2,280.037 (90), $p < .001$	0.895	0.099 [0.096, 0.103]	0.044
3-factor model	47	-82,175.205	164,444.410	164,750.246	1,808.868 (88), $p < .001$	0.918	0.089 [0.085, 0.092]	0.043
7-factor (EFA) model	**64**	**-80,992.031**	**162,112.062**	**162,528.520**	**636.086 (71), $p < .001$**	**0.974**	**0.056 [0.025, 0.060]**	**0.023**
5-factor (EFA at 22) model	53	-81817.452	163740.904	164085.783	1,460.301 (82), $p < .001$	0.935	0.082 [0.078, 0.085]	0.038
Age 17								
1-factor model	45	-26,845.349	53,780.699	54,018.884	1,193.192 (90), $p < .001$	0.863	0.132 [0.125, 0.139]	0.052
3-factor model	47	-26,584.367	53,262.733	53,511.505	954.540 (88), $p < .001$	0.894	0.118 [0.111, 0.124]	0.052
6-factor (EFA) model	**59**	**-26,038.266**	**52,194.532**	**52,506.820**	**445.131 (76), $p < .001$**	**0.957**	**0.081 [0.074, 0.088]**	**0.046**
5-factor (EFA at 22) model	53	-26420.653	52947.306	53227.836	806.819 (82), $p < .001$	0.913	0.111 [0.104, 0.118]	0.05
Age 22								
1-factor model	45	-66,527.338	133,144.675	133,429.737	2,225.326 (90), $p < .001$	0.877	0.119 [0.115, 0.123]	0.056
3-factor model	47	-66,227.482	132,548.964	132,846.696	1,986.397 (88), $p < .001$	0.891	0.113 [0.109, 0.118]	0.056
5-factor (EFA) model	**53**	**-65,234.209**	**130,574.417**	**130,910.157**	**1,248.103 (82), $p < .001$**	**0.936**	**0.090 [0.085, 0.094]**	**0.042**

Note. N age 16 = 4,950. *N* age 17 =1,470. *N* age 22 = 4,166. EFA = exploratory factor analysis. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Bold typeset represents best fitting model at each age.

Supplementary Table 2.5

Confirmatory Factor Analysis of Paranoia in Cotwin Subsample (of Model Suggested by EFA in Main Subsample)

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Age 16								
5-factor (EFA at 22) model	53	-81,814.842	163,735.684	164,080.659	1,367.760 (82), $p < .001$	0.936	0.081 [0.078, 0.085]	0.040
Age 22								
5-factor (EFA) model	53	-65,713.679	131,533.358	131,869.212	1,262.912 (82), $p < .001$	0.935	0.091 [0.087, 0.096]	0.039

Note. N age 16 = 4,959. *N* age 22 = 4,175. EFA = exploratory factor analysis. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. At age 17, the 5-factor EFA model (suggested in the main subsample at age 22) resulted in a nonpositive definite outcome so the results are not reported.

Supplementary Table 2.6

Exploratory Factor Analysis of Hallucinations Items in Main Subsample

Item	Standardised loadings (and variance explained by factor)								
	Age 16 (54%)			Age 17 (58%)			Age 22 (58%)		
	F1 (21%)	F2 (17%)	F3 (16%)	F1 (23%)	F2 (18%)	F3 (17%)	F1 (31%)	F2 (15%)	F3 (12%)
1. Hear sounds or music that people near you don't hear?	-0.05	**0.80**	0.00	**0.83**	-0.07	0.03	**0.88**	-0.05	-0.02
2. See things that other people cannot?	0.31	**0.49**	-0.01	**0.60**	0.09	0.11	**0.70**	0.05	0.02
3. Feel that someone is touching you, but when you look nobody is there?	0.11	**0.59**	0.14	**0.74**	0.11	0.00	**0.55**	0.05	0.18
4. Hear noises or sounds when there is nothing about to explain them?	-0.05	0.06	**0.80**	0.20	**0.69**	-0.04	0.38	**0.50**	-0.03
5. Detect smells which don't seem to come from your surroundings?	**0.46**	0.14	0.20	0.19	0.16	**0.44**	0.01	0.01	**0.97**
6. See shapes, lights, or colours even though there is nothing really there?	**0.60**	0.05	0.00	0.20	0.07	**0.45**	**0.43**	0.22	-0.06
7. Notice smells or odours that people next to you seem unaware of?	**0.78**	-0.02	0.00	-0.01	-0.01	**0.83**	**0.57**	0.09	0.11
8. Experience unusual burning sensations or other strange feelings in or on your body that can't be explained?	**0.53**	0.06	0.05	0.16	0.21	**0.26**	**0.53**	-0.06	0.06
9. Hear voices commenting on what you're thinking or doing?	0.09	-0.06	**0.72**	-0.07	**0.87**	0.05	-0.03	**0.92**	0.03

Supplementary Table 2.6.a

Factor Correlations

	Age 16		Age 17		Age 22		
	F1	F2	F1	F2	F1	F2	F3
F2	0.77	1.00	0.67	1.00	0.63	1.00	-
F3	0.69	0.69	0.81	0.65	0.62	0.43	1.00

Note. N at age 16 = 4,953. *N* at age 17 = 1,472. *N* at age 22 = 4,225. F = factor. Principal axis factoring with oblique (Oblimin) rotation. Bold typeset indicates strongest factor loading for each item at each age. Mean item complexity at 16 = 1.2. Mean item complexity at 17 = 1.3. Mean item complexity at 22 = 1.2.

Supplementary Table 2.7

Confirmatory Factor Analysis of Hallucinations in Main Subsample: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Age 16								
1-factor model	27	-52,432.388	104,918.776	105,094.469	475.373 (27), p <.001	0.936	0.093 [0.085, 0.100]	0.038
3-factor (EFA) model	**30**	**-51,998.172**	**104,056.344**	**104,251.558**	**137.679 (24), p <.001**	**0.984**	**0.049 [0.041, 0.057]**	**0.019**
4-factor model	33	-51,328.683	104,230.432	104,445.168	210.054 (21), p <.001	0.974	0.067 [0.059, 0.075]	0.025
Age 17								
1-factor model	27	-17,429.475	34,912.949	35,055.898	229.569 (27), p < .001	0.931	0.104 [0.092, 0.117]	0.040
3-factor (EFA) model	**30**	**-17,255.042**	**34,570.083**	**34,728.915**	**65.990 (24), p < .001**	**0.986**	**0.050 [0.036, 0.064]**	**0.021**
4-factor model	33	-17,270.220	34,606.440	34,781.154	81.833 (21), p < .001	0.980	0.064 [0.049, 0.078]	0.025
Age 22								
1-factor model	27	-30,058.149	60,170.298	60,341.336	248.415 (27), p < .001	0.929	0.099 [0.088, 0.110]	0.039
3-factor (EFA) model	29	-29,704.001	59,466.003	59,649.709	109.543 (25), p < .001	0.974	0.063 [0.051, 0.075]	0.027
3-factor (EFA at 16/17) model	30	-29,692.837	59,445.673	59,635.714	108.519 (24), p < .001	0.975	0.063 [0.051, 0.075]	0.027
4-factor model	**33**	**-29,658.717**	**59,383.433**	**59,592.479**	**100.861 (21), p < .001**	**0.978**	**0.063 [0.051, 0.076]**	**0.023**

Note. N age 16 = 4,950; *N* age 17 =1,472*; N* age 22 = 4,166. EFA = exploratory factor analysis. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Bold typeset represents best fitting model at each age.

Supplementary Table 2.8

Confirmatory Factor Analysis of Hallucinations in Cotwin Subsample (of Model Suggested by EFA in Main Subsample)

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Age 16								
3-factor (EFA) model	30	-51,265.179	102,590.339	102,785.621	100.738 (24), p <.001	0.988	0.041 [0.033, 0.050]	0.017
Age 17								
3-factor (EFA) model	30	-17,274.146	34,608.291	34,767.102	47.098 (24), p = .003	0.992	0.038 [0.021, 0.054]	0.017
Age 22								
3-factor (EFA at 16/17) model	30	-28,530.760	57,121.520	57,311.618	85.437 (24), p <.001	0.980	0.055 [0.043, 0.068]	0.024

Note. N age 16 = 4,958. *N* age 17 =1,471. *N* age 22 = 4,174. EFA = exploratory factor analysis. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual.

Supplementary Table 2.9

Longitudinal Measurement Invariance Analysis of Hallucinations in Cotwin Subsample: Model Fit Results

	Parameters	Fit indices			Comparison of fit indices between nested models		
		CFI	RMSEA [90% CI]	SRMR	Δ CFI	Δ RMSEA	Δ SRMR
Configural invariance model (no constraints)	144	0.983	0.014 [0.012, 0.015]	0.022	-	-	-
Metric invariance model (factor loadings constrained)	132	0.983	0.014 [0.012, 0.015]	0.025	0.000	0.000	-0.003
Scalar invariance model (factor loadings and intercepts constrained)	120	0.972	0.017 [0.016, 0.019]	0.030	0.011	-0.003	-0.005
Partial scalar invariance model (factor loadings and intercepts constrained) [a]	122	0.981	0.014 [0.013, 0.016]	0.025	0.002 [b]	0.000 [b]	-0.003 [b]

Note. N = 6,032. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Δ denotes change value. [a] Item 1 intercepts free to vary. [b] Change values compared to metric invariance model. The partial strict model resulted in non-positive definite latent variable matrix so the results are not reported. The measurement model was a 3-factor model.

Supplementary Table 2.10

Exploratory Factor Analysis of Negative Symptoms Items in Main Subsample

Item	Standardised loadings (and variance explained by factor)											
	Age 16				Age 17				Age 22			
	F1 (19%)	F2 (18%)	F3 (14%)	F4 (9%)	F1 (20%)	F2 (18%)	F3 (15%)	F4 (11%)	F1 (19%)	F2 (18%)	F3 (8%)	F4 (11%)
1. Often fails to smile or laugh at things others would find funny	-0.05	0.01	**0.72**	0.00	-0.05	-0.03	**0.75**	-0.01	-0.01	0.03	0.14	**0.59**
2. Seems emotionally "flat", for example, rarely changes the emotions he/she shows	0.12	0.04	**0.65**	0.04	0.07	0.04	**0.72**	0.02	0.27	0.13	-0.04	**0.46**
3. Usually gives brief, one word replies to questions, even if encouraged to say more	**0.82**	0.03	0.04	-0.07	**0.88**	0.02	-0.02	-0.01	**0.72**	0.03	-0.10	0.12
4. Often does not have much to say for himself/herself	**0.85**	-0.02	-0.03	0.05	**0.85**	-0.02	0.03	0.02	**0.85**	-0.01	0.07	-0.06
5. Often sits around for a long time doing nothing	-0.01	**0.77**	0.05	-0.06	0.04	**0.81**	0.04	-0.08	-0.03	**0.82**	-0.06	0.03
6. Has a lack of energy and motivation	0.05	**0.76**	0.01	0.08	0.01	**0.74**	0.01	0.16	0.09	**0.63**	0.10	-0.03
7. Has very few interests or hobbies	0.06	0.35	-0.01	**0.51**	0.05	0.28	0.05	**0.52**	0.06	**0.41**	0.37	0.03
8. Has few or no friends	0.04	-0.08	0.21	**0.52**	0.10	-0.04	0.09	**0.58**	0.09	0.05	**0.51**	0.24

Supplementary Table 2.10.a

Factor Correlations

	Age 16			Age 17			Age 22		
	F1	F2	F3	F1	F2	F3	F1	F2	F3
F2	0.51	1.00	-	0.61	1.00	-	0.55	1.00	-
F3	0.67	0.48	1.00	0.77	0.63	1.00	0.34	0.44	1.00
F4	0.37	0.54	0.42	0.56	0.71	0.56	0.64	0.56	0.39

Note. N age 16 = 4,976. *N* age 17 = 1,471. *N* age 22 = 5,244. F = factor. Principal axis factoring with oblique (Oblimin) rotation. Bold typeset indicates strongest factor loading for each item at each age. Mean item complexity at 16 = 1.2. Mean item complexity at 17 = 1.1. Mean item complexity at 22 = 1.2.

Supplementary Table 2.11

Confirmatory Factor Analysis of Negative Symptoms in Main Subsample: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Age 16								
1-factor model	24	-28,955.589	57,959.178	58,115.465	1,378.970 (20), $p < .001$	0.775	0.179 [0.171, 0.187]	0.075
2-factor model	25	-27,993.865	56,037.731	56,200.530	547.372 (19), $p < 001$	0.912	0.115 [0.107, 0.123]	0.056
4-factor (EFA) model	30	-27,479.635	55,019.269	55,214.629	115.805 (14), $p < .001$	0.983	0.058 [0.048, 0.068]	0.028
5-factor model	**32**	**-27,382.813**	**54,829.625**	**55,038.009**	**31.484 (12), $p = .002$**	**0.997**	**0.027 [0.016, 0.039]**	**0.009**
5H-factor model	28	-27,509.060	55,074.119	55,256.455	139.674 (16), $p < .001$	0.980	0.060 [0.051, 0.069]	0.029
Age 17								
1-factor model	24	-9,753.859	19,555.717	19,682.733	444.502 (20), $p < .001$	0.849	0.168 [0.155, 0.182]	0.060
2-factor model	25	-9,463.351	18,976.702	19,109.010	148.524 (19), $p < .001$	0.954	0.095 [0.081, 0.110]	0.040
4-factor (EFA) model	30	-9,333.553	18,727.105	18,885.876	16.746 (14), $p = .270$	0.999	0.016 [0.000, 0.040]	0.015
5-factor model	**32**	**-9,325.675**	**18,715.350**	**18,884.718**	**8.400 (12), $p = .753$**	**1.000**	**0.000 [0.000, 0.026]**	**0.009**
5H-factor model	28	-9,336.363	18,728.726	18,876.911	19.594 (16), $p = .239$	0.999	0.017 [0.000, 0.039]	0.016
Age 22								
1-factor model	24	-34,446.792	68,941.583	69,098.840	940.153 (20), $p < .001$	0.860	0.138 [0.130, 0.145]	0.058
2-factor model	25	-33,945.172	67,940.343	68,104.153	480.377 (19), $p < .001$	0.931	0.099 [0.091, 0.107]	0.046
4-factor (EFA) model	29	-33,658.919	67,375.838	67,565.856	217.032 (15), $p < .001$	0.971	0.072 [0.064, 0.081]	0.026
5-factor model	**32**	**-33,554.719**	**67,173.437**	**67,383.113**	**110.133 (12), $p < .001$**	**0.986**	**0.057 [0.047, 0.066]**	**0.019**
5H-factor model	28	-33,633.770	67,323.539	67,507.006	185.894 (16), $p < .001$	0.975	0.065 [0.057, 0.073]	0.027

Note. *N* age 16 = 4,974; *N* age 17 = 1,469; *N* age 22 = 5,179. EFA = exploratory factor analysis. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Bold typeset represents best fitting model at each age.

Supplementary Table 2.12

Confirmatory Factor Analysis of Negative Symptoms in Cotwin Subsample (of Model Suggested by EFA in Main Subsample)

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Age 16								
4-factor (EFA) model	30	27,736.599	55,533.198	55,728.575	76.584 (14), $p < .001$	0.989	0.047 [0.037, 0.057]	0.024
Age 17								
4-factor (EFA) model	30	-9,000.982	18,061.964	18,220.816	30.802 (14), $p = .006$	0.994	0.039 [0.020, 0.058]	0.019
Age 22								
4-factor (EFA) model	29	-33,398.283	66,854.567	67,044.596	285.644 (15), $p < .001$	0.960	0.084 [0.076, 0.093]	0.030

Note. N age 16 = 4,958; *N* age 17 =1,471; *N* age 22 = 5,181. EFA = exploratory factor analysis. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual.

Supplementary Table 2.13

Longitudinal Measurement Invariance Analysis of Negative Symptoms in Cotwin Subsample: Model Fit Results

	Parameters	Fit indices			Comparison of fit indices between nested models		
		CFI	RMSEA [90% CI]	SRMR	Δ CFI	Δ RMSEA	Δ SRMR
Configural invariance model (no constraints)	189	0.986	0.017 [0.015, 0.019]	0.018	-	-	-
Metric invariance model (factor loadings constrained)	183	0.984	0.018 [0.016, 0.020]	0.021	0.002	-0.001	-0.003
Scalar invariance model (factor loadings and intercepts constrained)	177	0.981	0.019 [0.017, 0.021]	0.022	0.003	-0.001	-0.001
Strict invariance model (factor loadings, intercepts and residual variances constrained)	165	0.967	0.025 [0.023, 0.027]	0.030	0.014	-0.006	-0.008
Partial strict invariance model (factor loadings, intercepts and residual variances constrained, excluding item 2) [a]	171	0.976	0.022 [0.020, 0.023]	0.025	0.005 [b]	-0.003 [b]	-0.003 [b]

Note. N = 6,336. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Δ denotes change value. [a] The change in CFI value from the scalar model to the strict model exceeded the acceptable limit (of 0.010). Consultation of the modification indices and subsequent free estimation of the item 2 parameters provided acceptable deterioration in model fit. [b] Change values compared to scalar invariance model. The measurement model was a 5-factor model.

Chapter 3 – Latent growth curve modelling of paranoia, hallucinations, and negative symptoms

3.1 – Introduction

The importance of studying PENS repeatedly over time was outlined in Section 1.5.1. The current Section will outline the conceptual underpinnings of using latent growth curve modelling (LGCM) to summarise change over time; briefly relating this to existing findings on the latent development of PENS (described in Section 1.5.5).

The concept of latent growth modelling was introduced in Section 1.5.5. As discussed, one way to conceptualise *change over time* is to assume that each individual has an underlying, or 'latent' trajectory that whilst cannot be directly measured, can be statistically and conceptually inferred because it is assumed to give rise to the repeated measures that have been observed (Curran & Willoughby, 2003). Within a structural equation modelling framework, a latent growth curve model (LGCM) parameterises within-person change over time both in terms of *averages*, and in terms of between-person differences, or *variability* in this change (Ram & Grimm, 2007). Importantly in the context of the current Chapter, implicit in the LGCM framework is that whilst individuals are allowed to differ in terms of the averages, they are ultimately homogeneous as a sample. This differs to the growth *mixture* model, which extends the LGCM by allowing for heterogeneity in the sample to emerge through the specification of multiple latent subgroups or classes – which is the focus of Chapter 4. Prior to any mixture modelling, however, it is important to first summarise the developmental course of an outcome for the sample, *before* any grouping variables, either observed or latent, are introduced. It is further important to identify the

optimal functional form of growth for the data, for example, linear, quadratic – detailed in Section 3.2.3.2 (Berlin et al., 2014; Curran & Hussong, 2003; Ram & Grimm, 2009).

In the context of the current Thesis, only three of the previous studies that have used latent variable modelling to analyse PEs have reported the sample-wide characteristics of growth and the model fit of the sample-wide LGCM. Two of these studies reported that the latent development of aggregated PEs decreased on average across adolescence from an average initial mid-level/low-level starting point (Lin et al., 2011; Wigman, van Winkel, Raaijmakers, et al., 2011, respectively). The other study reported an average initial low-level in adulthood that did not systematically increase or decrease over two years (Wigman, van Winkel, Jacobs, et al., 2011). These studies did not report on the *variability* around the averages, and further did not report whether any competing growth forms had been tested. NS in the community have not been previously investigated using latent variable modelling.

The current Chapter aimed to test a series of alternative forms of growth, and to characterise growth at the sample-wide level for the PENS dimensions. A supplement to these aims was to test the adequacy of using the cluster method to account for the relatedness between individuals in the sample. It was hypothesised that, i) linear growth would adequately describe growth in the PENS dimensions. Based on the descriptive statistics of the sample (Tables 2.1-2.3), it was further hypothesised that, ii) average trajectories would decline over time for paranoia and hallucinations, and contrastingly, iii) average trajectories would increase for NS – and that, iv) variability would be significant for both baseline scores and for change over time for each of the measures.

3.2 – Methods

3.2.1 – Participants

The TEDS sample is described in Section 2.2.1.1. For the main analyses conducted in Chapter 3, data from both twins was used, with standard errors adjusted for familial clustering. Individuals completed questions relating to paranoia and hallucinations at mean ages 16.32 years (*SD* 0.68; range 14.91-21.34), 17.06 years (*SD* 0.88; range 15.55-19.0), and 22.85 years (*SD* 0.88; range 21.16-25.19). Parents completed questions relating to their twins' NS at mean ages 16.32 years (*SD* 0.68; range 14.91-19.45), 17.06 years (*SD* 0.88; range 15.55-19.0), and 22.30 years (*SD* 0.93; range 20.56-25.59).

N for paranoia at ages 16, 17, and 22 were 9,898, 2,937, and 8,340, respectively. *N* for hallucinations at ages 16, 17, and 22 were 9,907, 2,940, and 8,338, respectively. *N* for NS at ages 16, 17, and 22 were 9,944, 2,939, and 10,355 respectively (Table 4.1).

Cross-age *N* were 12,051, 12,056, and 12,662, for paranoia, hallucinations, and NS, respectively. These *N* reflect the inclusion of all participants with complete and incomplete longitudinal data (Supplementary Table 4.1).

3.2.2 – Measures

Paranoia, hallucinations, and NS were assessed using the subscales of the SPEQ (Ronald et al., 2014), described in Section 2.2.2. Paranoia, hallucinations, and NS items are listed in Supplementary Information 2.1-2.2.

3.2.3 – Statistical analyses

3.2.3.1 – Overview of analyses

Prior to the main analyses (described in Section 3.2.3.2, below), a series of methods were tested in an exploratory manner to determine the optimal way to model the

nonindependence of the data arising from the genetic relatedness between the twins. The alternative modelling strategies and the results of these models are presented in the Appendix for this Chapter (Section 3.5). For the main analyses, a series of alternative growth forms were tested, as follows.

3.2.3.2 – LGCM

Four different LGCM were run to test the optimal functional form of growth for the data for each PENS dimension. The following models were tested. Model 1) intercept-only model, which specifies no systematic change over time. One latent factor was specified (the intercept), in which all factor loadings were fixed to one. The mean and variance of the latent intercept factor, as well as the time point-specific residual variances were estimated.

Model 2) linear growth model, which specifies that the latent growth process is captured by an initial baseline (intercept) and a linear slope. The means and variances of the two latent factors (as well as the covariance between them), and the time point-specific residual variances were estimated. Like in the intercept-only model, the factor loadings of the intercept were fixed to one. The slope factor loadings were set to reflect the passage of time between measurement occasions: age 16 set to zero, age 17 set to one (i.e., 17 - 16 = 1), and age 22 set to six (i.e., 22 – 16 = 6).

Model 3) quadratic growth model, which specifies that the latent growth process is captured by an intercept, a linear slope, and a quadratic slope. The means and variances of the three latent factors intercept (as well as the covariances between them), and the time point-specific residual variances were estimated. Factor loadings for the intercept and linear slope were the same as for the linear model. The quadratic slope factor loadings were the square values of the linear slope loadings: age 16 set to zero (i.e., $0^2 = 0$), age 17 set to one (i.e., $1^2 = 1$), and age 22 set to 36 (i.e., $6^2 = 36$). Because a quadratic model is not identified with only three measurement occasions, the quadratic slope variance parameters were not estimated, to

achieve a just-identified model. In addition, it was planned that residual variances would be constrained to equality to achieve over-identification (i.e., to estimate model fit statistics). Though see Section 3.3 for modifications made to the residual variances.

Model 4) latent basis model, which specifies that the latent growth process is captured by an intercept, and a freely estimated slope. This model allowed the factor loading between the first and last measurement occasions to be freely estimated. The means and variances of the two latent factors (as well as the covariance between them), and the time point-specific residual variances were estimated. The slope factor mean in this model represents the total unit change from the first to the last measurement occasion, and the estimated factor loading represents the proportion of total change up until the associated time point. Factor loadings for the slope factor were fixed to zero at age 16, freely estimated at age 17, and fixed to one at age 22. Because a latent basis model is just identified with only three measurement occasions, it was planned that residual variances would be constrained to equality to achieve over-identification (though see modifications in Section 3.3).

3.2.3.3 – Model fit

A series of goodness of fit indices were used to assess the standalone model fit of the LGCM: these indices were CFI, RMSEA, and SRMR. Whilst the use of cut off values is debated (Marsh et al., 2004), CFI values > 0.95/0.90, RMSEA values < 0.06, and SRMR values < 0.08 were considered to reflect generally acceptable fit (Hu & Bentler, 1999; Marsh et al., 2004; van de Schoot et al., 2012).

For assessing the relative fit between the LGCM, BIC was primarily used, with lower values indicative of better fit. A difference between the values in excess of a value of two was considered to reflect 'positive' evidence, and a difference between the values in excess of 10 was considered 'very strong' evidence (Neath & Cavanaugh, 2012). AIC was referred to where the difference in BIC values was less than two, with lower values indicative of

better fit. A difference between AIC values in excess of two was considered 'strong' evidence (Burnham & Anderson, 2004).

3.2.3.4 – Data modelling

Any data that was missing was assumed to be missing at random, accommodated using FIML estimation. Observed total score data at each age was modelled and a robust version of the FIML estimator was used (MLR) to correct for multivariate non-normality of the residuals of the observed scores. MLR adjusts both the *SE* and the overall test statistic. All models were estimated using the lavaan package (Rosseel, 2012) in R (version 2.5.2).

3.3 – Results

3.3.1 – LGCM

3.3.1.1 – Paranoia

Table 3.1 shows the model fit results for the LGCM for paranoia. As expected, the intercept-only model provided a poor fit to the data across fit indices. The linear growth model provided acceptable standalone fit to the data (CFI = 0.996, RMSEA = 0.033 [0.020, 0.047], SRMR = 0.018). The over-identified quadratic model provided an acceptable fit to the data. The over-identified latent basis model resulted in an improper solution, with at least one element of the latent variable covariance matrix being non-positive definite (i.e., indicating either a correlation greater than or equal to one, a negative variance, or a linear dependency between factors). Removing the residual variance at age 22 but allowing free estimation of the age 16 and 17 residual variances resulted in a proper solution, and this model provided an acceptable fit the data that was indistinguishable to the linear model in terms of CFI, RMSEA, and SRMR. BIC and AIC values suggested marginally better fit of the modified latent basis model. The adjustment to the age 22 residual variance was made because this estimate was nonsignificant in the linear model.

The linear model was selected in the interest of parsimony. Parameter estimates for the linear growth model are shown in Table 3.2. The average baseline score (intercept) was 12.238 (*SE* = 0.121, *z* = 101.141, *p* < .001) and the average yearly change in reporting paranoia was -0.369 (*SE* = 0.024, *z* = -15.138, *p* < .001). Variability around these averages was 83.987 (*SE* = 3.221, *z* = 26.027, *p* < .001) for the intercept, or 9.164 in standard deviation units. For the slope factor, variability was much less (3.012, *SE* = 0.571, *z* = 5.271, *p* <.001, or 1.736 in standard deviation units). Covariance between the latent factors was negative (-5.683, *SE* = 0.536, *z* = -10.596, *p* < .001) and was moderate in strength (*r* = -0.363). Figure 3.1 shows a plot of the mean estimated trajectory against a random draw of observed scores.

3.3.1.2 – Hallucinations

Table 3.3 shows the model fit results for the LGCM for hallucinations. As expected, the intercept-only model provided a poor fit to the data across fit indices. The linear model provided an acceptable fit to the data in terms of CFI (0.933) and SRMR (0.070), though less so in terms of RMSEA (0.117). The over-identified quadratic model resulted in an improper solution, with at least one element of the latent variable covariance matrix being non-positive definite (indicating either a correlation greater than or equal to one, a negative variance, or a linear dependency between factors). Removing the residual variance at age 22 but allowing free estimation of the age 16 and 17 residual variances resulted in a proper solution, and this model provided the best fit to the data, both in terms of standalone fit (CFI = 0.999, RMSEA = 0.015 [0.000, 0.043], SRMR = 0.012) and relative fit. A solution could not be obtained for the over-identified latent basis model. Removing the residual variance at age 22 but allowing free estimation of the age 16 and 17 residual variances resulted in a proper solution, and this model provided acceptable fit to the data across fit indices. The adjustment to the age 22 residual variance (in the quadratic and latent basis models) was made because this estimate was nonsignificant in the linear model.

The constrained quadratic model and latent basis models best represented the functional form of growth for hallucinations. However, it was decided that the complexity of the quadratic model in tandem with the necessary constraints for both models were not worth the gain in fit compared to the linear model (e.g., Grimm et al., 2011). The linear model was selected in the interest of parsimony; considered to adequately represent the functional form of growth owing to its acceptable standalone fit (as reported above).

Parameter estimates for the linear model are shown in Table 3.4. The average baseline score (intercept) was 4.876 (*SE* = 0.073, *z* = 67.164 *p* < .001) and the average yearly change in reporting hallucinations was -0.526 (*SE* = 0.013, *z* = -41.960, *p* < .001). Variability around these averages was 27.798 (*SE* = 1.227, *z* = 22.798, *p* < .001) for the intercept, or 5.272 in standard deviation units. For the slope factor, variability was much less (0.600, *SE* = 0.137, *z* = 4.361, *p* < .001, or 0.775 in standard deviation units). Covariance between the latent factors was negative (-3.125, *SE* = 0.205, *z* = -15.257, *p* < .001) and was high in magnitude (*r* = -0.763). Figure 3.2 shows a plot of the mean estimated trajectory against a random draw of observed scores.

3.3.1.3 – Negative symptoms

Table 3.5 shows the model fit results for the LGCM for NS. The intercept-only model provided an acceptable fit to the data across fit indices. A linear growth model provided acceptable fit to the data (CFI = 0.965, RMSEA = 0.024 [0.011, 0.041], SRMR = 0.014) and provided the best standalone fit across models. The over-identified quadratic model provided an acceptable fit to the data. A solution could not be obtained for the over-identified latent basis model. There was no justification for removing residual variances (as was the case for paranoia and hallucinations), and removal of the slope variance – motivated by the non-significance of this estimate in the linear model, resulted in an improper solution. No further adjustments were made.

The linear model was selected. Parameter estimates for the modified linear model are shown in Table 3.6. The average baseline score (intercept) was 2.256 (*SE* = 0.038, *z* = 59.453, *p* < .001) and the average total change in reporting negative symptoms across the developmental period was 0.071 (*SE* = 0.007, *z* = 10.355, *p* < .001). Variability around these averages was 6.917 (*SE* = 0.361, *z* = 19.184, *p* < .001) for the intercept, or 2.630 in standard deviation units. For the slope factor, variability was nonsignificant (0.056, *SE* = 0.056, *z* = 0.996, *p* = .319, or 0.237 in standard deviation units), as was the factor covariance (-0.084, *SE* = 0.053, *z* = -1.583, *p* = .113). Figure 3.3 shows a plot of the mean estimated trajectory against a random draw of observed scores.

Table 3.1

Latent Growth Curve Modelling of Paranoia for Different Functional Forms of Growth: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Intercept-only model	5	-80,247.673	160,505.345	160,542.330	352.740 (4), $p < .001$	0.823	0.105 [0.096, 0.115]	0.088
Linear growth model	8	-79,983.474	159,982.947	160,042.123	17.657 (1), $p < .001$	0.996	0.033 [0.020, 0.047]	0.018
Quadratic growth model [a]	7	-80,092.438	160,198.877	160,250.655	134.876 (2), $p < .001$	0.925	0.097 [0.084, 0.112]	0.085
Latent basis growth model [b]	7	-79,982.140	159,980.279	160,039.454	10.527 (1), $p = .001$	0.997	0.031 [0.018, 0.045]	0.025

Note. N = 12,051. Related and unrelated individuals included, using cluster-robust *SE*. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. [a] Quadratic slope variance-covariance parameters not estimated. Residual variances constrained to equality. [b] Residual variances constrained to equality. Residual variance at age 22 not estimated.

Table 3.2

Parameter Estimates for Paranoia from Linear Growth Model

	Mean				Variance			
	Estimate	Standard error	*z*	*p*	Estimate	Standard error	*z*	*p*
Intercept	12.238	0.121	101.141	< .001	83.987	3.221	26.072	< .001
Slope	-0.369	0.024	-15.138	< .001	3.012	0.571	5.271	< .001
16 years	-	-	-	-	29.503	2.742	10.760	< .001
17 years	-	-	-	-	79.662	4.731	16.838	< .001
22 years	-	-	-	-	8.064	18.633	0.433	0.672

	Estimate	Standard error	*z*	*p*	Standardised estimate
Factor covariance	-5.683	0.536	-10.596	< .001	-0.363

Note. N = 12,051. Related and unrelated individuals included, using cluster-robust *SE*. Unstandardised estimates (unless otherwise indicated).

Table 3.3

Latent Growth Curve Modelling of Hallucinations for Different Functional Forms of Growth: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Intercept only model	5	-66,359.938	132,729.876	132,766.862	1,581.152 (4), $p < .001$	0.000	0.274 [0.263, 0.286]	0.247
Linear growth model	8	-64,621.298	129,258.596	129,317.775	189.755 (1), $p < .001$	0.933	0.117 [0.101, 0.133]	0.070
Quadratic growth model [a]	8	-64,541.081	129,098.162	129,157.340	2.193 (1), $p < .001$	0.999	0.015 [0.000, 0.043]	0.012
Latent basis growth model [b]	7	-64,571.621	129,159.243	129,218.421	20.891 (1), $p <.001$	0.972	0.073 [0.051, 0.105]	0.042

Note. N = 12,056. Related and unrelated individuals included, using cluster-robust *SE*. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. [a] Quadratic slope variance-covariance parameters not estimated. Residual variance at age 22 not estimated. [b] Residual variance at age 22 not estimated.

Table 3.4

Parameter Estimates for Hallucinations from Linear Growth Model

	Mean				Variance			
	Estimate	Standard error	*z*	*p*	Estimate	Standard error	*z*	*p*
Intercept	4.876	0.073	67.164	< .001	27.980	1.227	22.978	< .001
Slope	-0.526	0.013	-41.960	< .001	0.600	0.137	4.361	< .001
16 years	-	-	-	-	9.852	1.136	8.672	< .001
17 years	-	-	-	-	28.224	1.624	17.379	< .001
22 years	-	-	-	-	5.034	4.242	1.187	.246

	Estimate	Standard error	*z*	*p*	Standardised estimate
Factor covariance	-3.125	0.205	-15.257	< .001	-0.763

Note. *N* = 12,056. Related and unrelated individuals included, using cluster-robust *SE*. Unstandardised estimates (unless otherwise indicated).

Table 3.5

Latent Growth Curve Modelling of Negative Symptoms for Different Functional Forms of Growth: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Intercept only model	5	-59,574.888	119,159.775	119,197.007	83.728 (4), p <.001	0.965	0.057 [0.047, 0.068]	0.033
Linear growth model	8	-59,493.463	119,002.926	119,062.497	8.211 (1), p <.001	0.998	0.024 [0.011, 0.041]	0.014
Quadratic growth model [a]	7	-59,538.377	119,090.754	119,142.879	28.503 (2), p <.001	0.980	0.060 [0.042, 0.081]	0.045

Note. N = 12,662. Related and unrelated individuals included, using cluster-robust *SE*. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. [a] Quadratic slope variance-covariance parameters not estimated. Residual variances constrained to equality. A proper solution could not be obtained for a latent basis model so no results are reported.

Table 3.6

Parameter Estimates for Negative Symptoms from Linear Growth Model

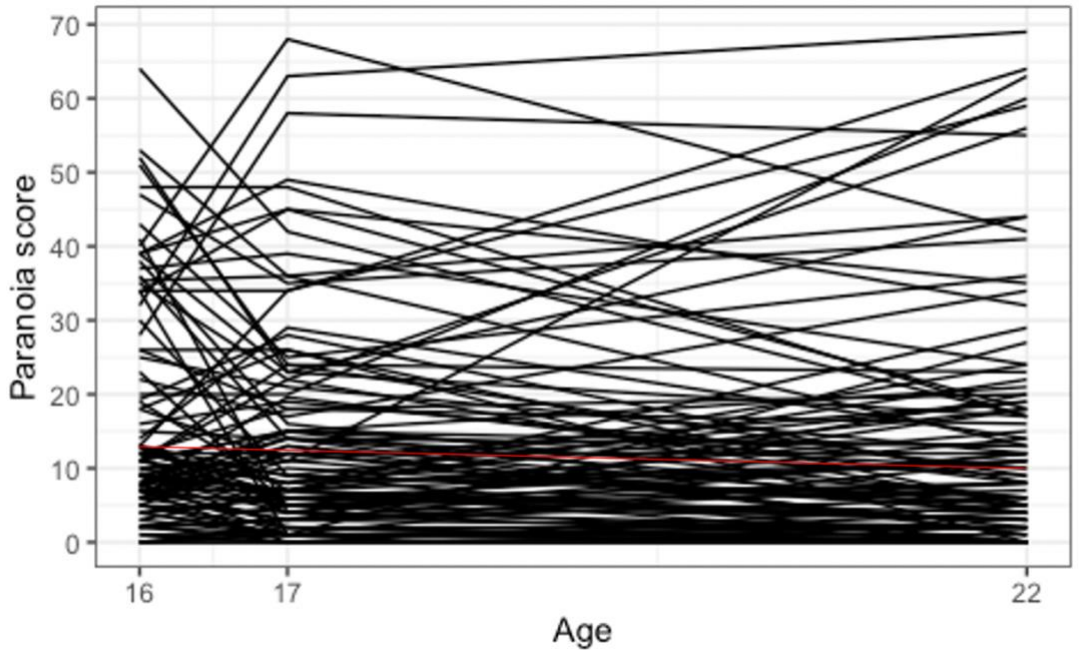
	Mean				Variance			
	Estimate	Standard error	*z*	*p*	Estimate	Standard error	*z*	*p*
Intercept	2.256	0.038	59.453	< .001	6.917	0.361	19.18	< .001
Slope	0.071	0.007	10.355	< .001	0.056	0.056	0.996	.319
16 years	-	-	-	-	3.446	0.325	10.603	< .001
17 years	-	-	-	-	5.704	0.557	10.241	< .001
22 years	-	-	-	-	5.183	1.802	2.876	.004

	Estimate	Standard error	*z*	*p*	Standardised estimate
Factor covariance	-0.084	0.053	-1.583	.113	-0.143

Note. N = 12,662. Related and unrelated individuals included, using cluster-robust *SE*. Unstandardised estimates (unless otherwise indicated).

Figure 3.1

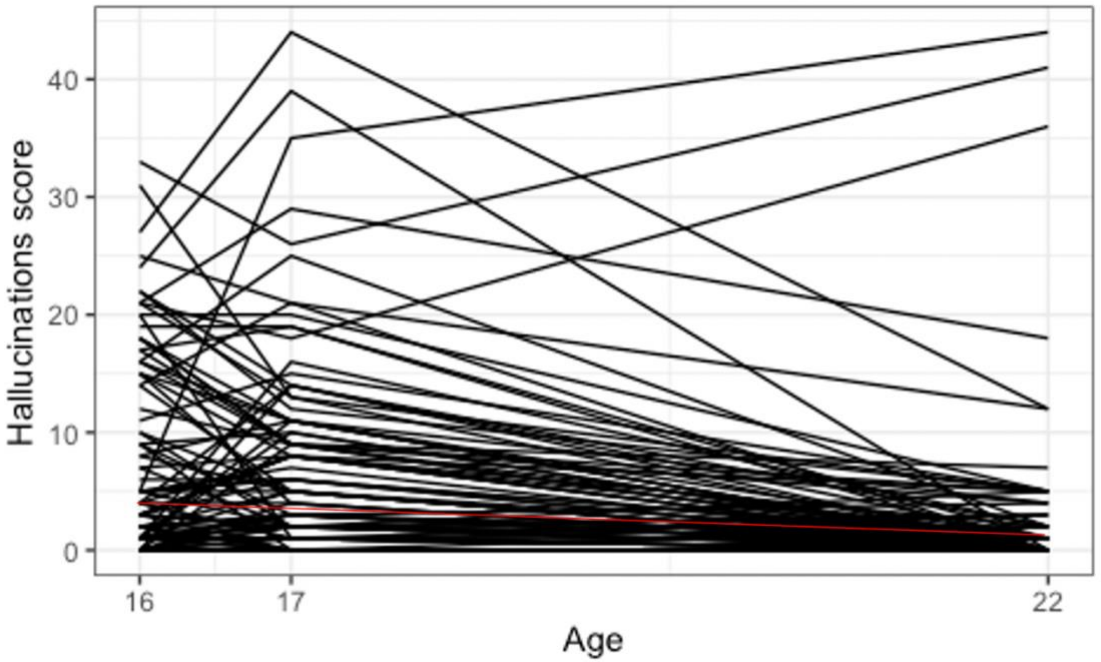
Spaghetti Plot of Individual Trajectories for Observed Paranoia Scores



Note. Individual trajectories are shown for a random draw of 100 individuals with complete data (seed 20). Mean trajectory estimated using a linear growth model across the whole sample (N = 12,051), plotted in red. Parameter estimates for the mean trajectory reported in Table 3.2.

Figure 3.2

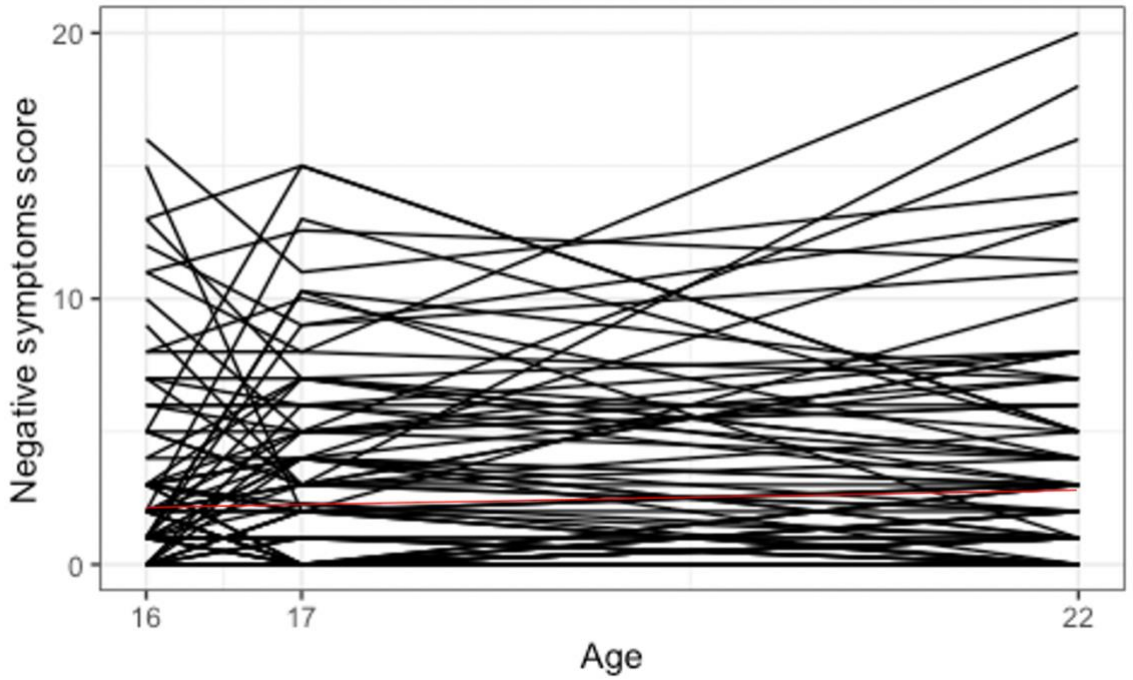
Spaghetti Plot of Individual Trajectories for Observed Hallucinations Scores



Note. Individual trajectories are shown for a random draw of 100 individuals with complete data (seed 20). Mean trajectory estimated using a linear growth model across the whole sample (*N* = 12,056), plotted in red. Parameter estimates for the mean trajectory reported in Table 3.4.

Figure 3.3

Spaghetti Plot of Individual Trajectories for Observed Negative Symptoms Scores



Note. Individual trajectories are shown for a random draw of 100 individuals with complete data (seed 20). Mean trajectory estimated using a linear growth model across the whole sample (*N* = 12,662), plotted in red. Parameter estimates for the mean trajectory reported in Table 3.6.

3.4 – Discussion

This Chapter investigated the latent developmental course of paranoia, hallucinations, and NS, measured as separate dimensions across ages 16, 17, and 22 in the community.

As was hypothesised, the linear growth model provided an acceptable approximation of the data for paranoia, hallucinations, and NS. Whilst for hallucinations the quadratic model and latent basis model in fact both provided a better fit than the linear model, these models were highly constrained, both for initial model (over-)identification and to obtain a plausible solution. Such data-driven constraints render the models at risk of having been overfit to sample-specific variability, thus limiting their generalisability and interpretability (Preacher, 2006), and so the linear model was preferred given its acceptable fit. However, replication in an independent sample, with at least four time points of data, is necessary to understand the extent to which repeated measures of hallucinations may be influenced by nonlinear aspects of (latent) growth.

The results of the linear growth models suggested that the within-person development of both paranoia and hallucinations from adolescence to emerging adulthood is characterised by relatively low baseline scores that show moderate but significant decline over time. These findings are broadly in line with previous findings of aggregated PEs measured across adolescence (Lin et al., 2011; Wigman, van Winkel, Raaijmakers, et al., 2011), though they differ from a study in adulthood, in which these experiences did not systematically change over time (Wigman, van Winkel, Jacobs, et al., 2011). The current results further suggested that there is significant between-person variability for both paranoia and hallucinations in terms of both baseline scores and in terms of systematic change in these scores over time. The latent factor covariances reflect that individuals with a higher-than-average latent baseline score are more likely to have a lower-than-average latent rate of change over time

(and vice versa). This between-person variability and co-variability of the latent growth parameters is the point of departure for subsequent growth mixture modelling (Chapter 4).

For NS, the opposite pattern of systematic change over time was found. The results suggested that the sample-wide, within-person development of these symptoms from adolescence to emerging adulthood is characterised by relatively low baseline scores that show a modest but significant increase over time. Whilst there are no published findings on the *latent* development of NS in the community to my knowledge, the results are broadly in line with findings from a study that found an increase in the prevalence of NS across adolescence into emerging adulthood (Dominguez et al., 2010). The current results also suggested that there is significant between-person variability in terms of scores of NS at age 16, though the nonsignificant slope factor variance indicated that individuals do not significantly differ in their rates of change over time. Subsequent growth mixture modelling for NS is thus motivated by the between-person variability in latent intercepts.

A subsidiary aim of this Chapter was to test the adequacy of using the cluster method to account for the relatedness between individuals in the sample. As shown from the results presented in the Appendix (Supplementary Information 3.1), using data from both twins with adjusted standard errors was deemed acceptable for accounting for the nonindependence of the data. This was based on the model fit results and the similar parameter estimates between the methods, as well as the relative parsimony of the cluster method compared to the interchangeable dyads method. The better fit of the model using the interchangeable dyads method (compared to the cluster method) for hallucinations suggested that there may be some differences in the extent to which latent growth factors (and residuals) covary within monozygotic and dyzygotic twin dyads. Notwithstanding, the good fit of the models using the interchangeable dyads method for each of the measures indicated that the latent growth process for each of paranoia, hallucinations, and NS can be considered sufficiently equivalent

for both members of a twin-pair, for both monozygotic and dyzygotic twins. This provided confidence in the subsequent growth modelling using the cluster method, whereby zygosity was effectively ignored.

The results in this Chapter add to only a handful of other studies that have reported on sample-wide characteristics of latent growth in PEs analysed broadly (Lin et al., 2011; Wigman, van Winkel, Jacobs, et al., 2011; Wigman, van Winkel, Raaijmakers, et al., 2011). They are the first to report on the latent development of paranoia and hallucinations, *separately*, and they are the first to report on latent development of NS in the community. The current Chapter further presents a detailed evaluation of alternative forms of growth. Notwithstanding, future studies of PENS dimensions with data from more than three measurement occasions would allow for a yet more comprehensive evaluation of nonlinear forms of growth.

This Chapter reported the sample-wide characteristics of latent growth for paranoia, hallucinations, and NS reported across ages 16, 17, and 22 in the community. The results will further aid subsequent growth mixture modelling (Chapter 4), having established the adequacy of, i) using a linear growth form to represent latent growth in the PENS dimensions, and ii) using the cluster method to account for the nonindependence of twin data in the current dataset.

3.5 – Appendix

Supplementary Information 3.1

Modelling the Nonindependence of Data

Methods: A series of models were conducted to determine the adequacy of using the cluster method (b, below) to model the nonindependence of the data. A linear LGCM was used to test the different modelling techniques, a) using data from one (randomly selected) individual per twin pair, b) using data from both individuals in each twin pair, with family ID specified as a cluster unit and standard errors adjusted for this clustering, and, c) using data from both individuals in each twin pair, specifying an interchangeable dyads model to account for monozygotic twin pair-/dyzygotic twin pair-specific nonindependence. The interchangeable dyads model tested the extent to which the latent growth process was equivalent for both twins within twin-pairs, irrespective of zygosity, whilst allowing for within-pair covariance differences (Olsen & Kenny, 2006).

Results: Supplementary Tables 3.1-3.3 show the model fit results of the linear LGCM for each modelling technique, for paranoia, hallucinations, and NS, respectively. For paranoia and NS, all methods resulted in acceptable standalone model fit across fit indices, with CFI values comparable between all methods (1.00).

For hallucinations, CFI values were acceptable (i.e., > 0.90) for all methods, though were highest for the interchangeable dyads method (0.974). SRMR values were acceptable for all methods (< 0.08), though RMSEA values were notably less acceptable (> 0.06) for all but the interchangeable dyads method.

Supplementary Tables 3.4-3.6 show the parameter estimates derived using the alternative techniques, for paranoia, hallucinations, and NS, respectively. Parameter estimates derived from the different methods for each of the measures were similar, varying by less

than 0.5 units. In the interest of parsimony and consistency, and given the broadly acceptable model fit, the cluster method was selected to take forward across measures.

Supplementary Table 3.1

Latent Growth Curve Modelling of Paranoia Using Alternative Modelling Techniques: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Cluster (family) [a]								
Linear growth model	8	-79,983.471	159,982.952	160,042.121	17.662 (1), $p < .001$	0.996	0.033 [0.020, 0.046]	0.025
One twin per pair [b]								
Linear growth model	8	-39,894.293	79,804.584	79,858.212	12.124 (1), $p < .001$	0.997	0.045 [0.000, 0.000]	0.022
Interchangeable dyads [c]								
Linear growth model	18	-78,701.226	157,438.434	157,559.696	39.544 (36), $p = .323$	0.995	0.012 [0.001, 0.023]	0.034

Note. [a] N = 12,051. [b] N = 6,029. [c] N = 12,051. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual.

Supplementary Table 3.2

Latent Growth Curve Modelling of Hallucinations Using Alternative Modelling Techniques: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Cluster (family) [a]								
Linear growth model	8	-64,621.298	129,258.596	129,317.775	189.755 (1), $p < .001$	0.935	0.117 [0.000, 0.000]	0.070
One twin per pair [b]								
Linear growth model	8	-32,404.073	64,824.146	64,877.782	85.346 (1), $p < .001$	0.954	0.107 [0.000, 0.000]	0.063
Interchangeable dyads [c]								
Linear growth model	20	-63,583.160	127,206.320	127,341.053	62.911 (34), $p = .002$	0.974	0.028 [0.017, 0.039]	0.067

Note. [a] N = 12,056. [b] N = 6,030. [c] N = 12,056. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual.

Supplementary Table 3.3

Latent Growth Curve Modelling of Negative Symptoms Using Alternative Modelling Techniques: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
Cluster (family) [a]								
Linear growth model	8	-59,493.463	119,002.926	119,062.497	8.211 (1), $p < .001$	1.00	0.024 [0.011, 0.041]	0.014
One twin per pair [b]								
Linear growth model	8	-29,806.044	59,628.089	59,682.110	5.701 (1), $p < .001$	1.00	0.022 [0.000, 0.000]	0.013
Interchangeable dyads [c]								
Linear growth model	20	-57,809.718	115,659.435	115,794.500	52.764 (34), $p = .021$	1.00	0.019 [0.008, 0.029]	0.055

Note. [a] N = 12,662. [b] N = 6,327. [c] N = 12,662. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual.

Supplementary Table 3.4

Parameter Estimates for Paranoia derived from the Alternative Modelling Techniques

	Mean				Variance				Factor covariance			
	Estimate	Standard error	*z*	*p*	Estimate	Standard error	*z*	*p*	Estimate	Standard error	*z*	*p*
Cluster (family) [a]												
Linear growth model												
Intercept	12.238	0.121	101.141	< .001	83.987	3.221	26.072	< .001				
Slope	-0.369	0.024	-15.138	< .001	3.012	0.571	5.271	< .001	-5.683	0.536	-10.596	< .001
One twin per pair [b]												
Linear growth model												
Intercept	12.305	0.150	82.315	< .001	84.341	4.365	19.320	< .001				
Slope	-0.370	0.032	-11.471	< .001	2.746	0.748	3.673	< .001	-5.185	0.712	-7.283	< .001
Interchangeable dyads [c]												
Linear growth model												
Intercept	12.251	0.121	101.431	< .001	84.171	3.177	26.495	< .001				
Slope	-0.376	0.024	-15.394	< .001	2.921	0.499	5.850	< .001	-5.709	0.523	-10.916	< .001

Note. [a] N = 12,051. [b] N = 6,029. [c] N = 12,051. Unstandardised estimates.

Supplementary Table 3.5

Parameter Estimates for Hallucinations derived from the Alternative Modelling Techniques

	Mean				Variance				Factor covariance			
	Estimate	Standard error	*z*	*p*	Estimate	Standard error	*z*	*p*	Estimate	Standard error	*z*	*p*
Cluster (family) [a]												
Linear growth model												
Intercept	4.876	0.073	67.164	< .001	27.980	1.227	22.798	< .001				
Slope	-0.526	0.013	-41.960	< .001	0.600	0.137	4.361	< .001	-3.125	0.205	-15.257	< .001
One twin per pair [b]												
Linear growth model												
Intercept	4.980	0.091	54.597	< .001	28.323	1.686	16.799	< .001				
Slope	-0.539	0.016	-32.757	< .001	0.573	0.163	3.510	< .001	-3.075	0.285	-10.791	< .001
Interchangeable dyads [c]												
Linear growth model												
Intercept	4.856	0.073	66.310	< .001	28.119	1.240	22.672	< .001				
Slope	-0.526	0.013	-41.800	< .001	0.601	0.138	4.370	< .001	-3.157	0.207	-15.218	< .001

Note. [a] N = 12,056. [b] N = 6,030. [c] N = 12,056. Unstandardised estimates.

Supplementary Table 3.6

Parameter Estimates for Negative Symptoms derived from the Alternative Modelling Techniques

	Mean				Variance				Factor covariance			
	Estimate	Standard error	*z*	*p*	Estimate	Standard error	*z*	*p*	Estimate	Standard error	*z*	*p*
Cluster (family) [a]												
Linear growth model												
Intercept	2.256	0.038	59.453	< .001	6.917	0.361	19.184	< .001				
Slope	0.071	0.007	10.355	< .001	0.056	0.056	0.996	.319	-0.084	0.053	-1.583	.113
One twin per pair [b]												
Linear growth model												
Intercept	2.273	0.045	51.029	< .001	7.027	0.456	15.416	< .001				
Slope	0.073	0.008	8.164	< .001	0.044	0.073	0.608	.543	-0.066	0.068	-0.974	.330
Interchangeable dyads [c]												
Linear growth model												
Intercept	2.279	0.038	59.511	< .001	7.068	0.365	19.353	< .001				
Slope	0.071	0.007	10.241	< .001	0.052	0.057	0.901	.368	-0.087	0.055	-1.594	.111

Note. [a] N = 12,662. [b] N = 6,327. [c] N = 12,662. Unstandardised estimates.

Chapter 4 – Growth mixture modelling of paranoia, hallucinations, and negative symptoms

4.1 – Introduction

The current Chapter builds on the findings presented in Chapter 3, by focussing on *different developmental trajectories* within the sample. As discussed in Section 1.5.2, previous studies have found that persistence compared to transience of PENS appears to be predictive of poor clinical and functional outcomes (e.g., De Loore et al., 2011; Dominguez et al., 2010; Janssens et al., 2016). Therefore, identifying subgroups of individuals who follow distinct trajectories can be considered the first step in seeking to understand the antecedents, correlates and outcomes associated with the differential developmental course of PENS.

Building on studies that have manually classified individuals according to similarities in their trajectories (as reviewed in Section 1.5.5) – the latent growth curve framework can be extended to identify *unobserved*, latent subgroups of individuals who follow similar trajectories, using growth mixture modelling (GMM). Previous studies that have used GMM to estimate latent trajectory classes have identified either a persistently high or increasing class for aggregated PEs measured across adolescence (Bourque et al., 2017; Lin et al., 2011; Mackie et al., 2011; Thapar et al., 2012; Wigman, van Winkel, Raaijmakers, et al., 2011), and adulthood (Wigman, van Winkel, Jacobs, et al., 2011). The findings of these studies are important, because they have found that membership in the most elevated of the estimated latent trajectory classes (e.g., persistently high, or increasing, compared to decreasing, or persistently low) is associated with a range of suboptimal correlates including low

socioeconomic status (SES), emotional and behavioural problems, and a range of poor outcomes including mental health care use. Thus, these findings broadly concur with findings derived from studies that have manually classified individuals into trajectory groups (see Section 5.1). The current Chapter builds on the prior literature by modelling latent heterogeneity in the development of paranoia and hallucinations measured as separate dimensions, and by modelling latent heterogeneity in the development of NS in the community – which, to my knowledge has not previously been done.

The analyses in this Chapter investigated whether and to what extent individuals can be classified into distinct, latent trajectory classes for paranoia, hallucinations, and NS. This is of standalone interest, and further will provide the basis for the subsequent testing of associations between membership in the latent trajectory classes with previously reported childhood and adulthood characteristics, and with previously unreported polygenic propensity scores for a range of psychiatric and educational outcomes – which is the focus of Chapter 5.

As preregistered, it was hypothesised that multiple latent trajectory classes including a persistent trajectory class would be identified across PENS (https://osf.io/pax6k; Supplementary Information 4.1).

4.2 – Methods

4.2.1 – Participants

The TEDS sample is described in Section 2.2.1.1. For the study conducted in Chapter 4, data from both twins was used, with standard errors adjusted for familial clustering. Individuals completed questions relating to paranoia and hallucinations at mean ages 16.32 years (*SD* 0.68; range 14.91-21.34), 17.06 years (*SD* 0.88; range 15.55-19.0), and 22.85 years (*SD* 0.88; range 21.16-25.19). Parents completed questions relating to their twins' NS at

mean ages 16.32 years (*SD* 0.68; range 14.91-19.45), 17.06 years (*SD* 0.88; range 15.55-19.0), and 22.30 years (*SD* 0.93; range 20.56-25.59).

N for paranoia at ages 16, 17, and 22 were 9,898, 2,937, and 8,340, respectively. *N* for hallucinations at ages 16, 17, and 22 were 9,907, 2,940, and 8,338, respectively. *N* for NS at ages 16, 17, and 22 were 9,944, 2,939, and 10,355 respectively (Table 4.1).

Cross-age *N* for paranoia = 12,049, hallucinations = 12,054, and negative symptoms = 12,652, reflecting the inclusion of all participants with complete and incomplete longitudinal data. At least one value of *age* in parallel with the PENS data was required for the models (Section 4.2.3.3), so the minor discrepancies between the *N* in this Chapter and those in Chapter 3 reflect the exclusion of individuals without this age data.

Individuals with PENS data at age 22 as well as either age 16 or ages 16 and 17, had higher SES scores and were more likely to be female than individuals without PENS data at age 22 (Supplementary Tables 4.1-4.3).

4.2.2 – Measures

Paranoia, hallucinations, and NS were assessed using the subscales of the SPEQ (Ronald et al., 2014), described in Section 2.2.2. Paranoia, hallucinations, and NS items are listed in Supplementary Information 2.1-2.3.

4.2.3 – Statistical analyses

4.2.3.1 – Overview of analyses

GMM was used to investigate latent heterogeneity in the development of each of paranoia, hallucinations, and NS.

4.2.3.2 – GMM

The repeated measures were represented as a function both of the latent growth parameters and of the probability associated with the categorical latent class variable (i.e., the probability of latent class membership) (Ram & Grimm, 2009). Figuratively, this can be understood such that individuals were classified according to similarities in their latent trajectories. Figure 4.1 shows a path diagram of a linear GMM.

4.2.3.3 – Modelling of time

Individual time scores were incorporated in the GMM by allowing individual (random) slope factor loadings through the application of definition variables (Mehta & West, 2000). This approach was used because of the known within-wave variability of time (age) in the sample (Table 4.1). The definition variable approach is reflected in the path diagram of the GMM shown in Figure 4.1.

4.2.3.4 – Parameters

The parameters estimated in the GMM were as follows: a) the means of the latent intercept and slope growth factors, b) the variances of the growth factors, c) the residual variances (interpreted as *wave*-specific residual variances in individual time score models), and d) the covariance between the latent growth factors. For the 1-class GMM (which is functionally equivalent to an LGCM), one set of parameters (a-d, above) was estimated. For models with more than one class ($k > 1$), these parameters were estimated for each class.

4.2.3.5 – Model fitting approach

4.2.3.5.1 – k-class models

Based on the findings of Chapter 3, all GMM models were specified to reflect a linear form of growth. A 1-class model was first estimated. Following the 1-class model, a sequentially increasing number of classes was specified, up to the point where there were consistent convergence issues (Jung & Wickrama, 2008).

Within each *k*-class (where *k* refers to the number of classes), two models were initially run: A latent class growth analysis (LCGA) model, which constrained the growth factor variances and covariances to zero, and an unconstrained GMM (Model 0), in which all parameters (a-d, Section 4.2.3.4) were allowed to differ between the classes.

4.2.3.5.2 – Constrained variance parameter models

Where there were convergence issues with Model LCGA and Model 0 (above), a series of constrained variance parameter models were run. These procedures follow the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS; van de Schoot et al., 2017).

Models with constraints on one variance parameter (Models 1A-1C) and two variance parameters (Models 2A-2C) were tested. Specification was as per Model 0, with specific equality constraints as follows: Model 1A: Within-class residual variances. Model 1B: Between-class residual variances. Model 1C: Between-class growth factor variances. Model 2A: Within-class and between-class residual variances. Model 2B: Within-class residual variances and between-class growth factor variances. Model 2C: Between-class residual variances and between-class growth factor variances.

4.2.3.6 – Model selection

For each *k*-class, the model with the lowest BIC value was selected. These models were rerun using the two seed values corresponding to the highest replicated loglikelihood value (Jung & Wickrama, 2008; Shireman et al., 2016). Replication using the seed numbers corresponding to specific start values indicates that the best loglikelihood is likely to be a global and not just a local solution, which would reflect that there are multiple solutions (Shireman et al., 2016).

Where BIC values were indistinguishable (difference < 10), the AIC values were referred to and the model with the lowest AIC value (difference > 2) was selected. The best fitting overall model was determined by jointly considering, i) BIC values (and AIC where

necessary), ii) entropy values (which reflect the model's ability to classify individuals into separate classes, with an entropy value of one reflecting perfect classification accuracy), iii) empirical plausibility of the within-class parameter estimates, and iv) theoretical plausibility of the latent classes.

4.2.3.7 – Post hoc sensitivity tests

Two sets of post hoc sensitivity tests were conducted. One, to test a more parsimonious parameterisation of the data – where the *k*-1-class model of the overall best fitting *k*-class model was unconstrained (i.e., Model 0), models 1A-2C for *k*-1 were also run. A homoscedastic model (Model 2C) was also run if the best fitting *k*-class model was unconstrained and further constrained models had not already been run.

Two, to test for the significance of the difference between the slopes – where the slopes of the latent classes in the best fitting model appeared visually parallel, two tests were run: i) an equivalent model with constrained slope factor means, and ii) Wald tests of the differences between the slopes. Better fit of the original model (compared to the model with the constrained slope factor means), and a significant Wald test statistic (*W*, which is chi-square distributed) would imply that the difference between the slope factor means is significant – suggesting that the latent classes differ in terms of the magnitude of their slopes.

4.2.3.8 – Complete data analyses

The same model-fitting procedures that were applied to data from the whole sample were applied using data only from individuals with complete data.

4.2.3.9 – Estimation

Details of the initial stage starts, final stage optimizations and initial stage iterations, as well adjustments to all models are provided in the decision-making flowchart shown in Supplementary Figure 4.1.

4.2.3.10 – Trajectory descriptors

For consistency, growth factor parameters were labelled in the following way: Positive slope factor mean with significant *z* statistic = 'increasing'. Negative slope factor mean with significant *z* statistic = 'decreasing'. Positive or negative slope factor mean with nonsignificant *z* statistic and low-level intercept factor mean = 'stable'. Positive or negative slope factor mean with nonsignificant *z* statistic and high-level intercept factor mean = 'persistent'.

4.2.3.11 – Data modelling

Mplus (version 8.6) was used for all data modelling. Any data that was missing was assumed to be missing at random, accommodated using FIML estimation. Observed total score data at each age was modelled, and a robust version of the FIML estimator was used (MLR) to correct for multivariate non-normality of the residuals of the observed scores. MLR adjusts both the standard errors and the overall test statistic. Wald tests were corrected using the MLR estimated covariance matrix. Variation in time scores (age) was modelled by allowing random slope factor loadings using the TSCORES application in Mplus.

4.3 – Results

Descriptive statistics for PENS data and age data and are reported in Table 4.1.

Model-fitting results for converged models are shown in Table 4.2. Estimated parameters are shown in Table 4.3, and trajectory plots from the best fitting models are shown in Figures 4.2-4.4, for paranoia, hallucinations, and NS, respectively.

4.3.1 – Paranoia

4.3.1.1 – Model fitting results

For the 1-class and 2-class models, the unconstrained GMM (Model 0) with freely estimated variances both within and between classes provided a superior fit compared to the LCGA models. This suggests within-class variability, or individual differences in the growth factors. For the 3-class models, the unconstrained GMM also fit better than the LCGA, though convergence was only possible with fixed parameters (as detailed below). Entropy values were higher for the 3-class models than for the 2-class models, though were notably less than one across all *k*-class models. Supplementary Table 4.4 shows that none of the 4-class models converged.

The 3-class Model 0 had the lowest BIC of all best fitting *k*-class models (Supplementary Table 4.4). Of note, estimation of this model (3-class Model 0) resulted in the fixing of the slope factor variance for one of the classes (subsequently referred to as the 'low-decreasing' class, as below). This constraint was applied (by Mplus) to avoid singularity of the information matrix, suggesting an estimated variance of zero for this parameter. The model was rerun using the start values from the constrained model, with the slope factor (co)variance parameters fixed to zero (as recommended by Mplus product support; L. Muthén, personal communication, 2021). Parameter estimates and classification probabilities for all best fitting *k*-class models are shown in Supplementary Tables 4.5 and 4.6, respectively.

4.3.1.2 – Model selection

In line with the model selection criteria (Section 4.2.3.6), the 3-class Model 0 was selected as the best fitting model owing to its relative fit (lowest BIC value), relative high entropy value, empirical plausibility of the within-class parameter estimates, and the

theoretical plausibility of the latent classes (i.e., the 3-class model was in line with the hypothesis that a persistent class would be identified).

The 3-class Model 0 estimated that, for most individuals, latent trajectories were characterised by mid-level (56.40%, 'mid-decreasing') or low-level (20.66%, 'low-decreasing') paranoia that decreased over time (Table 4.2, Figure 4.2, Supplementary Table 4.6). Latent trajectories for a smaller percentage of individuals (22.92%, 'high-persistent') were characterised by higher initial levels of paranoia that persisted over time. Variability around the growth factors was significant for the mid-decreasing and high-persistent latent classes. For the low-decreasing class, intercept variability was nonsignificant, and slope factor variance was fixed to zero (as noted previously).

Supplementary Table 4.6 shows that for the 3-class Model 0, individuals whose most likely class membership was the high-persisting class (of which there was a 75% probability) – probability of classification error was 25%: there was a 23% probability that they could be in the mid-decreasing class, and a 2% probability that they could be in the low-decreasing class. For individuals whose most likely class membership was either the mid-decreasing class or low-decreasing class (of which there was an 88% probability for each), probability of classification error was 12%.

4.3.1.3 – Post hoc sensitivity tests

Constrained 2-class models (Models 1A-2C) were run because the best fitting 2-class model (i.e., the *k*-1 model) was unconstrained. A 3-class homoscedastic model (Model 2C) was also run because the best fitting 3-class model was unconstrained. Better fit of the 3-class Model 0 was found compared both to the 2-class Models 1A-2C (Supplementary Table 4.7), and to a 3-class homoscedastic model (Model 2C) (*df* = 16, log-likelihood = -77,086.757, BIC = 154,324.861, entropy = 0.686).

The slopes of the best fitting model (3-class Model 0) appeared visually parallel across the classes. Constraining the slope factor means across classes resulted in worse fit (log-likelihood = -74,342.311, BIC = 148,891.350, entropy = 0.651) than the model with freely estimated slopes. Wald tests of the difference between the slopes were significant (mid-decreasing, high-persistent: $W(1) = 32.188$, $p < .001$; mid-decreasing, low-decreasing: $W(1) = 13.139$, $p < .001$; low-decreasing, high-persistent: $W(1) = 12.704$, $p < .001$). The results of both sets of analysis suggest significant differences in the average rates of change in paranoia between the classes.

4.3.1.4 – Complete data analyses

Model fitting results of the GMM conducted for individuals with complete data only are shown in Supplementary Table 4.8. Like the results for the whole sample, a 3-class unconstrained GMM provided the best fit to the data. Parameter estimates were broadly similar, with the most notable exception that the latent class characterised by high baseline paranoia scores in the complete-data subsample followed a decreasing trajectory, compared to a persistently high trajectory in the whole sample (Supplementary Table 4.9).

4.3.2 – Hallucinations

4.3.2.1 – Model fitting results

For the 1-class model, the unconstrained GMM (Model 0) with freely estimated variances both within and between classes provided a superior fit compared to the LCGA model. This suggests within-class variability, or individual differences in the growth factors. For the 2-class models, neither the LCGA nor the unconstrained GMM converged normally. Specifically, both models resulted in non-positive definite estimations. Convergence was obtained for models 1A, 2A and 2B that were run subsequently. Entropy values were less

than one to a similar extent for the 2-class models and the 3-class model. Supplementary Table 4.10 shows that of the 3-class models, only Model 2A converged.

The 2-class Model 1A had the lowest BIC of all best fitting *k*-class models (Supplementary Table 4.10). Parameter estimates and classification probabilities for all best fitting *k*-class models are shown in Supplementary Tables 4.11 and 4.12 respectively.

4.3.2.2 – Model selection

The 2-class Model 1A was selected as the best fitting model owing to its relative fit (lowest BIC value), relative high entropy value, and empirical plausibility of the within-class parameter estimates. In terms of the theoretical plausibility of the latent classes, it was hypothesised that a persistent trajectory class would be identified. The 2-class model did not identify a persistent trajectory class, however, the notably worse relative fit of the 3-class model (which did identify a persistent class) together with the additional constraints that were required for convergence (i.e., between-class residual variances in addition to within-class residual variances) did not support selection of the 3-class model (Model 2A). The 2-class model (Model 1A) was selected as providing the best relative representation of the data.

The 2-class Model 1A estimated that all individuals' latent trajectories followed a decreasing developmental course, with one latent subgroup characterised by mid-level hallucinations scores at baseline (54.84%, 'mid-decreasing'), and another characterised by low-level scores at baseline (45.16%, 'low-decreasing') (Table 4.2, Figure 4.2, Supplementary Table 4.12). There was significant variability around the growth factors for both classes.

Supplementary Table 4.12 shows that for the 2-class Model 1A, individuals whose most likely class membership was the mid-decreasing class (of which there was a 97% probability), probability of classification error was 3%. For individuals whose most likely

class membership was the low-decreasing class (of which there is a 91% probability), probability of classification error was 9%.

4.3.2.3 – Post hoc sensitivity tests

The parsimony sensitivity tests were not conducted, because Models 1A-2C are not applicable to 1-class models, and 2-class constrained models had already been run.

The slopes of the best fitting model (2-class Model 1A) appeared visually parallel across the classes. Constraining the slope factor means across classes resulted in worse fit (log-likelihood = -54,431.913, BIC = 108,975.593, entropy = 0.763) than the model with freely estimated slopes. A Wald test of the difference between the slopes was significant, suggesting that for individuals classified in the mid-decreasing compared to low-decreasing class, hallucinations decreased at a significantly greater rate (W (1) = 904.142, $p < .001$). The results of both sets of analysis suggest significant differences in the average rates of change in hallucinations between the classes.

4.3.2.4 – Complete data analyses

Model fitting results of the GMM conducted for individuals with complete data only are shown in Supplementary Table 4.13. A model with constrained within-class residual variances provided the best fit to the data, however a 3-class model provided the best fit, compared to a 2-class model for the whole sample. Nonetheless, parameter estimates were broadly similar, with average decline over time for all classes, albeit with latent classes characterised by both lower and higher baseline hallucinations scores (Supplementary Table 4.14).

4.3.3 – Negative symptoms

4.3.3.1 – Model fitting results

For both the 1-class and 2-class models, the unconstrained GMM (Model 0) with freely estimated variances both within and between classes provided a superior fit compared to the LCGA models (where growth factor variances were fixed at zero).

For the 3-class models, neither the unconstrained GMM nor the LCGA converged normally. This led to a series of constrained models being tested. Models with one variance parameter constrained (Models 1A-1C) resulted in convergence issues. Supplementary Table 4.15 shows that for the models with two variance parameters constrained, only Models 2A and 2C converged normally. Entropy values were higher for the 2-class models than for the 3-class models.

The 2-class Model 0 had the lowest BIC of all best fitting *k*-class models (Supplementary Table 4.15). Parameter estimates and classification probabilities for all best fitting *k*-class models are shown in Supplementary Tables 4.16 and 4.17, respectively.

4.3.3.2 – Model selection

The 2-class Model 0 was selected as the best fitting model owing to its relative fit (lowest BIC value), relative high entropy value, and empirical plausibility of the within-class parameter estimates. In terms of the theoretical plausibility of the latent classes, it was hypothesised that a persistent trajectory class would be identified. The 2-class model estimated latent trajectories that increased over time for both classes. Whilst the 3-class model identified a persistent class, the constraints that were required for convergence (i.e., between-class residual variances and within-class residual variances) together with the poorer relative fit, did not support selection of the 3-class model (Model 2A). The 2-class model (Model 1A) was selected as providing the best relative representation of the data.

The 2-class Model 0 estimated that all individuals' latent trajectories followed an increasing developmental course, with one latent subgroup characterised by mid-level negative symptoms scores at baseline (55.07%%, 'mid-increasing'), and another characterised by low-level scores at baseline (44.93%, 'low-increasing') (Table 4.2, Figure 4.2, Supplementary Table 4.17). There was significant variability around all growth factors except the slope factor in the low-increasing class.

Supplementary Table 4.17 shows that for the 2-class Model 0, individuals whose most likely class membership was the mid-increasing class (of which there was a 92% probability), probability of classification error was 8%. For individuals whose most likely class membership was the low-increasing class (of which there was a 97% probability), probability of classification error was 3%.

4.3.3.4 – Post hoc sensitivity tests

The parsimony sensitivity tests for Models 1A-2C were not conducted because they are not applicable to 1-class models.

For the planned sensitivity analyses, a homoscedastic 2-class model did not fit the data as well (*df* = 12, log-likelihood = -55,901.090, BIC = 111,914.528, entropy = 0.557) as the unconstrained model.

The slopes of the best fitting model (2-class Model 0) appeared visually parallel across the classes. Constraining slope factor means across classes resulted in worse fit (log-likelihood = -50,744.690, BIC = 101,642.510, AIC = 101,522.381, entropy = 0.784) than the model with freely estimated slopes. A Wald test of the difference between the slopes was significant, indicating that NS increased at a greater rate in the mid-increasing class compared to the low-increasing class (W (1) = 18.243, $p < .001$).

4.3.3.5 – Complete data analysis

Model fitting results of the GMM conducted for individuals with complete data only are shown in Supplementary Table 4.18. Like for the models estimated in the whole sample, a 2-class unconstrained GMM provided the best fit to the data. Parameter estimates were broadly similar, though of note, the latent class characterised by mid-level baseline NS scores in the complete-data subsample followed a stable trajectory (Supplementary Table 4.19), compared to an increasing trajectory in the whole sample.

Table 4.1

Descriptive Statistics for Paranoia, Hallucinations, Negative Symptoms, and Age

	Paranoia			Hallucinations			Negative symptoms		
	Age 16	Age 17	Age 22	Age 16	Age 17	Age 22	Age 16	Age 17	Age 22
N for PENS data	9,898	2,937	8,340	9,907	2,940	8,338	9,944	2,939	10,355
Mean PENS (*SD*)	12.12 (10.63)	14.44 (13.64)	10.09 (11.51)	4.72 (6.11)	6.74 (7.57)	1.72 (4.13)	2.19 (3.19)	2.91 (3.94)	2.64 (3.60)
PENS range	0-72	0-75	0-74	0-45	0-45	0-44	0-24	0-24	0-24
Skewness	1.60	1.46	1.87	2.12	1.53	4.46	2.41	2.09	2.25
N >3 *SD*	121 (1.22%)	34 (1.16%)	143 (1.71%)	157 (1.58%)	30 (1.02%)	153 (1.83%)	191 (1.92%)	61 (2.08%)	206 (1.99%)
Coefficient α	0.93	0.95	0.94	0.88	0.90	0.87	0.83	0.87	0.84
N for age data	9,922	2,963	8,508	9,928	2,963	8,507	9,979	2,966	10,418
Mean age (*SD*)	16.32 (0.69)	17.06 (0.88)	22.85 (0.88)	16.32 (0.68)	17.06 (0.88)	22.86 (0.88)	16.32 (0.68)	17.06 (0.88)	22.30 (0.93)
Age range (years)	14.91-21.34	15.55-19.00	21.16-25.19	14.91-21.34	15.55-19.00	21.16-25.19	14.91-19.45	15.55-19.00	20.56-25.59
Skewness	-0.27	0.01	0.02	-0.27	0.01	0.02	-0.30	-0.01	0.13

Note. PENS = psychotic experiences and negative symptoms.

Table 4.2

Growth Mixture Model Fit Results for Converged Models of Paranoia, Hallucinations, and Negative Symptoms

	k	Model	Par.	Constraints	LL	BIC	AIC	Entropy [1]
Paranoia	1	Model LCGA	5	No growth factor variances	-81519.705	163086.393	163049.410	-
	1	Model 0	8	None	-79987.442	160050.058	159990.885	-
	2	Model LCGA	11	No growth factor variances	-76234.770	152572.904	152491.540	0.634
	2	Model 0	17	None	-75775.359	151710.463	151584.718	0.596
	3	Model LCGA	17	No growth factor variances	-74487.990	149135.725	149009.981	0.669
	3 [a]	Model 0	24	None	-74316.664	**148858.850**	148681.328	0.656
Hallucinations	1	Model LCGA	5	No growth factor variances	-65917.295	131881.575	131844.589	-
	1	Model 0	8	None	-64673.683	129422.544	129363.367	-
	2	Model 1A	13	Within-class residual variances	-53996.157	**108114.477**	108018.314	0.776
	2	Model 2A	12	Within-class and between-class residual variances	-60064.952	120242.670	120153.904	0.744
	2	Model 2B	11	Within-class residual variances and between-class growth factor variances	-54440.670	108984.709	108903.340	0.779
	3	Model 2A	18	Within-class and between-class residual variances	-59209.341	118587.830	118454.682	0.768
Negative symptoms	1	Model LCGA	5	No growth factor variances	-61820.215	123687.658	123650.430	-
	1	Model 0	8	None	-59459.934	118995.433	118935.868	-
	2	Model LCGA	11	No growth factor variances	-51529.472	103162.846	103080.945	0.790
	2	Model 0	17	None	-50727.482	**101615.540**	101488.965	0.788
	3	Model 2A	18	Within-class and between-class residual variances	-53174.429	106518.879	106384.859	0.708
	3	Model 2C	16	Between-class residual variances and between-class growth factor variances	-54517.112	109185.352	109066.223	0.684

Note. This table shows the results of the growth mixture models that converged. Full model fitting results are shown in Supplementary Tables 5.4 for paranoia, 5.10 for hallucinations, and 5.15 for negative symptoms. *k* = number of classes. Par. = number of estimated parameters for final model. LL = log-likelihood value. [1] = No calculation for 1-class model. Bold typeset indicates lowest BIC value for each of paranoia, hallucinations, and negative symptoms. Log-likelihood values were replicated for each best fitting *k*-class model using the two random seed values with the highest log-likelihoods. [a] = slope factor variance (and covariance) fixed to zero for class #3.

Table 4.3

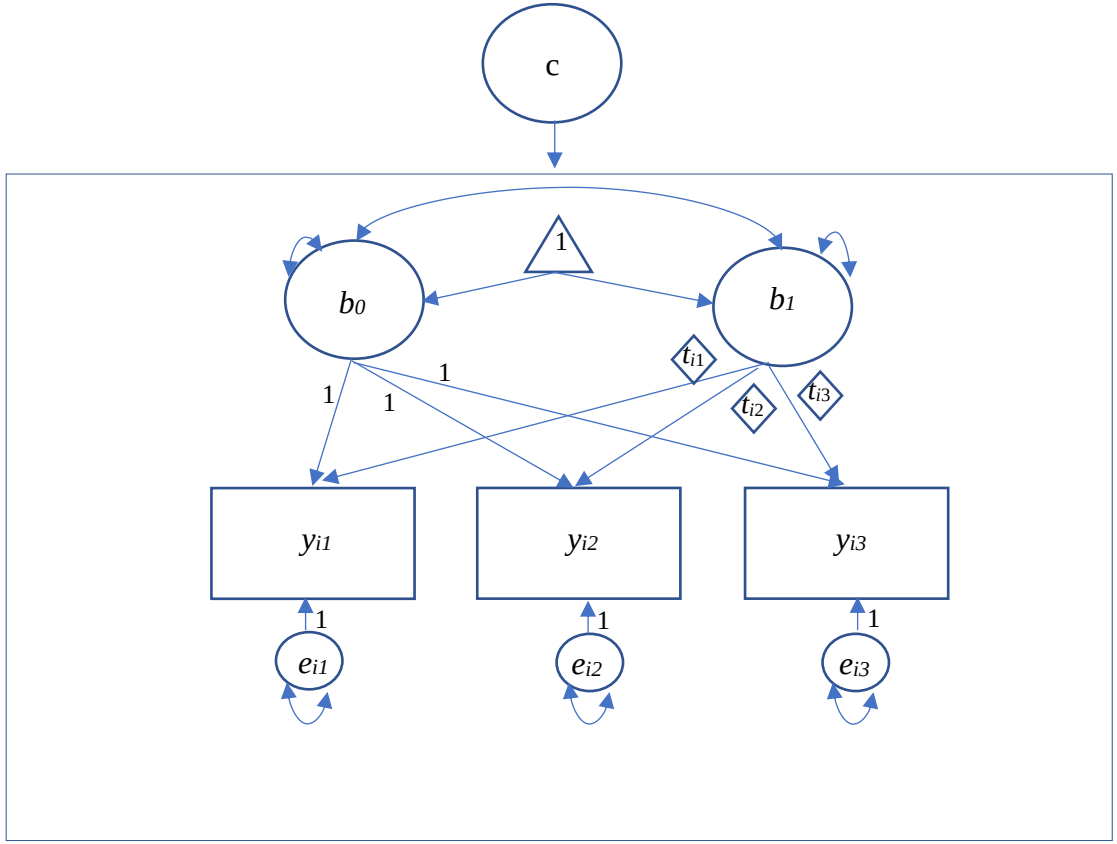
Parameter Estimates for Each Best Fitting Growth Mixture Model for Paranoia, Hallucinations, and Negative Symptoms

	k	Model	Parameter	Class 1				Class 2				Class 3			
				Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*
Paranoia	3	Model 0	Intercept	10.075 (0.284)	< .001	15.564 (1.530)	< .001	22.639 (0.423)	< .001	87.410 (7.500)	< .001	2.786 (0.295)	< .001	0.119 (0.079)	.130
			Linear slope	-0.474 (0.025)	< .001	0.331 (0.061)	< .001	-0.073 (0.064)	.257	1.877 (0.214)	< .001	-0.335 (0.027)	< .001	0[a]	-
			W1	-	-	19.526 (1.539)	< .001	-	-	91.913 (7.573)	< .001	-	-	5.797 (0.723)	< .001
			W2	-	-	25.816 (2.168)	< .001	-	-	163.038 (10.676)	< .001	-	-	4.320 (0.616)	< .001
			W3	-	-	23.833 (2.729)	< .001	-	-	190.028 (7.797)	< .001	-	-	0.406 (0.141)	.004
			Covariance	-	-	-2.261 (0.259)	< .001	-	-	-12.193 (1.181)	< .001	-	-	0[a]	-
Hallucinations	2	Model 1A	Intercept	8.828 (0.139)	< .001	25.651 (1.603)	< .001	1.209 (0.055)	< .001	1.736 (0.135)	< .001	-	-	-	-
			Linear slope	-0.754 (0.20)	< .001	0.237 (0.072)	< .001	-0.158 (0.007)	< .001	0.034 (0.002)	< .001	-	-	-	-
			W1	-	-	27.066 (1.332)	< .001	-	-	0.189 (0.015)	< .001	-	-	-	-
			W2	-	-	27.066 (1.332)	< .001	-	-	0.189 (0.015)	< .001	-	-	-	-
			W3	-	-	27.066 (1.332)	< .001	-	-	0.189 (0.015)	< .001	-	-	-	-
			Covariance	-	-	-2.385 (0.261)	< .001	-	-	-0.244 (0.017)	< .001	-	-	-	-
Negative symptoms	2	Model 0	Intercept	3.682 (0.085)	< .001	7.089 (0.465)	< .001	0.189 (0.014)	< .001	0.031 (0.011)	.004	-	-	-	-
			Linear slope	0.095 (0.011)	< .001	0.093 (0.041)	.022	0.034 (0.008)	< .001	0.001 (0.001)	.577	-	-	-	-
			W1	-	-	5.595 (0.418)	< .001	-	-	0.130 (0.010)	< .001	-	-	-	-
			W2	-	-	8.220 (0.785)	< .001	-	-	0.142 (0.013)	< .001	-	-	-	-
			W3	-	-	8.692 (1.387)	< .001	-	-	0.356 (0.058)	< .001	-	-	-	-
			Covariance	-	-	-0.269 (0.069)	< .001	-	-	0.000 (0.002)	.819	-	-	-	-

Note. k = number of classes. W1-W3 = data collection waves 1-3. Variance of W1-W3 represents residual variance at waves 1-3. Covariance represents covariance between the intercept and slope factors. Model 0: Unconstrained model. Model 1A: Model with within-class residual variances constrained. [a] = parameter fixed to zero.

Figure 4.1

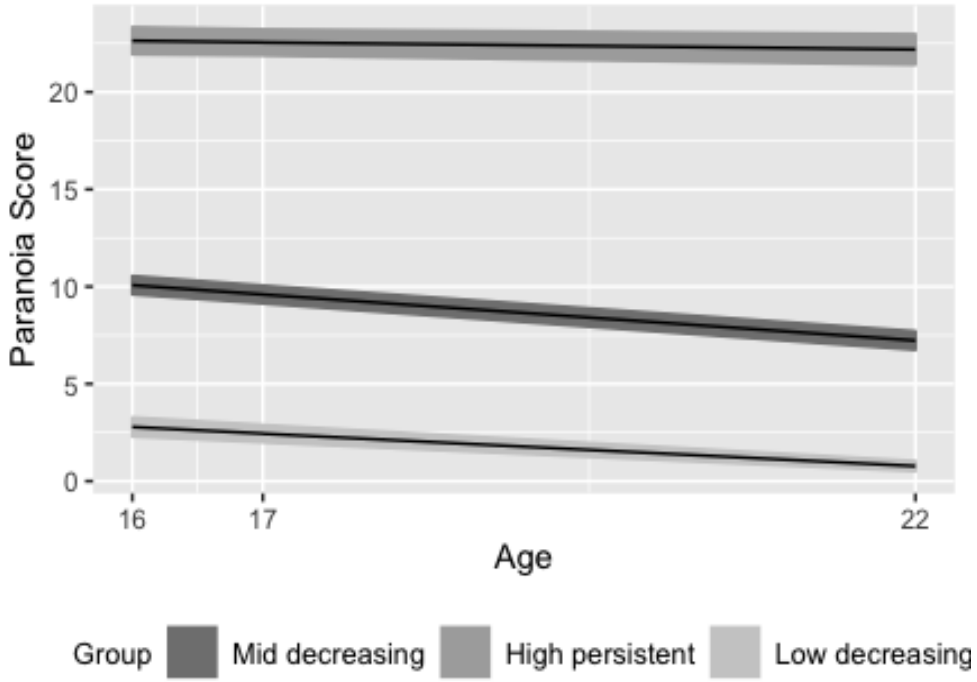
Linear Growth Mixture Model with Individual Time Scores



Note. Figure 4.1 is a simplified, figurative representation of a linear growth mixture model with individually varying time scores. Boxes represent observed variables; circles represent latent variables; curved arrows represent (co)variance; straight arrows represent regression paths; the triangle represents a constant; diamonds represent definition variables (reflecting individual times of measurement). The 'c' latent variable represents the categorical latent class variable, which moderates the model parameters within the box. b_0 is a continuous latent intercept factor, and b_1 is a continuous slope factor. *y* represents the observed score at times 1, 2, and 3, for individual *i*. Residual terms (*e*) are individual-specific and residual variances are wave-specific.

Figure 4.2

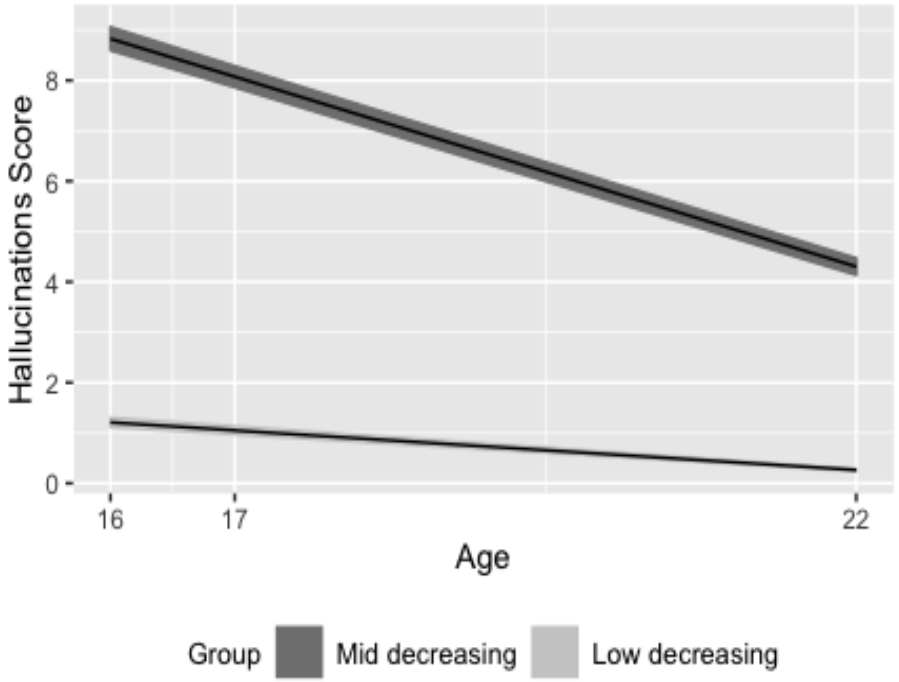
Plot of Estimated Trajectories from Best Fitting Growth Mixture Model of Paranoia



Note. Lines represent mean trajectories; bands represent 95% confidence intervals. Parameter estimates for the trajectories are reported in Table 4.3

Figure 4.3

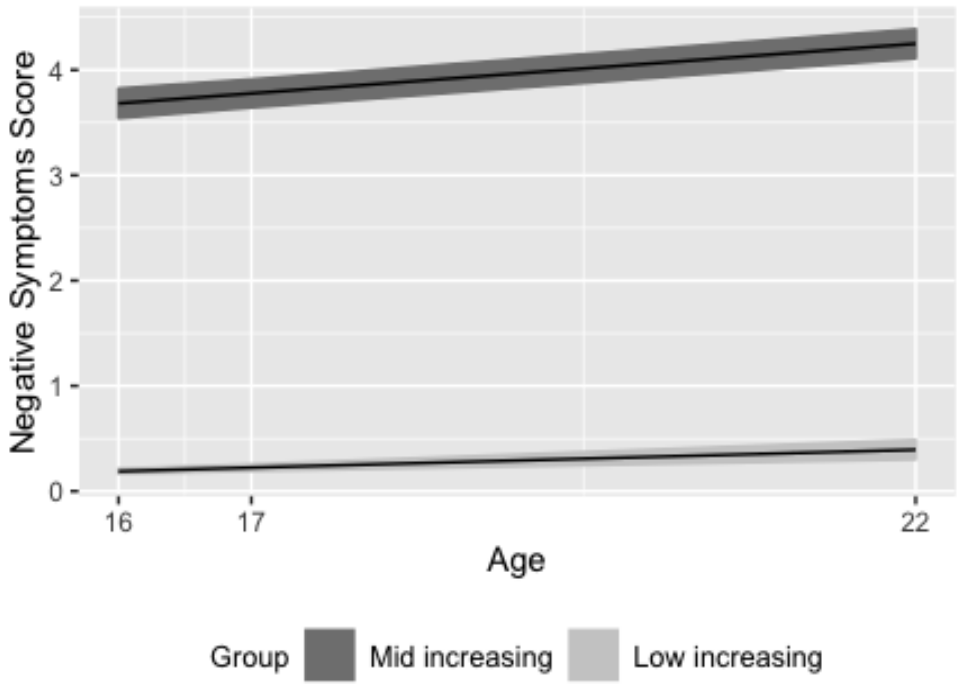
Plot of Estimated Trajectories from Best Fitting Growth Mixture Model of Hallucinations



Note. Lines represent mean trajectories; bands represent 95% confidence intervals. Parameter estimates for the trajectories are reported in Table 4.3

Figure 4.4

Plot of Estimated Trajectories from Best Fitting Growth Mixture Model of Negative Symptoms



Note. Lines represent mean trajectories; bands represent 95% confidence intervals. Parameter estimates for the trajectories are reported in Table 4.3

4.4 – Discussion

This Chapter investigated to the extent to which latent heterogeneity described the developmental course of paranoia, hallucinations, and NS reported from mid-adolescence to emerging adulthood. Three trajectory classes emerged for paranoia, two for hallucinations, and two for NS. Across the dimensions, trajectory classes were largely distinguished by different scores at age 16, but also by different rates of change over time. This is the first study to investigate the latent trajectories of NS, and of PEs analysed as separate dimensions.

Of the models selected as providing the best representation of the data, a high and persisting latent trajectory class was identified only for paranoia. The empirical identification of a high-persistent trajectory class is in line with previous latent trajectory findings that have identified a persistent/increasing class for aggregated PEs (i.e., Bourque et al., 2017; Lin et al., 2011; Mackie et al., 2011, 2013; Thapar et al., 2012; Wigman, van Winkel, Jacobs, et al., 2011; Wigman, van Winkel, Raaijmakers, et al., 2011). The percentage of individuals most likely to be assigned to this class for paranoia (~ 23%) mirrors the ~ 20% persistence rate estimated through meta-analysis of aggregated PEs reported across the lifespan, from studies that manually classified individuals (Linscott & van Os, 2013). Notably, however, the rate of persistence found in the current Chapter was higher than in previous studies that have estimated trajectories of aggregated PEs using latent variable modelling, both in adolescence (1-16% for persistent/increasing scores) (Bourque et al., 2017; Lin et al., 2011; Mackie et al., 2011, 2013; Thapar et al., 2012; Wigman, van Winkel, Raaijmakers, et al., 2011), and adulthood (12%) (Wigman, van Winkel, Jacobs, et al., 2011). I speculate that the previous latent variable modelling estimates of persistence may be attenuated in comparison to the paranoia estimate in the current Chapter, because they include information on hallucinations as well as paranoia/delusions, as discussed below.

Whilst it was hypothesised that a persistent class would be identified for hallucinations as well as paranoia, the 2-class hallucinations model that did *not* include a high-persistent class was selected based on the better fit of the 2-class model compared to the 3-class model (which required constraints to aid convergence). The estimates of the 2-class model suggested that a decreasing developmental course across each trajectory class, and thus across all individuals, best represents the data. The current study is the first to my knowledge to have estimated trajectories of PEs in the community and *not* to have found empirical evidence to suggest either an increasing or persistent latent trajectory class (i.e., Bourque et al., 2017; Lin et al., 2011; Mackie et al., 2011, 2013; Thapar et al., 2012; Wigman, van Winkel, Jacobs, et al., 2011; Wigman, van Winkel, Raaijmakers, et al., 2011). The novel hallucinations findings reported in this Chapter may suggest that prior findings of an increasing/persistent trajectory (for aggregated PEs) were contingent on the inclusion of paranoia/delusions scores. Notwithstanding, considering the empirically-driven constraints that were embedded in the final GMM in this Chapter – future research should test whether a high-persistent class for paranoia but not hallucinations is replicated in other community samples of young people using other measures.

It was also hypothesised that a persistent trajectory would be identified for NS. The selection of a model that included a high-persistent class (i.e., the 3-class model) was not supported empirically, and the 2-class model was selected. Whilst the 2-class model did not include a high-persistent class, the parameter estimates suggested an overall increase over time across all individuals. These results dovetail broadly with results that have shown an increase in the prevalence of NS in young people with increasing age (Dominguez et al., 2010). The current results may further be considered in line with findings from a sample of individuals meeting criteria for first episode of psychosis, in which most individuals were

classified into subgroups characterised by either increasing or stable symptoms (Austin et al., 2015).

It is important to acknowledge that the empirical identification of multiple latent classes, as reported in the current Chapter, could reflect one of several realities (Bauer & Curran, 2003, 2004). One possible reality is that the identified latent classes, whilst acknowledging that they remain *statistical approximations*, can be understood as being representative of the latent growth characteristics of a heterogenous sample of individuals, in-line with theory. Another is that the identified latent classes (which represent multiple mixtures of normal distributions) are merely an empirical approximation of an overall nonnormal distribution. Whilst there is always a need to replicate GMM findings in other samples and with other measures (Bauer & Curran, 2003, 2004), replication will be important particularly in the context of the current paranoia and hallucinations findings given the empirically-driven constraints that were embedded in the final models.

In summary, the results in this Chapter suggest that the development of paranoia, hallucinations, and NS reported in the community across adolescence into emerging adulthood, appears to be represented by multiple, latent classes. Investigating the dimensions separately allowed for distinct patterns of growth and heterogeneity to emerge. A remaining question is the extent to which the empirically-identified latent trajectory classes show associations with some of the correlates and precursors that have previously been found to associate with persistent PENS, as well as polygenic scores that have not previously been tested – which is the focus of Chapter 5.

4.5 – Appendix

Supplementary Information 4.1

Preregistration of Hypotheses

Hypotheses were preregistered at https://osf.io/pax6k on 02/11/20 (where full details of the preregistration can be viewed).

Deviations from the original hypotheses are italicised and are detailed further below. 1) For paranoia, hallucinations, and NS, it is predicted that there will be significant phenotypic stability across all ages 16, 17 and 21 years (directional). 2) It is predicted that multiple, distinct latent trajectory classes will be identified through trajectory modelling. It is predicted that this will include a 'persistent' class for each of paranoia, hallucinations, and NS (directional). 3) It is predicted that, compared to a baseline/low scoring trajectory class, persistence will be differentially associated with factors within the following three categories: a) early life factors (more psychological difficulties, *higher phenotypic p factor scores*, more life events and lower educational attainment), b) genetic and other familial factors (lower family socio-economic status, more family psychiatric history and higher polygenic scores for adult psychiatric outcomes *including a polygenic p factor*) and, c) early adulthood factors (more psychological difficulties, recent life events and lower educational attainment). It is predicted that male gender will also associate with persistent negative symptoms compared to the other trajectory classes (directional).

The results pertaining to the first hypothesis are reported in Chapter 2 (Supplementary Table 2.2). After preregistration, it was decided that the results of the first hypothesis would be included but that the analyses/results would not be a main focus. This is because rank order stability (correlation) reflects a different aspect of temporal stability to the rest of the

analyses in this Thesis (i.e., within-person stability, as described in Section 3.1), and only phenotypic pairwise complete data was included in the rank order stability analyses.

It was originally planned that '*p*' factor scores would be calculated, but these analyses were not conducted owing to time constraints.

Supplementary Table 4.1

Paranoia Data Time-Point Characteristics

	One time point			Two time points		Three time points	Total
	Age 16 only	Age 17 only	Age 22 only	Age 16 and 17 only	Age 16 and 22 only	Age 16, 17 and 22	
N	2,745 (22.78%)	0 (0%)	2,150 (17.85%)	966 (8.02%)	4,219 (35.02%)	1,968 (16.33%)	12,051
SES	-0.10 (0.98)	NA	0.09 (1.01)	0.07 (0.99)	0.33 (0.98)	0.25 (0.98)	NA
Female	41.09%	0%	62.98%	44.82%	63.43%	64.02%	NA
Genotyped	1,464 (20.65%)	0 (0%)	1,107 (15.62%)	541 (7.64%)	2,702 (38.12%)	1,275 (17.99%)	7,089 (58.82%)

Note. *N* = number of individuals with paranoia total score data across data collection waves. SES = socioeconomic status mean (*SD*). NA = not applicable.

Supplementary Table 4.2

Hallucinations Data Time-Point Characteristics

	One time point			Two time points		Three time points	Total
	Age 16 only	Age 17 only	Age 22 only	Age 16 and 17 only	Age 16 and 22 only	Age 16, 17 and 22	
N	2,750 (22.81%)	1 (0.1%)	2,148 (17.82%)	967 (8.02%)	4,218 (34.99%)	1,972 (16.36%)	12,056
SES	-0.10 (0.98)	-1.23 (NA)	0.09 (1.01)	0.07 (0.99)	0.33 (0.98)	0.25 (0.98)	NA
Female	41.05%	0%	63.04%	44.88%	63.39%	64.05%	NA
Genotyped	1,467 (20.68%)	0 (0%)	1,106 (15.59%)	543 (7.66%)	2,701 (38.08%)	1,276 (17.99%)	7,093 (58.83%)

Note. *N* = number of individuals with hallucinations total score data across data collection waves. SES = socioeconomic status mean (*SD*). NA = not applicable.

Supplementary Table 4.3

Negative Symptoms Data Time-Point Characteristics

	One time point			Two time points		Three time points	Total
	Age 16 only	Age 17 only	Age 22 only	Age 16 and 17 only	Age 16 and 22 only	Age 16, 17 and 22	
N	1,762 (13.92%)	1 (0.1%)	2,717 (21.46%)	544 (4.30%)	5,244 (41.42%)	2,394 (18.91%)	12,662
SES	-0.18 (0.95)	-0.06 (NA)	0.18 (1.02)	-0.22 (0.98)	0.38 (0.96)	0.29 (0.96)	NA
Female	47.62%	0%	50.42%	54.60%	56.50%	58.60%	NA
Genotyped	880 (11.82%)	1 (0.1%)	1,437 (19.49%)	286 (3.62%)	3,310 (44.73%)	1,529 (20.74%)	7,443 (58.78%)

Note. *N* = number of individuals with negative symptoms total score data across data collection waves. SES = socioeconomic status mean (*SD*). NA = not applicable.

Supplementary Table 4.4

Full Growth Mixture Model Fit Results for Paranoia

k	Model	Par.	Constraints	LL	BIC	AIC	Entropy [1]
1	Model LCGA	5	No growth factor variances	-81,519.705	163,086.393	163,049.410	-
1	Model 0	8	None	-79,987.442	**160,050.058**	159,990.885	-
2	Model LCGA	11	No growth factor variances	-76,234.770	152,572.904	152,491.540	0.634
2	Model 0	17	None	-75,775.359	**151,710.463**	151,584.718	0.596
3	Model LCGA	17	No growth factor variances	-74,487.990	149,135.725	149,009.981	0.669
3	Model 0	24	None	-74,316.664	**148,858.850**	148,681.328	0.656
4	Model LCGA	23	No growth factor variances	-	-	-	-
4	Model 0	35	None	-	-	-	-
4	Model 1A	27	Within-class residual variances	-	-	-	-
4	Model 1B	27	Between-class residual variances	-	-	-	-
4	Model 1C	29	Between-class growth factor variances	-	-	-	-
4	Model 2A	24	Within-class and between-class residual variances	-	-	-	-
4	Model 2B	21	Within-class residual variances and between-class growth factor variances	-	-	-	-
4	Model 2C	20	Between-class residual variances and between-class growth factor variances	-	-	-	-

Note. *k* = number of classes. Par. = number of estimated parameters (for final model if converged, for unadjusted model if not converged). LL = log-likelihood value. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. [1] = No calculation for 1-class model. Bold typeset indicates lowest BIC value for each *k*-class model. Log-likelihood values replicated for best fitting *k*-class models using the two random seed values with the highest log-likelihoods.

Supplementary Table 4.5

Parameter Estimates for Each Best Fitting k-Class Model for Paranoia

k	Model	Parameter	Class 1				Class 2				Class 3			
			Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*
1	Model 0	Intercept	12.362 (0.125)	< .001	80.615 (3.077)	< .001	-	-	-	-	-	-	-	-
		Linear slope	-0.335 (0.022)	< .001	0.373 (0.275)	.175	-	-	-	-	-	-	-	-
		W1	-	-	36.480 (2.648)	< .001	-	-	-	-	-	-	-	-
		W2	-	-	75.924 (4.924)	< .001	-	-	-	-	-	-	-	-
		W3	-	-	89.665 (11.341)	< .001	-	-	-	-	-	-	-	-
		Covariance	-	-	-3.998 (0.463)	< .001	-	-	-	-	-	-	-	-
2	Model 0	Intercept	20.458 (0.400)	< .001	87.372 (6.170)	< .001	7.654 (0.161)	<.001	17.929 (1.167)	< .001	-	-	-	-
		Linear slope	-0.142 (0.052)	.006	1.472 (0.173)	< .001	-0.458 (0.023)	<.001	0.215 (0.046)	< .001	-	-	-	-
		W1	-	-	78.336 (6.203)	< .001	-	-	12.397 (0.991)	< .001	-	-	-	-
		W2	-	-	146.201 (9.415)	< .001	-	-	14.340 (1.153)	< .001	-	-	-	-
		W3	-	-	169.488 (7.580)	< .001	-	-	13.739 (1.706)	< .001	-	-	-	-
		Covariance	-	-	-10.362 (0.975)	< .001	-	-	-1.708 (0.162)	< .001	-	-	-	-
3	Model 0	Intercept	10.075 (0.284)	< .001	15.564 (1.530)	<.001	22.639 (0.423)	<.001	87.410 (7.500)	< .001	2.786 (0.295)	< .001	0.119 (0.079)	.130
		Linear slope	-0.474 (0.025)	< .001	0.331 (0.061)	<.001	-0.073 (0.064)	.257	1.877 (0.214)	< .001	-0.335 (0.027)	< .001	0 [a]	-
		W1	-	-	19.526 (1.539)	<.001	-	-	91.913 (7.573)	< .001	-	-	5.797 (0.723)	< .001
		W2	-	-	25.816 (2.168)	<.001	-	-	163.038 (10.676)	< .001	-	-	4.320 (0.616)	< .001
		W3	-	-	23.833 (2.729)	<.001	-	-	190.028 (7.797)	< .001	-	-	0.406 (0.141)	.004
		Covariance	-	-	-2.261 (0.259)	<.001	-	-	-12.193 (1.181)	< .001	-	-	0 [a]	-

Note. *k* = number of classes. W1-W3 = data collection waves 1-3. Variance of W1-W3 represents residual variance at data collection waves 1-3. Covariance represents covariance between intercept and slope. Model 0: Unconstrained model. [a] = parameter manually fixed to zero.

Supplementary Table 4.6

Most Likely Class Classification Values for Each Best Fitting k-Class Model for Paranoia

k	Model		Classification probabilities			Final class counts and proportions
			Class 1	Class 2	Class 3	
1	Model 0	Class 1	1.000	-	-	12,049 (100%)
2	Model 0	Class 1 Class 2	0.774 0.046	0.226 0.954	- -	3,766 (31.26%) 8,283 (68.74%)
3[a]	Model 0	Class 1 Class 2 Class 3	0.881 0.231 0.117	0.039 0.749 0.000	0.081 0.020 0.883	6,798 (56.40%) 2,762 (22.92%) 2,489 (20.66%)

Note. *k* = number of classes. Model 0: Unconstrained model. [a] = constrained slope factor variance in class #3. Values based on most likely latent class membership.

Supplementary Table 4.7

Growth Mixture Model Fit Results for 2-Class Models of Paranoia (Sensitivity Analysis)

k	Model	Par.	Constraints	LL	BIC	AIC	Entropy
2	1A	13	Within-class residual variances	-75,820.928	151,764.013	151,667.855	0.600
2	1B	14	Between-class residual variances	-76,433.696	152,998.946	152,895.392	0.580
2	1C	15	Between-class growth factor variances	-75,859.851	151,860.654	151,749.703	0.617
2	2A	12	Within-class and between-class residual variances	-76,969.025	154,050.811	153,962.050	0.632
2	2B	11	Within-class residual variances and between-class growth factor variances	-75,886.302	151,875.967	151,794.603	0.617
2	2C	12	Between-class residual variances and between-class growth factor variances	-77,924.647	155,962.054	155,873.293	0.496

Note. *k* = number of classes. Par. = number of estimated parameters. LL = log-likelihood value.

Supplementary Table 4.8

Growth Mixture Model Fit Results for Paranoia for Individuals with Complete Data

k	Model	Par.	Constraints	LL	BIC	AIC	Entropy [1]
1	Model LCGA	5	No growth factor variances	-23,646.701	47,331.335	47,303.413	-
1	Model 0	8	None	-22,660.808	**45,382.290**	45,337.616	-
2	Model LCGA	11	No growth factor variances	-21,740.007	43,563.441	43,502.014	0.840
2	Model 0	17	None	-21,435.265	**42,999.462**	42,904.530	0.768
3	Model LCGA	17	No growth factor variances	-21,238.092	42,605.117	42,510.184	0.846
3	Model 0	26	None	-21,072.670	**42,342.530**	42,197.339	0.804

Note. N = 1,967 with complete data. k = number of classes. Par. = number of estimated parameters. LL = log-likelihood value. [1] = No calculation for 1-class model. Bold typeset indicates lowest BIC value for each k-class model. Log-likelihood values replicated for best fitting k-class models using the two random seed values with the highest log-likelihoods.

Supplementary Table 4.9

Parameter Estimates for Each Best Fitting k-Class Model for Paranoia for Individuals with Complete Data

k	Model	Parameter	Class 1				Class 2				Class 3			
			Mean (SE)	*P*	Variance (SE)	*P*	Mean (SE)	*P*	Variance (SE)	*P*	Mean (SE)	*P*	Variance (SE)	*P*
1	Model 0	Intercept	15.185 (0.333)	< .001	136.345 (6.768)	< .001	-	-	-	-	-	-	-	-
		Linear slope	-0.568 (0.047)	< .001	0.963 (0.539)	.074	-	-	-	-	-	-	-	-
		W1	-	-	54.810 (4.462)	< .001	-	-	-	-	-	-	-	-
		W2	-	-	54.528 (4.585)	< .001	-	-	-	-	-	-	-	-
		W3	-	-	88.379 (19.973)	< .001	-	-	-	-	-	-	-	-
		Covariance	-	-	-7.581 (0.931)	< .001	-	-	-	-	-	-	-	-
2	Model 0	Intercept	7.339 (0.289)	< .001	17.948 (1.589)	< .001	24.559 (0.679)	< .001	116.570 (9.709)	< .001	-	-	-	-
		Linear slope	-0.409 (0.045)	< .001	0.361 (0.097)	< .001	-0.753 (0.099)	< .001	2.087 (0.686)	.002	-	-	-	-
		W1	-	-	11.690 (1.429)	< .001	-	-	99.928 (8.261)	< .001	-	-	-	-
		W2	-	-	13.652 (1.381)	< .001	-	-	110.071 (9.190)	< .001	-	-	-	-
		W3	-	-	9.626 (3.864)	.013	-	-	163.261 (26.624)	< .001	-	-	-	-
		Covariance	-	-	-1.721 (0.234)	< .001	-	-	-11.654 (1.624)	< .001	-	-	-	-
3	Model 0	Intercept	3.156 (0.362)	< .001	3.188 (0.828)	< .001	9.401 (0.360)	< .001	16.764 (1.987)	< .001	26.321 (0.636)	< .001	109.061 (10.276)	< .001
		Linear slope	-0.392 (0.045)	< .001	0.057 (0.024)	.019	-0.404 (0.052)	< .001	0.469 (0.118)	< .001	-0.796 (0.108)	< .001	2.153 (0.653)	< .001
		W1	-	-	6.741 (1.967)	.001	-	-	17.651 (2.038)	< .001	-	-	106.351 (1.987)	< .001
		W2	-	-	3.261 (0.778)	< .001	-	-	22.480 (2.423)	< .001	-	-	120.581 (9.928)	< .001
		W3	-	-	0.453 (0.344)	.187	-	-	20.136 (4.729)	< .001	-	-	185.067 (25.704)	< .001
		Covariance	-	-	-0.423 (0.115)	< .001	-	-	-2.489 (0.338)	< .001	-	-	-12.233 (1.791)	< .001

Note. *k* = number of classes. W1-W3 = data collection waves 1-3. Variance of W1-W3 represents residual variance at data collection waves 1-3. Covariance represents covariance between intercept and slope. Model 0: Unconstrained model.

Supplementary Table 4.10

Full Growth Mixture Model Fit Results for Hallucinations

k	Model	Par.	Constraints	LL	BIC	AIC	Entropy [1]
1	Model LCGA	5	No growth factor variances	-65,917.295	131,881.575	131,844.589	-
1	Model 0	8	None	-64,673.683	**129,422.544**	129,363.367	-
2	Model LCGA	11	No growth factor variances	-	-	-	-
2	Model 0	17	None	-	-	-	-
2	Model 1A	13	Within-class residual variances	-53,996.157	**108,114.477**	108,018.314	0.776
2	Model 1B	13	Between-class residual variances	-	-	-	-
2	Model 1C	15	Between-class growth factor variances	-	-	-	-
2	Model 2A	12	Within-class and between-class residual variances	-60,064.952	120,242.670	120,153.904	0.744
2	Model 2B	11	Within-class residual variances and between-class growth factor variances	-54,440.670	108,984.709	108,903.340	0.779
2	Model 2C	12	Between-class residual variances and between-class growth factor variances	-	-	-	-
3	Model LCGA	17	No growth factor variances	-	-	-	-
3	Model 0	26	None	-	-	-	-
3	Model 1A	20	Within-class residual variances	-	-	-	-
3	Model 1B	20	Between-class residual variances	-	-	-	-
3	Model 1C	22	Between-class growth factor variances	-	-	-	-
3	Model 2A	18	Within-class and between-class residual variances	-59,209.341	**118,587.830**	118,454.682	0.768
3	Model 2B	15	Within-class residual variances and between-class growth factor variances	-	-	-	-
3	Model 2C	16	Between-class residual variances and between-class growth factor variances	-	-	-	-

Note. *k* = number of classes. Par. = number of estimated parameters (for final model if converged, for unadjusted model if not converged). LL = log-likelihood value. [1] = No calculation for 1-class model. Bold typeset indicates lowest BIC value for each *k*-class model. Log-likelihood values replicated for best fitting *k*-class models using the two random seed values with the highest log-likelihoods.

Supplementary Table 4.11

Parameter Estimates for Each Best Fitting k-Class Model for Hallucinations

k	Model	Parameter	Class 1				Class 2				Class 3			
			Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*
1	Model 0	Intercept	5.031 (0.074)	< .001	26.878 (1.241)	< .001	-	-	-	-	-	-	-	-
		Linear slope	-0.475 (0.011)	< .001	0.253 (0.090)	.005	-	-	-	-	-	-	-	-
		W1	-	-	12.799 (1.092)	< .001	-	-	-	-	-	-	-	-
		W2	-	-	26.480 (1.558)	< .001	-	-	-	-	-	-	-	-
		W3	-	-	12.101 (3.472)	< .001	-	-	-	-	-	-	-	-
		Covariance	-	-	-2.437 (0.184)	< .001	-	-	-	-	-	-	-	-
2	Model 1A	Intercept	8.828 (0.139)	< .001	25.651 (1.603)	< .001	1.209 (0.055)	< .001	1.736 (0.135)	< .001	-	-	-	-
		Linear slope	-0.754 (0.20)	< .001	0.237 (0.072)	< .001	-0.158 (0.007)	< .001	0.034 (0.002)	< .001	-	-	-	-
		W1	-	-	27.066 (1.332)	< .001	-	-	0.189 (0.015)	< .001	-	-	-	-
		W2	-	-	27.066 (1.332)	< .001	-	-	0.189 (0.015)	< .001	-	-	-	-
		W3	-	-	27.066 (1.332)	< .001	-	-	0.189 (0.015)	< .001	-	-	-	-
		Covariance	-	-	-2.385 (0.261)	< .001	-	-	-0.244 (0.017)	< .001	-	-	-	-
3	Model 2A	Intercept	2.050 (0.125)	< .001	0.025 (0.519)	.962	10.917 (0.425)	< .001	24.983 (2.494)	< .001	18.514 (1.073)	< .001	218.790 (69.883)	< .001
		Linear slope	-0.206 (0.016)	< .001	0.001 (0.022)	.980	-1.117 (0.033)	< .001	0.885 (0.145)	< .001	0.325 (0.614)	.596	109.451 (54.558)	.045
		W1	-	-	5.846 (0.214)	< .001	-	-	5.846 (0.214)	< .001	-	-	5.846 (0.214)	< .001
		W2	-	-	5.486 (0.214)	< .001	-	-	5.486 (0.214)	< .001	-	-	5.486 (0.214)	< .001
		W3	-	-	5.486 (0.214)	< .001	-	-	5.486 (0.214)	< .001	-	-	5.486 (0.214)	< .001
		Covariance	-	-	-0.003 (0.100)	.973	-	-	-4.011 (0.477)	< .001	-	-	-103.138 (46.195)	.026

Note. k = number of classes. W1-W3 = data collection waves 1-3. Variance of W1-W3 represents residual variance at waves 1-3. Model 0: Unconstrained model. Model 1A: Model with within-class residual variances constrained. Model 2A: Model with within-class and between-class residual variances constrained.

Supplementary Table 4.12

Most Likely Class Classification Values for Each Best Fitting k-Class Model for Hallucinations

k	Model		Classification probabilities			Final class counts and proportions
			Class 1	Class 2	Class 3	
1	Model 0	Class 1	1.000	-	-	12,054 (100%)
2	Model 1A	Class 1 Class 2	0.972 0.090	0.028 0.910	- -	6,610 (54.84%) 5,444 (45.16%)
3	Model 2A	Class 1 Class 2 Class 3	0.978 0.241 0.046	0.022 0.748 0.242	0.000 0.011 0.712	9,142 (75.84%) 2,563 (21.26%) 349 (2.90%)

Note. *k* = number of classes. Model 0: Unconstrained model. Model 1A: Model with within-class residual variances constrained. Model 2A: Model with within-class and between-class residual variances constrained. Values based on most likely latent class membership.

Supplementary Table 4.13

Growth Mixture Model Fit Results for Hallucinations for Individuals with Complete Data

k	Model	Par.	Constraints	LL	BIC	AIC	Entropy [1]
1	Model LCGA	5	No growth factor variances	-19,599.230	39,236.391	39,208.460	-
1	Model 0	8	None	-18,822.735	**37,706.161**	37,661.470	-
2	Model LCGA	11	No growth factor variances	-	-	-	-
2	Model 0	17	None	-	-	-	-
2	Model 1A	13	Within-class residual variances	-16,408.676	**32,915.974**	32,843.35	0.890
2	Model 1B	13	Between-class residual variances	-	-	-	-
2	Model 1C	15	Between-class growth factor variances	-	-	-	-
2	Model 2A	12	Within-class and between-class residual variances	-17,974.140	36,039.316	35,972.280	0.791
2	Model 2B	11	Within-class residual variances and between-class growth factor variances	-16,582.515	33,248.483	33,187.034	0.901
2	Model 2C	12	Between-class residual variances and between-class growth factor variances	-	-	-	-
3	Model LCGA	17	No growth factor variances	-	-	-	-
3	Model 0	26	None	-	-	-	-
3	Model 1A	20	Within-class residual variances	-15,667.163	**31,486.051**	31,374.325	0.878
3	Model 1B	20	Between-class residual variances	-	-	-	-
3	Model 1C	22	Between-class growth factor variances	-	-	-	-
3	Model 2A	18	Within-class and between-class residual variances	-17,690.300	35,517.152	35,416.599	0.740
3	Model 2B	15	Within-class residual variances and between-class growth factor variances	-15,800.621	31,722.623	31,633.242	0.908
3	Model 2C	16	Between-class residual variances and between-class growth factor variances	-	-	-	-

Note. *N* = 1,971 with complete data. *k* = number of classes. Par. = number of estimated parameters (for final model if converged, for unadjusted model if not converged). LL = log-likelihood value. [1] = No calculation for 1-class model. Bold typeset indicates lowest BIC value for each *k*-class model. Log-likelihood values replicated for best fitting k-class models using the two random seed values with the highest log-likelihoods.

Supplementary Table 4.14

Parameter Estimates for Each Best Fitting k-Class Model for Hallucinations for Individuals with Complete Data

k	Model	Parameter	Class 1				Class 2				Class 3			
			Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*
1	Model 0	Intercept	7.148 (0.197)	< .001	46.678 (2.781)	< .001	-	-	-	-	-	-	-	-
		Linear slope	-0.742 (0.027)	< .001	0.467 (0.213)	.028	-	-	-	-	-	-	-	-
		W1	-	-	20.858 (2.038)	< .001	-	-	-	-	-	-	-	-
		W2	-	-	19.003 (1.657)	< .001	-	-	-	-	-	-	-	-
		W3	-	-	16.978 (7.640)	.026	-	-	-	-	-	-	-	-
		Covariance	-	-	-4.496 (0.380)	< .001	-	-	-	-	-	-	-	-
2	Model 1A	Intercept	1.518 (0.103)	< .001	1.692 (0.234)	< .001	11.779 (0.289)	< .001	37.283 (3.456)	< .001	-	-	-	-
		Linear slope	-0.184 (0.014)	< .001	0.032 (0.007)	< .001	-1.191 (0.039)	< .001	0.341 (0.141)	.016	-	-	-	-
		W1	-	-	0.907 (0.072)	< .001	-	-	34.093 (2.126)	< .001	-	-	-	-
		W2	-	-	0.907 (0.072)	< .001	-	-	34.093 (2.126)	< .001	-	-	-	-
		W3	-	-	0.907 (0.072)	< .001	-	-	34.093 (2.126)	< .001	-	-	-	-
		Covariance	-	-	-0.232 (0.039)	< .001	-	-	-3.484 (0.478)	< .001	-	-	-	-
3	Model 1A	Intercept	0.294 (0.026)	< .001	0.092 (0.015)	< .001	3.070 (0.270)	< .001	2.097 (0.755)	.006	13.809 (0.467)	< .001	29.004 (3.839)	< .001
		Linear slope	-0.038 (0.004)	< .001	0.002 (0.001)	.048	-0.344 (0.036)	< .001	0.047 (0.015)	.002	-1.391 (0.052)	< .001	0.244 (0.187)	.193
		W1	-	-	0.093 (0.006)	< .001	-	-	3.027 (0.341)	< .001	-	-	41.796 (3.063)	< .001
		W2	-	-	0.093 (0.006)	< .001	-	-	3.027 (0.341)	< .001	-	-	41.796 (3.063)	< .001
		W3	-	-	0.093 (0.006)	< .001	-	-	3.027 (0.341)	< .001	-	-	41.796 (3.063)	< .001
		Covariance	-	-	-0.013 (0.003)	< .001	-	-	-0.315 (0.106)	.003	-	-	-2.529 (0.571)	< .001

Note. *k* = number of classes. W1-W3 = data collection waves 1-3. Variance of W1-W3 represents residual variance at data collection waves 1-3. Covariance represents covariance between intercept and slope. Model 0: Unconstrained model. Model 1A: Model with within-class residual variances constrained.

Supplementary Table 4.15

Full Growth Mixture Model Fit Results for Negative Symptoms

k	Model	Par.	Constraints	LL	BIC	AIC	Entropy [1]
1	Model LCGA	5	No growth factor variances	-61,820.215	123,687.658	123,650.430	-
1	Model 0	8	None	-59,459.934	**118,995.433**	118,935.868	-
2	Model LCGA	11	No growth factor variances	-51,529.472	103,162.846	103,080.945	0.790
2	Model 0	17	None	-50,727.482	**101,615.540**	101,488.965	0.788
3	Model LCGA	17	No growth factor variances	-	-	-	-
3	Model 0	26	None	-	-	-	-
3	Model 1A	20	Within-class residual variances	-	-	-	-
3	Model 1B	20	Between-class residual variances	-	-	-	-
3	Model 1C	22	Between-class growth factor variances	-	-	-	-
3	Model 2A	18	Within-class and between-class residual variances	-53,174.429	**106,518.879**	106,384.859	0.708
3	Model 2B	15	Within-class residual variances and between-class growth factor variances	-	-	-	-
3	Model 2C	16	Between-class residual variances and between-class growth factor variances	-54,517.112	109,185.352	109,066.223	0.684

Note. *k* = number of classes. Par. = number of estimated parameters (for final model if converged, for unadjusted model if not converged). LL = log-likelihood value. [1] = No calculation for 1-class model. Bold typeset indicates lowest BIC value for each *k*-class model (indicative of best fit). Log-likelihood values replicated for best fitting *k*-class models using the two random seed values with the highest log-likelihoods.

Supplementary Table 4.16

Parameter Estimates for Each Best Fitting k-Class Model for Negative Symptoms

k	Model	Parameter	Class 1				Class 2				Class 3			
			Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*
1	Model 0	Intercept	2.256 (0.039)	< .001	6.903 (0.338)	< .001	-	-	-	-	-	-	-	-
		Linear slope	0.064 (0.007)	< .001	0.010 (0.027)	.705	-	-	-	-	-	-	-	-
		W1	-	-	3.551 (0.265)	< .001	-	-	-	-	-	-	-	-
		W2	-	-	5.622 (0.551)	< .001	-	-	-	-	-	-	-	-
		W3	-	-	6.682 (0.943)	< .001	-	-	-	-	-	-	-	-
		Covariance	-	-	-0.069 (0.045)	.126	-	-	-	-	-	-	-	-
2	Model 0	Intercept	3.682 (0.085)	< .001	7.089 (0.465)	< .001	0.189 (0.014)	< .001	0.031 (0.011)	.004	-	-	-	-
		Linear slope	0.095 (0.011)	< .001	0.093 (0.041)	.022	0.034 (0.008)	< .001	0.001 (0.001)	.577	-	-	-	-
		W1	-	-	5.595 (0.418)	< .001	-	-	0.130 (0.010)	< .001	-	-	-	-
		W2	-	-	8.220 (0.785)	< .001	-	-	0.142 (0.013)	< .001	-	-	-	-
		W3	-	-	8.692 (1.387)	< .001	-	-	0.356 (0.058)	< .001	-	-	-	-
		Covariance	-	-	-0.269 (0.069)	< .001	-	-	0.000 (0.002)	.819	-	-	-	-
3	Model 2A	Intercept	3.557 (0.150)	< .001	3.525 (0.523)	< .001	0.779 (0.048)	< .001	0.003 (0.240)	.991	7.974 (0.219)	< .001	20.865 (1.532)	< .001
		Linear slope	0.094 (0.031)	.003	0.284 (0.044)	< .001	0.021(0.026)	.422	0.000 (0.032)	.997	0.288 (0.056)	< .001	1.436 (0.100)	< .001
		W1	-	-	1.987 (0.107)	< .001	-	-	1.987 (0.107)	< .001	-	-	1.987 (0.107)	< .001
		W2	-	-	1.987 (0.107)	< .001	-	-	1.987 (0.107)	< .001	-	-	1.987 (0.107)	< .001
		W3	-	-	1.987 (0.107)	< .001	-	-	1.987 (0.107)	< .001	-	-	1.987 (0.107)	< .001
		Covariance	-	-	-0.868 (0.110)	< .001	-	-	0.000 (0.055)	.996	-	-	-3.766 (0.293)	< .001

Note. *k* = number of classes. W1-W3 = data collection waves 1-3. Variance of W1-W3 represents residual variance at waves 1-3. Model 0: Unconstrained model. Model 2A: Model with within-class and between-class residual variances constrained.

Supplementary Table 4.17

Most Likely Class Classification Values for Each Best Fitting k-Class Model for Negative Symptoms

k	Model		Classification probabilities			Final class counts and proportions
			Class 1	Class 2	Class 3	
1	Model 0	Class 1	1.000	-	-	12652 (100%)
2	Model 0	Class 1 Class 2	0.922 0.028	0.078 0.972	- -	6967 (55.07%) 5685 (44.93%)
3	Model 2A	Class 1 Class 2 Class 3	0.727 0.033 0.244	0.239 0.967 0.053	0.033 0.000 0.704	2836 (22.42%) 8745 (69.12%) 1071 (8.47%)

Note. k = number of classes. Model 0: Unconstrained model. Model 2A: Model with within-class and between-class residual variances constrained. Values based on most likely latent class membership.

Supplementary Table 4.18

Growth Mixture Model Fit Results for Negative Symptoms for Individuals with Complete Data

k	Model	Par.	Constraints	LL	BIC	AIC	Entropy [1]
1	Model LCGA	5	No growth factor variances	-20,132.185	40,303.266	40274.371	-
1	Model 0	8	None	-18,694.883	**37,451.999**	37,405.767	-
2	Model LCGA	11	No growth factor variances	-16,425.614	32,936.798	32873.228	0.891
2	Model 0	17	None	-15,996.565	**32,125.375**	32027.131	0.858
3	Model LCGA	17	No growth factor variances	-	-	-	-
3	Model 0	26	None	-	-	-	-
3	Model 1A	20	Within-class residual variances	-	-	-	-
3	Model 1B	20	Between-class residual variances	-	-	-	-
3	Model 1C	22	Between-class growth factor variances	-	-	-	-
3	Model 2A	18	Within-class and between-class residual variances	-17,183.824	**34,507.672**	34,403.649	0.779
3	Model 2B	15	Within-class residual variances and between-class growth factor variances	-	-	-	-
3	Model 2C	16	Between-class residual variances and between-class growth factor variances	-17,500.544	35,125.554	35,033.089	0.785

Note. N = 2,390 with complete data. k = number of classes. Par. = number of estimated parameters (for final model if converged, for unadjusted model if not converged). LL = log-likelihood value. [1] = No calculation for 1-class model. Bold typeset indicates lowest BIC value for each k-class model. Loglikelihood values replicated for best fitting k-class models using the two random seed values with the highest loglikelihoods.

Supplementary Table 4.19

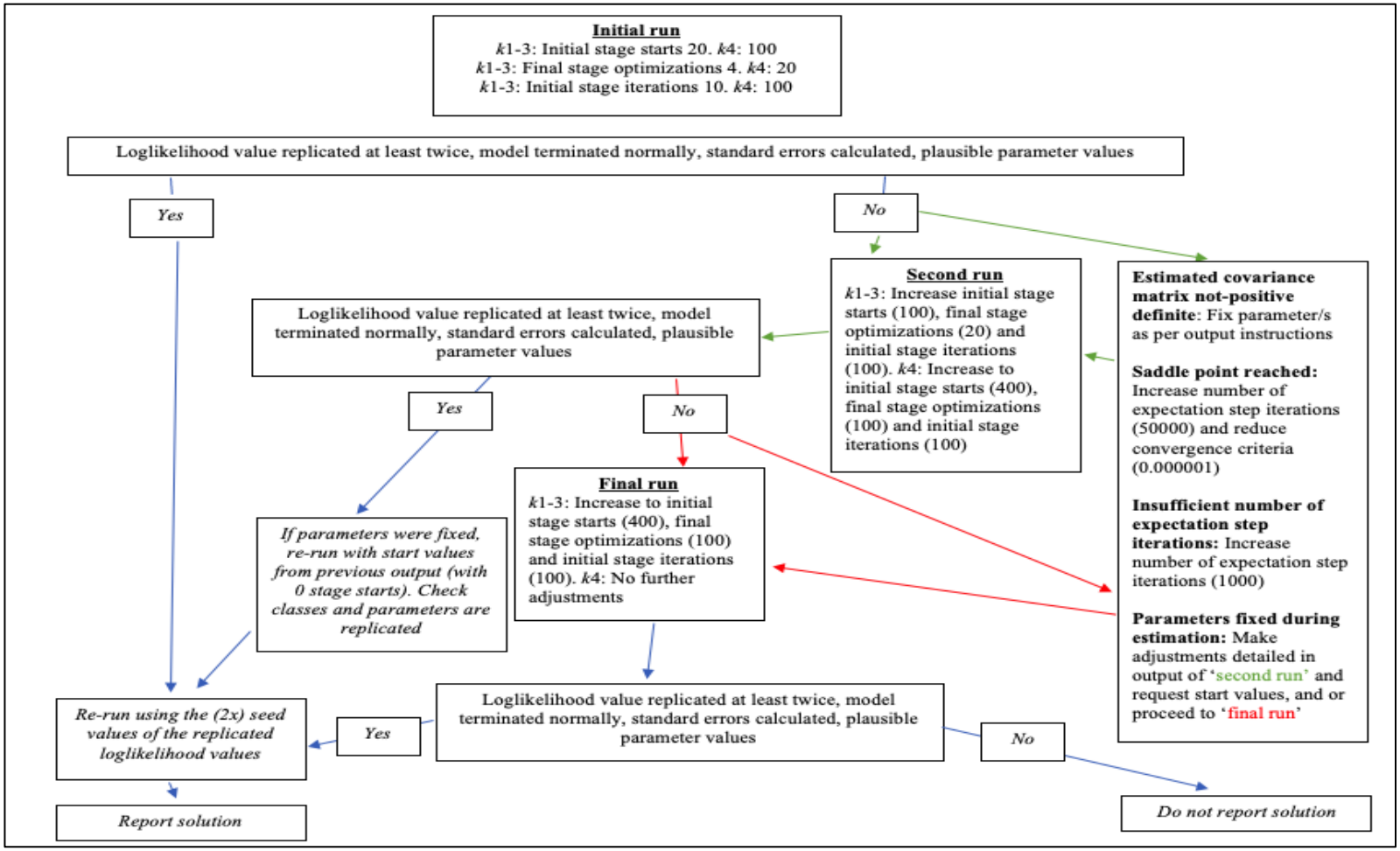
Parameter Estimates for Each Best Fitting k-Class Model for Negative Symptoms for Individuals with Complete Data

k	Model	Parameter	Class 1				Class 2				Class 3			
			Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*	Mean (*SE*)	*p*	Variance (*SE*)	*p*
1	Model 0	Intercept	2.747 (0.095)	< .001	11.163 (0.800)	< .001	-	-	-	-	-	-	-	-
		Linear slope	0.046 (0.014)	.001	0.033 (0.052)	.521	-	-	-	-	-	-	-	-
		W1	-	-	4.914 (0.487)	< .001	-	-	-	-	-	-	-	-
		W2	-	-	4.410 (0.605)	< .001	-	-	-	-	-	-	-	-
		W3	-	-	7.723 (1.702)	< .001	-	-	-	-	-	-	-	-
		Covariance	-	-	-0.238 (0.084)	.005	-	-	-	-	-	-	-	-
2	Model 0	Intercept	0.402 (0.128)	.002	0.181 (0.114)	.110	4.923 (0.364)	< .001	11.387 (1.097)	< .001	-	-	-	-
		Linear slope	0.056 (0.013)	< .001	0.002 (0.007)	.781	0.040 (0.026)	.125	0.152 (0.095)	.110	-	-	-	-
		W1	-	-	0.252 (0.066)	< .001	-	-	9.220 (1.183)	< .001	-	-	-	-
		W2	-	-	0.406 (0.144)	.005	-	-	8.258 (1.376)	< .001	-	-	-	-
		W3	-	-	0.923 (0.167)	< .001	-	-	11.153 (2.974)	< .001	-	-	-	-
		Covariance	-	-	-0.003 (0.008)	.700	-	-	-0.445 (0.150)	.003	-	-	-	-
3	Model 2A	Intercept	0.909 (0.143)	< .001	0.006 (0.765)	.994	4.054 (1.714)	.018	4.104 (5.068)	.418	8.880 (0.972)	<.001	20.758 (4.933)	< .001
		Linear slope	0.021 (0.045)	.636	0.000 (0.069)	.997	0.050 (0.218)	.820	0.358 (0.287)	.212	0.142 (0.206)	.490	1.145 (0.191)	< .001
		W1	-	-	3.213 (0.225)	< .001	-	-	3.213 (0.225)	< .001	-	-	3.213 (0.225)	< .001
		W2	-	-	3.213 (0.225)	< .001	-	-	3.213 (0.225)	< .001	-	-	3.213 (0.225)	< .001
		W3	-	-	3.213 (0.225)	< .001	-	-	3.213 (0.225)	< .001		-	3.213 (0.225)	< .001
		Covariance	-	-	-0.001 (0.379)	.999	-	-	-1.114 (0.994)	.262		-	-3.002	.002

Note. *k* = number of classes. W1-W3 = data collection waves 1-3. Variance of W1-W3 represents residual variance at data collection waves 1-3. Covariance represents covariance between intercept and slope. Model 0: Unconstrained model. Model 2A: Model with within-class and between-class residual variances constrained.

Supplementary Figure 4.1

Decision-Making Flowchart for Growth Mixture Models



Chapter 5 – Associations between the developmental trajectories of paranoia, hallucinations, and negative symptoms with polygenic scores, and with characteristics reported in childhood and adulthood

5.1 – Introduction

Chapter 4 presented the results of the growth mixture modelling (GMM) that was used to investigate the latent trajectories of paranoia, hallucinations, and NS reported across adolescence into emerging adulthood. Following on from GMM, it is of interest to establish the extent to which the empirically identified trajectory classes show associations with external variables. This Section will outline further why this is an important endeavour and will discuss previous findings that the current Chapter will build on.

As was highlighted in Section 4.4, the latent trajectory classes that were identified in Chapter 4 can be understood in terms of being statistical approximations that are believed to be representative of the underlying growth characteristics of a heterogeneous sample of individuals. However, they could also (merely) be a statistical artefact of a multivariate nonnormal distribution: Ascertaining the extent to which the latent classes show theoretically-aligned associations with external variables can be considered as contributing towards construct validation of the latent trajectory classes (Bauer & Curran, 2003, 2004).

Previous GMM studies have reported associations between the most elevated latent trajectory class with childhood trauma and other adverse life events, and emotional/behavioural problems (Bourque et al., 2017; Lin et al., 2011; Mackie et al., 2011; Thapar et al., 2012; Wigman, van Winkel, Raaijmakers, et al., 2011). Further, studies that have manually classified individuals into trajectory groups have also found associations

similar to those reported the GMM studies, above, and have additionally reported associations between persistence and familial psychiatric history, lower SES, and lower educational attainment in childhood (Cougnard et al., 2007; Janssens et al., 2016; Kalman et al., 2019; Rammos et al., 2021; Steenkamp et al., 2021). The associations between persistence and environmental risk factors (e.g., adverse life events, SES) are in line with the expectations of the proneness-persistence-impairment model of psychosis, discussed in Section 1.5.3 (van Os et al., 2009). The findings further highlight that factors reflecting *broad developmental vulnerability* are associated with persistent PEs (e.g., emotional/behavioural problems, familial psychiatric history, low educational attainment). No studies have reported on the latent development of PENS dimensions, so it is important to establish the extent to which the latent trajectory classes (identified in Chapter 4) are associated with the previously reported, theoretically meaningful, correlates for aggregated PEs, as above.

In terms of genetic factors, little is known about their influence on the development of PENS (discussed in Section 1.5.4). The one previous study that utilised polygenic scores as an index of genetic liability reported a null association between schizophrenia GPS and persistence of aggregated PEs across ages 12-24 (Rammos et al., 2021). Probing associations between schizophrenia GPS and the development of PENS is intuitively important under the assumptions of the continuum model of psychosis (Section 1.1.3). However, because previous findings and theory suggest that PENS may reflect vulnerability not only to psychotic disorders but to poor functional and clinical outcomes *broadly* (Healy et al., 2019; Kaiser et al., 2011; van Os & Reininghaus, 2016; Yung et al., 2009), the extent to which the development of PENS dimensions is associated with polygenic liability for a *range* of phenotypes including psychiatric disorders, clinical help-seeking, intelligence and educational attainment, is of further interest.

The current study builds on prior research by investigating dimension-specific associations for the emergent latent trajectory classes identified in Chapter 4 with, i) behaviours and family background characteristics previously found to be associated with aggregated measures of PEs, and ii) polygenic scores for a range of outcomes. It was hypothesised that persistence across PENS would be associated with the following: i) family psychiatric history and lower SES, ii) more emotional and behavioural difficulties, more life events, and lower educational attainment (both in childhood and adulthood), and iii) higher GPS of psychiatric and clinical help-seeking outcomes, and lower GPS of intelligence and educational attainment. It was also predicted that male sex would be associated with persistent NS, in light of findings and theory suggesting that male sex is associated with a vulnerability to NS (e.g., Dominguez et al., 2010; Roy et al., 2001). These hypotheses were preregistered (https://osf.io/pax6k; Supplementary Information 4.1). Minor deviations from the original preregistration are detailed in Supplementary Information 4.1.

5.2 – Methods

5.2.1 – Participants

The TEDS sample is described in Section 2.2.1.1. For the study conducted in Chapter 5 (like in Chapter 4), data from both twins was used, with standard errors adjusted for familial clustering. Individuals completed questions relating to paranoia and hallucinations at mean ages 16.32 years (*SD* 0.68; range 14.91-21.34), 17.06 years (*SD* 0.88; range 15.55-19.0), and 22.85 years (*SD* 0.88; range 21.16-25.19). Parents completed questions relating to their twins' NS at mean ages 16.32 years (*SD* 0.68; range 14.91-19.45), 17.06 years (*SD* 0.88; range 15.55-19.0), and 22.30 years (*SD* 0.93; range 20.56-25.59).

For the analyses in the current Chapter, sample sizes varied according to the auxiliary variables being tested (detailed in the results tables). Maximum cross-age *N* for paranoia = 12,049, hallucinations = 12,054, and negative symptoms = 12,652.

5.2.2 – Measures

5.2.2.1 – PENS

Paranoia, hallucinations, and NS were assessed using the subscales of the SPEQ (Ronald et al., 2014), described in Section 2.2.2. Paranoia, hallucinations, and NS items are listed in Supplementary Information 2.1-2.2.

5.2.2.2 – Additional measures

Items used in the additional measures are listed in the TEDS study questionnaire booklets, which can be downloaded from https://www.teds.ac.uk/datadictionary/home.htm, where calculation of the scores is also described in detail. The additional measures are detailed briefly below.

5.2.2.2.1 – Family background characteristics

SES was a standardised composite of five variables derived from information reported by parents of the TEDS participants at first contact, including mother's age at birth of first child, mother's and father's qualifications and employment. *Family history of schizophrenia/bipolar disorder* was reported by parents at age 16, indicative of whether a parent or sibling of the participant has a diagnosis of schizophrenia or bipolar disorder.

5.2.2.2.2 – Age 7 characteristics

Educational attainment was a standardised composite of teacher-reported National Curriculum (UK) levels for English and Maths. *Life events* was a total score of 11 specific life events (present or absent) reported by parents over the last three years. *Emotional and behavioural problems* over the past school year were measured using the parent-report 20-

item total behaviour problems scale from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997).

5.2.2.2.3 – Age 22 characteristics

Educational attainment was a standardised composite derived from information reported by individuals regarding their current studies and qualifications, reflecting probable highest level of qualification after current study and degree classification for those who had already graduated. *Depressive symptoms* over the past two weeks were measured using eight items of the self-report Short Mood and Feeling Questionnaire (MFQ; Angold et al., 1995). *Emotional and behavioural problems* over the past six months were measured using the self-report SDQ (Goodman, 1997). *Life events* was a total score of 11 self-reported life events (present or absent) since the age of 16 (Coddington, 1972).

5.2.2.3 – GPS

Genotyping of participants is described in Supplementary Information 5.1. The GPSs were calculated by other TEDS collaborators (Selzam et al., 2018, 2019) using LDpred software (Vilhjálmsson et al., 2015), which uses a Bayesian method of estimation. The GPS calculation methods and the GWASs that the individual GPSs were based on are described in Supplementary Information 5.2.

The following GPSs were analysed in the current Chapter: years of education (GPS_{EDU}), intelligence (GPS_{IQ}), ever visited a psychiatrist for nerves, anxiety, tension, or depression (GPS_{PSYCH}), ever visited a general practitioner for nerves, anxiety, tension, or depression (GPS_{GP}), schizophrenia (GPS_{SCZ}), obsessive compulsive disorder (GPS_{OCD}), major depressive disorder (GPS_{MDD}), bipolar disorder (GPS_{BIP}), autism spectrum disorder (GPS_{ASD}), anorexia (GPS_{ANOREX}), and attention deficit hyperactivity disorder (GPS_{ADHD}).

In the current Chapter, standardized residuals of the GPS regressed on the first 10 principal components of ancestry, batch, and chip were used. GPS that are available to TEDS researchers correspond to three fractions (*f*) of causal markers (1, 0.3, and 0.01).

5.2.3 – Statistical analyses

5.2.3.1 – Overview of analyses

Regression analyses were conducted to assess the relationship between the latent class variable derived from the best fitting GMMs estimated in Chapter 4 and the variables described in Sections 5.2.2.2 and 5.2.2.3.

The variables described in Sections 5.2.2.2 and 5.2.2.3 were specified as auxiliary variables, using the automatic implementation of the '3-step' approach in Mplus with adjustment for classification error (described in detail in Asparouhov & Muthén, 2014; Vermunt, 2017). Using this approach, the GMM were first estimated (reproduced exactly as reported in Chapter 4). In the second step, the most likely latent class for each individual was calculated, with classification error estimated in this step. In the third step, the latent class variable (incorporating classification error) was then, i) regressed on each auxiliary variable (Section 5.2.3.2), and ii) used to estimate the class-specific means of each auxiliary variable (Section 5.2.3.3). The latter used the 'BCH' procedure, which also uses a 3-step process of estimation (described in detail in Asparouhov & Muthén, 2014; Bakk & Vermunt, 2016; Bolck et al., 2004).

5.2.3.2 – Multinomial logistic regression analyses of family background, childhood characteristics, and GPSs

The variables relating to family background, age 7 characteristics, and GPSs were specified as predictors of the latent class variable. Single-predictor regressions were first run

to test the associations between the latent class variable for each of paranoia, hallucinations, and NS, and each predictor, separately.

For the GPS variables, these regressions were first run for each GPS *f* (Supplementary Tables 5.1-5.3), and the most predictive GPS *f* (the GPS *f* with the highest *z* value) was then selected for the main analyses.

The FDR method (Benjamini & Hochberg, 1995) was used to correct for multiple testing within each group of measures (i.e., family background, age 7, GPS): First, for the single-predictor regressions, the results of the multiple tests were ranked according to their significance levels. The FDR-adjusted *p* value was defined as the highest-ranking test for which the *p* value was less than or equal to the rank number divided by the total number of tests, multiplied by α (.05). The resulting value was the corrected $q < .05$. Significant predictors (at $q < .05$) were next entered into multiple-predictor regressions, and the FDR-adjusted significance threshold was then calculated for the multiple-predictor results.

5.2.3.3 – Mean differences analyses

The class-specific means of the variables relating to the age 22 characteristics – in addition to the variables relating to family background, age 7 characteristics, and GPSs, were estimated. For each variable, a Wald test of the significance between the class-specific means (*df* 1) was conducted. For binary outcomes, the mean reflects the proportion of individuals with the response value of interest (detailed in Table 5.10).

For all analyses, the total number of comparisons that were made was used as the number of tests for calculating the FDR-adjusted significance values within each group of measures (i.e., family background, age 7, GPS, age 22). For paranoia, there were three comparisons of interest per variable (low-decreasing versus mid-decreasing, low-decreasing versus high-persistent, and mid-decreasing versus high-persistent), and one per variable for hallucinations and NS (because there were two latent classes and thus one comparison).

5.2.4 – Data modelling

Mplus (version 8.6) was used for all data modelling. The same procedures that were described in Chapter 4 for estimation of GMM were used in the current Chapter: Any data that was missing for the GMM was assumed to be missing at random and was accommodated using FIML estimation, using a robust version of the FIML estimator (MLR). For the third step of the 3-step procedure (the regressions), listwise deletion was applied to data missing on the auxiliary variables.

5.3 – Results

The regression results are discussed in terms of the 'most elevated' trajectory class (i.e., high-persistent for paranoia, mid-decreasing for hallucinations, and mid-increasing for NS) for ease of communication.

For paranoia, because comparisons between the high-persistent class and the low-decreasing class were the main focus of the hypotheses, the multiple-predictor regression results are discussed in terms of the high-persistent versus low-decreasing comparison. The reference class was the low-decreasing class for paranoia, unless otherwise stated.

The 95% confidence intervals around the odds ratios (OR) are reported as two numbers separated by a comma, in square brackets.

5.3.1 – Multinomial logistic regression analyses of family background, childhood characteristics, and GPSs

5.3.1.1 – Family background characteristics

Tables 5.1-5.3 show the results of the multinomial logistic regressions for the latent trajectory class variable regressed on the family background variables, for each of paranoia, hallucinations, and NS, respectively.

Male sex: As predicted, male sex was associated with increased odds of membership in the most elevated trajectory class compared to the least elevated trajectory class (the reference class) for NS (OR 1.295 [1.183, 1.418]). For paranoia (OR 0.684 [0.592, 0.790]) and hallucinations (OR 0.846 [0.776, 0.922]), male sex was associated with decreased odds of being in the most elevated trajectory class compared to the low-decreasing class. For paranoia, male sex was also associated with decreased odds of being in the high-persistent class compared to the mid-decreasing class (OR 0.806 [0.714, 0.909]), and the mid-decreasing class compared to the low-decreasing class (OR 0.849 [0.740, 0.975]).

SES: As predicted for hallucinations (OR 0.911 [0.870, 0.950]) and NS (OR 0.793 [0.754, 0.834]), higher SES was associated with decreased odds of membership in the most elevated trajectory class. For paranoia, opposite to the hypothesis, higher SES was associated with increased odds of being in the high-persistent trajectory class compared to the low-decreasing class (OR 1.248 [1.156, 1.347]). Higher SES was also associated with membership in the mid-decreasing compared to the low-decreasing class (OR 1.376 [1.282, 1.477]), though higher SES was associated with decreased odds for membership in the high-persistent compared to the mid-decreasing class (OR 0.907 [0.851, 0.966]).

Family psychiatric history: As predicted for paranoia, family history of schizophrenia (OR 2.668 [1.357, 4.632]) and bipolar disorder (OR 1.613 [1.095, 2.375]) were both associated with increased odds of being in the high-persistent class compared to the low-

decreasing class. Family history of schizophrenia was also associated with increased odds of membership in the mid-decreasing class compared to the low-decreasing class (OR 1.805 [1.038, 3.138]) and of membership in the high-persistent compared to the mid-decreasing class (OR 1.478 [1.041, 2.100]). For hallucinations, family history of schizophrenia (OR 1.307 [1.014, 1.684]) and bipolar disorder (OR 1.311 [1.060, 1.622]) were associated with increased odds of membership in the mid-decreasing class compared to the low-decreasing class.

Multiple-predictor models: In the multiple-predictor regressions, all associations remained significant for hallucinations and NS, and all except family history of bipolar disorder remained significant for paranoia.

5.3.1.2 – Age 7 characteristics

Tables 5.4-5.6 show the results of the multinomial logistic regressions for the latent trajectory class variable regressed on the age 7 variables, for each of paranoia, hallucinations, and NS, respectively.

Educational attainment: Higher educational attainment for hallucinations (OR 0.890 [0.840, 0.943]) and NS (OR 0.799 [0.752, 0.849]) was associated with decreased odds of membership in the most elevated trajectory class, as predicted. However, for paranoia, higher educational attainment was associated with *increased* odds of being in the most elevated trajectory class (OR 1.331 [1.210, 1.464]). Higher educational attainment was also associated with increased odds of being in the mid-decreasing compared to the low-decreasing class for paranoia (OR 1.371 [1.251, 1.502]).

Life events: As predicted, for all PENS, more life events were associated with increased odds of being in the most elevated trajectory class (OR 1.059-1.086 [1.014-1.107]). For paranoia, more life events were also associated with increased odds of being in the most elevated trajectory class compared to the mid-decreasing class (OR 1.101 [1.043, 1.163]).

Emotional and behavioural problems: As predicted, for all PENS, higher SDQ scores were associated with increased odds of being in the most elevated trajectory class (OR 1.043-1.126 [1.031-1.141]). For paranoia, higher SDQ scores were also associated with increased odds of being in the most elevated trajectory class compared to the mid-decreasing class (OR 1.053 [1.039, 1.067]).

Multiple-predictor models: In the multiple-predictor models, only SDQ remained significantly associated with PENS class membership for hallucinations and NS. For paranoia, SDQ, in addition to educational attainment, remained significant.

5.3.1.3 – GPS

Tables 5.7-5.9 show the results of the multinomial logistic regressions for the latent trajectory class variable regressed on the GPS, for each of paranoia, hallucinations, and NS, respectively.

In the single-predictor models, the GPSs for clinical help seeking ($GPS_{PSYCH,}$ GPS_{GP}), major depressive disorder (GPS_{MDD}), and attention deficit hyperactivity disorder (GPS_{ADHD}) were associated with increased odds of membership in the most elevated trajectory class compared to the reference class across PENS, as predicted (OR 1.065-1.228 [1.009-1.343]). Similarly, an increase in GPS for years of education (GPS_{EDU}) (and intelligence, GPS_{IQ}, for NS; OR 0.908 [0.860, 0.960]) was associated with decreased odds of being in the most elevated trajectory class for hallucinations (OR 0.929 [0.880, 0.981]) and NS (OR 0.772 [0.739, 0.817]). Against predictions, for paranoia, an increase in GPS_{EDU} (OR 1.250 [1.142, 1.369]) and GPS_{IQ} (OR 1.295 [1.181, 1.419]) were associated with increased odds of being in the most elevated trajectory class. The GPS for autism spectrum disorder (GPS_{ASD}) was associated with increased odds of membership in the most elevated trajectory class for paranoia (OR 1.288 [1.176, 1.410]) and hallucinations (OR 1.104 [1.045, 1.166).

The GPSs for schizophrenia (GPS_{SCZ}), obsessive compulsive disorder (GPS_{OCD}), bipolar disorder (GPS_{BIP}), and anorexia (GPS_{ANOREX}) were not associated with latent trajectory class membership for any PENS.

In the multiple-predictor models, for paranoia, GPS_{EDU}, GPS_{IQ}, GPS_{MDD}, GPS_{ASD}, and GPS_{ADHD} remained significant, predicting increased odds of membership in the high-persistent class compared to the low-decreasing class. For hallucinations, only GPS_{ASD} remained significant. For NS, only GPS_{EDU} remained significant.

5.3.2 – Mean differences analyses

Table 5.10 shows the class-specific means of the auxiliary variables. The results of the mean differences analyses are aligned with the results of the multinomial logistic regression analyses (Section 5.3.1), except the results for GPS_{ASD}. Hypotheses are referred to again in this Section to aid communication of the findings.

5.3.2.1 – Family background characteristics

Male sex: For paranoia and hallucinations, the proportion of males was lower in the most elevated class compared to the low-decreasing class. For NS, as predicted, the proportion of males was higher in the mid-increasing class compared to the low-increasing class.

SES: For hallucinations and NS, the means for SES were lower in the most elevated trajectory class compared to the reference class, as predicted. For paranoia, against the prediction, the mean for SES was higher in the high-persistent class compared to low-decreasing class.

Family psychiatric history: For paranoia and hallucinations, the proportion of individuals with a family history of schizophrenia and bipolar disorder was higher in the most

elevated class compared to the low-decreasing class. For NS, the proportions were not significantly different between the classes.

5.3.2.2 – Age 7 characteristics

Educational attainment: For hallucinations and NS, the means for educational attainment were lower in the most elevated trajectory class compared to the reference class, as predicted. For paranoia, against the prediction, the mean for educational attainment was higher in the high-persistent class compared to low-decreasing class.

Life events: Across PENS, the number of life events was higher in the most elevated trajectory class compared to the reference class, as predicted.

Emotional and behavioural problems: Across PENS, mean SDQ scores were higher in the most elevated trajectory class compared to the reference class, as predicted.

5.3.2.3 – GPSs

The means for the GPSs of clinical help seeking ($GPS_{PSYCH,}$ GPS_{GP}), major depressive disorder (GPS_{MDD}), and attention deficit hyperactivity disorder (GPS_{ADHD}) were higher in the most elevated trajectory class compared to the reference class across PENS, as predicted. Similarly, the means for years of education (GPS_{EDU}) (and intelligence, GPS_{IQ}, for negative symptoms) were lower in the most elevated trajectory class for hallucinations and negative symptoms. Against predictions, for paranoia, the means for GPS_{EDU} and GPS_{IQ} were higher in the most elevated trajectory class. The means for the GPS of autism spectrum disorder (GPS_{ASD}) were higher in the most elevated trajectory class compared to the reference class across PENS.

Across PENS, the means for the GPSs of schizophrenia (GPS_{SCZ}), obsessive compulsive disorder (GPS_{OCD}), bipolar disorder (GPS_{BIP}), and anorexia (GPS_{ANOREX}) did not significantly differ across latent classes.

5.3.2.4 – Age 22 characteristics

Educational attainment: For hallucinations and NS, the means for educational attainment were lower in the most elevated trajectory class compared to the reference class, as predicted. For paranoia, the mean for educational attainment was *higher* in the high-persistent class compared to the low-decreasing class.

Life events: Across PENS, the number of life events was higher in the most elevated trajectory class compared to the reference class, as predicted.

Depressive symptoms: Across PENS, MFQ scores were higher in the most elevated trajectory class compared to the reference class, as predicted.

Emotional and behavioural problems: Across PENS, SDQ scores were higher in the most elevated trajectory class compared to the reference class, as predicted.

Table 5.1

Multinomial Logistic Regression Results for Paranoia Latent Trajectory Class Regressed on Family Background Variables

		Single-predictor regressions					**Multiple-predictor regression, *N* = 8,942**				
Auxiliary variable	***N* for single-predictor regressions**	**Beta**		**Odds Ratio**			**Beta**		**Odds Ratio**		
		***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**
Male sex	12,049										
Low-dec vs mid-dec		-0.163 (0.070)	-2.327 (.020)*	0.849 (0.060)	0.740	0.975	-0.0271 (0.083)	-3.250 (.001)*	0.763 (0.064)	0.648	0.898
Low-dec vs high-pers		-0.380 (0.074)	-5.161 (< .001)*	0.684 (0.050)	0.592	0.790	-0.429 (0.087)	-4.927 (< .001)*	0.651 (0.057)	0.549	0.772
Mid-dec vs high-pers		-0.216 (0.061)	-3.517 (< .001)*	0.806 (0.050)	0.714	0.909	-0.159 (0.071)	-2.228 (.026)*	0.853 (0.061)	0.742	0.981
SES	11,368										
Low-dec vs mid-dec		0.319 (0.036)	8.862 (< .001)*	1.376 (0.050)	1.282	1.477	0.344 (0.042)	8.232 (< .001)*	1.410 (0.059)	1.299	1.531
Low-dec vs high-pers		0.221 (0.039)	5.682 (< .001)*	1.248 (0.049)	1.156	1.347	0.267 (0.045)	5.868 (< .001)*	1.306 (0.059)	1.194	1.427
Mid-dec vs high-pers		-0.098 (0.033)	-3.007 (.003)*	0.907 (0.030)	0.851	0.966	-0.077 (0.038)	-2.055 (.040)	0.926 (0.035)	0.860	0.996
Family history of schizophrenia	9,673										
Low-dec vs mid-dec		0.591 (0.282)	2.093 (.036)*	1.805 (0.265)	1.038	3.138	0.770 (0.346)	2.226 (.026)*	2.159 (0.746)	1.096	4.251
Low-dec vs high-pers		0.981 (0.281)	3.488 (< .001)*	2.668 (0.751)	1.537	4.632	1.102 (0.341)	3.327 (.001)*	3.011 (1.026)	1.545	5.870
Mid-dec vs high-pers		0.391 (0.179)	2.183 (.029)*	1.478 (0.265)	1.041	2.100	0.333 (0.201)	1.653 (.098)	1.395 (0.281)	0.940	2.070
Family history of bipolar disorder	9,459										
Low-dec vs mid-dec		0.196 (0.202)	0.972 (.331)	1.217 (0.245)	0.819	1.806	0.012 (0.210)	0.059 (.953)	1.012 (0.213)	0.671	1.529
Low-dec vs high-pers		0.478 (0.197)	2.422 (.015)*	1.613 (0.318)	1.095	2.375	0.214 (0.208)	1.026 (.305)	1.238 (0.258)	0.823	1.862

Mid-dec vs high-pers		0.282 (0.150)	1.881 (.060)	1.326 (0.199)	0.988	1.779	0.201 (0.161)	1.249 (.212)	1.223 (0.197)	0.892	1.677

Note. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-increasing' class was used as the reference category. The 'mid-decreasing' class was used as the reference category for the mid-dec vs high-pers comparison. Low-dec = low-decreasing class. Mid-dec = mid-decreasing class. High-pers = high-persistent class. *b* = unstandardized regression coefficient. SES = socioeconomic status. * = significant at $q < .05$ (FDR-adjusted $p < .042$ and $p < .029$ for single- and multiple-predictor regressions, respectively).

Table 5.2

Multinomial Logistic Regression Results for Hallucinations Latent Trajectory Class Regressed on Family Background Variables

		Single-predictor regressions					**Multiple-predictor regression, *N* = 8,946**				
Auxiliary variable	***N* for single-predictor regressions**	**Beta**		**Odds Ratio**			**Beta**		**Odds Ratio**		
		***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**
Male sex											
Low-dec vs mid-dec	12,054	-0.168 (0.044)	-3.807 (< .001)*	0.846 (0.037)	0.776	0.922	-0.241 (0.051)	-4.715 (< .001)*	0.786 (0.040)	0.711	0.868
SES											
Low-dec vs mid-dec	11,373	-0.093 (0.024)	-3.912 (< .001)*	0.911 (0.022)	0.870	0.955	-0.082 (0.027)	-3.006 (.003)*	0.92 (0.025)	0.873	0.972
Family history of schizophrenia											
Low-dec vs mid-dec	9,678	0.268 (0.130)	2.066 (.039)*	1.307 (0.169)	1.014	1.684	0.332 (0.147)	2.263 (.024)*	1.394 (0.205)	1.046	1.860
Family history of bipolar disorder											
Low-dec vs mid-dec	9,463	0.27 (0.109)	2.497 (.013)*	1.311 (0.142)	1.060	1.622	0.25 (0.118)	2.135 (.033)*	1.286 (0.151)	1.021	1.619

Note. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-decreasing' class was used as the reference category. *b* = unstandardized regression coefficient. SES = socioeconomic status. * = significant at $q < .05$ (FDR-adjusted $p < .05$ and $p < .05$ for single- and multiple-predictor regressions, respectively).

Table 5.3

Multinomial Logistic Regression Results for Negative Symptoms Latent Trajectory Class Regressed on Family Background Variables

		Single-predictor regressions					**Multiple-predictor regression, *N* = 11,961**				
Auxiliary variable	***N* for single-predictor regressions**	**Beta**		**Odds Ratio**			**Beta**		**Odds Ratio**		
		***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**
Male sex											
Low-inc vs mid-inc	12,652	0.259 (0.046)	5.603 (< .001)*	1.295 (0.060)	1.183	1.418	0.285 (0.048)	5.940 (< .001)*	1.330 (0.064)	1.211	1.461
SES											
Low-inc vs mid-inc	11,961	-0.232 (0.026)	-9.021 (< .001)*	0.793 (0.020)	0.754	0.834	-0.239 (0.026)	-9.184 (< .001)*	0.788 (0.020)	0.749	0.829
Family history of schizophrenia											
Low-inc vs mid-inc	9,737	0.231 (0.151)	1.533 (.125)	1.260 (0.190)	0.938	1.693	-	-	-	-	-
Family history of bipolar disorder											
Low-inc vs mid-inc	9,523	0.186 (0.126)	1.477 (.140)	1.205 (0.152)	0.941	1.543	-	-	-	-	-

Note. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-increasing' class was used as the reference category. *b* = unstandardized regression coefficient. Low-inc = low-increasing class. Mid-inc = mid-increasing class. SES = socioeconomic status. * = significant at $q < .05$ (FDR-adjusted $p < .025$ and $p < .05$ for single- and multiple-predictor regressions, respectively).

Table 5.4

Multinomial Logistic Regression Results for Paranoia Latent Trajectory Class Regressed on Age 7 Variables

		Single-predictor regressions					**Multiple-predictor regression, *N* = 7,421**				
Auxiliary variable	***N* for single-predictor regressions**	**Beta**		**Odds Ratio**			**Beta**		**Odds Ratio**		
		***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**
Educational attainment	7,662										
Low-dec vs mid-dec		0.315 (0.047)	6.768 (< .001)*	1.371 (0.064)	1.251	1.502	0.392 (0.051)	7.650 (< .001)*	1.480 (0.076)	1.339	1.637
Low-dec vs high-pers		0.286 (0.049)	5.867 (< .001)*	1.331 (0.065)	1.210	1.464	0.438 (0.053)	8.203 (< .001)*	1.550 (0.083)	1.396	1.721
Mid-dec vs high-pers		-0.030 (0.041)	-0.714 (.475)	0.971 (0.040)	0.895	1.053	0.046 (0.044)	1.048 (.295)	1.047 (0.046)	0.961	1.140
Life events	9,605										
Low-dec vs mid-dec		-0.014 (0.037)	-0.375 (.707)	0.986 (0.036)	0.918	1.060	0.001 (0.045)	0.014 (.989)	1.001 (0.045)	0.917	1.092
Low-dec vs high-pers		0.083 (0.037)	2.247 (.025)*	1.086 (0.040)	1.011	1.167	0.057 (0.045)	1.276 (.202)	1.059 (0.047)	0.970	1.155
Mid-dec vs high-pers		0.096 (0.028)	3.456 (.001)*	1.101 (0.031)	1.043	1.163	0.056 (0.032)	1.774 (.076)	1.058 (0.034)	0.994	1.126
SDQ	9,601										
Low-dec vs mid-dec		0.014 (.009)	1.529 (.126)	1.014 0(.009)	0.996	1.032	0.046 (0.011)	4.041 (< .001)*	1.047 (0.012)	1.024	1.071
Low-dec vs high-pers		0.065 (.009)	7.230 (< .001)*	1.067 (0.010)	1.049	1.086	0.097 (0.011)	8.479 (< .001)*	1.102 (0.013)	1.077	1.127
Mid-dec vs high-pers		0.051 (0.007)	7.545 (< .001)*	1.053 (0.007)	1.039	1.067	0.051 (0.008)	6.357 (< .001)*	1.052 (0.008)	1.036	1.069

Note. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-increasing' class was used as the reference category. The 'mid-decreasing' class was used as the reference category for the mid-dec vs high-pers comparison. Low-dec = low-decreasing class. Mid-dec = mid-decreasing class. High-pers = high-persistent class. *b* = unstandardized regression coefficient. SDQ = Strengths and Difficulties Questionnaire. * = significant at $q < .05$ (FDR-adjusted $p < .033$ and $p < .028$ for single-and multiple-predictor regressions, respectively).

Table 5.5

Multinomial Logistic Regression Results for Hallucinations Latent Trajectory Class Regressed on Age 7 Variables

		Single-predictor regressions					**Multiple-predictor regression, *N* = 7,424**				
Auxiliary variable	***N* for single-predictor regressions**	**Beta**		**Odds Ratio**			**Beta**		**Odds Ratio**		
		***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**
Educational attainment											
Low-dec vs mid-dec	7,665	-0.116 (0.029)	-3.954 (< .001)*	0.890 (0.026)	0.840	0.943	-0.063 (0.031)	-2.051 (.040)	0.939 (0.029)	0.883	0.997
Life events											
Low-dec vs mid-dec	9,611	0.060 (0.021)	2.878 (.004)*	1.062 (0.022)	1.019	1.107	0.029 (0.024)	1.233 (.218)	1.030 (0.025)	0.983	1.079
SDQ											
Low-dec vs mid-dec	9,607	0.042 (0.005)	8.023 (< .001)*	1.043 (0.005)	1.032	1.054	0.040 (0.006)	6.443 (< .001)*	1.040 (0.006)	1.028	1.053

Note. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-decreasing' class was used as the reference category. *b* = unstandardized regression coefficient. SDQ = Strengths and Difficulties Questionnaire. * = significant at $q < .05$ (FDR-adjusted $p < .05$ and $p < .017$ for single- and multiple-predictor regressions, respectively).

Table 5.6

Multinomial Logistic Regression Results for Negative Symptoms Latent Trajectory Class Regressed on Age 7 Variables

		Single-predictor regressions					**Multiple-predictor regression, *N* = 7,919**				
Auxiliary variable	***N* for single-predictor regressions**	**Beta**		**Odds Ratio**			**Beta**		**Odds Ratio**		
		***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**
Educational attainment											
Low-inc vs mid-inc	8,172	-0.224 (0.031)	-7.303 (< .001)*	0.799 (0.025)	0.752	0.849	-0.071 (0.033)	-2.125 (.034)	0.932 (0.031)	0.873	0.995
Life events											
Low-inc vs mid-inc	10,235	0.058 (0.022)	2.571 (.010)*	1.059 (0.024)	1.014	1.107	0.018 (0.026)	0.678 (.498)	1.018 (0.026)	0.967	1.071
SDQ											
Low-inc vs mid-inc	10,231	0.119 (0.006)	18.654 (< .001)*	1.126 (0.007)	1.112	1.141	0.117 (0.007)	15.749 (< .001)*	1.124 (0.008)	1.108	1.141

Note. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-increasing' class was used as the reference category. *b* = unstandardized regression coefficient. Low-inc = low-increasing class. Mid-inc = mid-increasing class. SDQ = Strengths and Difficulties Questionnaire). * = significant at $q < .05$ (FDR-adjusted $p < .05$ and $p < .017$ for single-and multiple-predictor regressions, respectively).

Table 5.7

Multinomial Logistic Regression Results for Paranoia Latent Trajectory Class Regressed on GPS Variables for Most Predictive f

		Single-predictor regression					Multiple-predictor regression				
		Beta		Odds Ratio			Beta		Odds Ratio		
GPS	***f***	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**
Years of education	**1**										
Low-dec vs mid-dec		0.244 (0.045)	5.389 (< .001)*	1.277 (0.058)	1.168	1.396	0.181 (0.065)	2.760 (.006)*	1.198 (0.078)	1.054	1.362
Low-dec vs high-pers		0.223 (0.046)	4.816 (< .001)*	1.250 (0.058)	1.142	1.369	0.124 (0.066)	1.884 (.060)	1.132 (0.075)	0.995	1.289
Mid-dec vs high-pers		-0.021 (0.038)	-0.550 (.583)	0.979 (0.037)	0.909	1.055	-0.056 (0.057)	-0.989 (.322)	0.945 (0.054)	0.846	1.057
IQ	**1**										
Low-dec vs mid-dec		0.200 (0.044)	4.525 (< .001)*	1.221(0.054)	1.120	1.331	0.152 (0.64)	2.393 (.017)	1.164 (0.074)	1.028	1.319
Low-dec vs high-pers		0.258 (0.047)	5.515 (< .001)*	1.295 (0.061)	1.181	1.419	0.207 (0.067)	3.099 (.002)*	1.230 (0.082)	1.079	1.401
Mid-dec vs high-pers		0.059 (0.039)	1.491 (.136)	1.060 (0.042)	0.982	1.146	0.055 (0.057)	0.961 (.337)	1.056 (0.060)	0.945	1.180
Psychiatrist	**0.3**										
Low-dec vs mid-dec		0.011 (0.046)	0.234 (.815)	1.011 (0.045)	1.079	1.254	0.081 (0.075)	1.072 (.284)	1.084 (0.082)	0.935	1.257
Low-dec vs high-pers		0.162 (0.047)	3.426 (.001)*	1.175 (0.055)	1.072	1.289	0.141 (0.079)	1.798 (.072)	1.152 (0.091)	0.987	1.344
Mid-dec vs high-pers		0.151 (0.038)	3.936 (< .001)*	1.163 (0.045)	1.079	1.254	0.061 (0.063)	0.964 (.335)	1.062 (0.067)	0.939	1.202
GP	**0.3**										
Low-dec vs mid-dec		-0.009 (0.049)	-0.189 (.850)	0.991 (0.049)	0.900	1.091	0.036 (0.082)	0.438 (.661)	1.037 (0.085)	0.883	1.217
Low-dec vs high-pers		0.186 (0.049)	3.800 (< .001)*	1.205 (0.059)	1.094	1.326	0.151 (0.082)	1.841 (.066)	1.163 (0.095)	0.990	1.366
Mid-dec vs high-pers		0.196 (0.038)	5.203 (< .001)*	1.216 (0.046)	1.130	1.309	0.115 (0.064)	1.813 (.070)	1.122 (0.071)	0.991	1.271
Schizophrenia	**0.01**										
Low-dec vs mid-dec		-0.069 (0.046)	-1.491 (.136)	0.933 (0.043)	0.852	1.022	-	-	-	-	-
Low-dec vs high-pers		-0.034 (0.047)	-0.719 (.472)	0.967 (0.045)	0.882	1.060	-	-	-	-	-
Mid-dec vs high-pers		0.035 (0.038)	0.934 (.350)	1.036 (0.039)	0.962	1.116	-	-	-	-	-
OCD	**0.01**										
Low-dec vs mid-dec		0.062 (0.045)	1.372 (.170)	1.064 (0.048)	0.974	1.162	-	-	-	-	-
Low-dec vs high-pers		0.010 (0.046)	0.209 (.835)	1.010 (0.046)	0.923	1.105	-	-	-	-	-
Mid-dec vs high-pers		0.052 (0.038)	1.372 (.170)	0.949 (0.036)	0.881	1.023	-	-	-	-	-
MDD	**0.3**										
Low-dec vs mid-dec		0.026 (0.044)	0.595 (.552)	1.027 (0.045)	0.942	1.119	-0.048 (0.064)	-0.761 (.447)	0.953 (0.061)	0.841	1.079
Low-dec vs high-pers		0.205 (0.046)	4.475 (<.001)*	1.228 (0.056)	1.122	1.343	0.046 (0.067)	0.683 (.495)	1.047 (0.070)	0.918	1.193
Mid-dec vs high-pers		0.179 (0.039)	4.599 (<.001)*	1.196 (0.047)	1.108	1.291	0.094 (0.057)	1.643 (.100)	1.099 (0.063)	0.982	1.229
Bipolar disorder	**1**										
Low-dec vs mid-dec		-0.005 (0.046)	-0.103 (.918)	0.995 (0.046)	0.909	1.090	-	-	-	-	-
Low-dec vs high-pers		-0.022 (0.047)	-0.476 (.634)	0.978 (0.046)	0.892	1.072	-	-	-	-	-

Mid-dec vs high-pers		-0.017 (0.038)	-0.460 (.645)	0.983 (0.037)	0.912	1.059	-	-	-	-	-
ASD	**0.3**										
Low-dec vs mid-dec		0.160 (0.044)	3.599 (< .001)*	1.173 (0.052)	1.076	1.280	0.177 (0.063)	2.805 (.005)*	1.193 (0.075)	1.055	1.350
Low-dec vs high-pers		0.253 (0.046)	5.464 (< .001)*	1.288 (0.060)	1.176	1.410	0.192 (0.065)	2.957 (.003)*	1.121 (0.079)	1.067	1.376
Mid-dec vs high-pers		0.093 (0.038)	2.417 (.016)*	1.097 (0.042)	1.018	1.183	0.015 (0.054)	0.283 (.777)	1.015 (0.055)	0.914	1.128
Anorexia	**0.01**										
Low-dec vs mid-dec		0.017 (0.046)	0.366 (.714)	1.017 (0.047)	0.929	1.114	-	-	-	-	-
Low-dec vs high-pers		0.083 (0.047)	1.778 (.075)	1.087 (0.051)	0.992	1.191	-	-	-	-	-
Mid-dec vs high-pers		0.066 (0.038)	1.736 (.082)	1.068 (0.041)	0.992	1.151	-	-	-	-	-
ADHD	**0.01**										
Low-dec vs mid-dec		0.082 (0.044)	1.842 (.065)	1.085 (0.048)	0.995	1.184	0.079 (0.060)	1.327 (.185)	1.083 (0.065)	0.963	1.217
Low-dec vs high-pers		0.166 (0.046)	3.602 (< .001)*	1.181 (0.055)	1.079	1.293	0.184 (0.064)	2.878 (.004)*	1.202 (0.077)	1.060	1.362
Mid-dec vs high-pers		0.085 (0.039)	2.181 (.029)	1.088 (0.042)	1.009	1.174	0.104 (0.054)	1.919 (.055)	1.110 (0.060)	0.998	1.235

Note. N =7,090. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-increasing' class was used as the reference category. The 'mid-decreasing' class was used as the reference category for the mid-dec vs high-pers comparison. Results shown for the most predictive GPS *f* pertaining to the low-decreasing versus high-persistent comparison. GPS = genome-wide polygenic score (standardised). *f* = fraction of causal markers. *b* = unstandardized regression coefficient. Low-dec = low-decreasing class. Mid-dec = mid-decreasing class. High-pers = high-persistent class. IQ = intelligence. Psychiatrist = ever visited a psychiatrist for nerves, anxiety, tension, or depression. GP = ever visited a general practitioner for nerves, anxiety, tension, or depression. OCD = obsessive compulsive disorder. MDD = major depressive disorder. ASD = autism spectrum disorder. ADHD = attention deficit hyperactivity disorder. * = significant at $q < .05$ (FDR-adjusted $p < .021$ and $p < .022$ for single- and multiple-predictor regressions, respectively).

Table 5.8

Multinomial Logistic Regression Results for Hallucinations Latent Trajectory Class Regressed on GPS Variables for Most Predictive f

		Single-predictor regressions					Multiple-predictor regression				
		Beta		Odds Ratio			Beta		Odds Ratio		
GPS	***f***	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**
Years of education	**1**										
Low-dec vs mid-dec		-0.074 (0.028)	-2.648 (.008)*	0.929 (0.026)	0.880	0.981	-0.063 (0.029)	-2.153 (.031)	0.939 (0.027)	0.887	0.994
IQ	**0.01**										
Low-dec vs mid-dec		0.025 (0.028)	0.892 (.373)	1.025 (0.028)	0.971	1.082	-	-	-	-	-
Visited a psychiatrist	**0.3**										
Low-dec vs mid-dec		0.091 (0.028)	3.288 (.001)*	1.095 (0.030)	1.037	1.156	0.032 (0.035)	0.922 (.357)	1.033 (0.036)	0.965	1.105
Visited a GP	**1**										
Low-dec vs mid-dec		0.117 (0.028)	4.220 (< .001)*	1.124 (0.031)	1.065	1.187	0.083 (0.036)	2.314 (.021)	1.087 (0.039)	1.013	1.166
Schizophrenia	**1**										
Low-dec vs mid-dec		-0.019 (0.028)	-0.698 (.485)	0.981 (0.027)	0.929	1.036	-	-	-	-	-
OCD	**0.01**										
Low-dec vs mid-dec		0.028 (0.027)	1.028 (.304)	1.029 (0.028)	0.975	1.085	-	-	-	-	-
MDD	**1**										
Low-dec vs mid-dec		0.063 (0.027)	2.284 (.022)*	1.065 (0.029)	1.009	1.124	-0.010 (0.031)	-0.324 (.746)	0.990 (0.030)	0.932	1.052
Bipolar disorder	**0.01**										
Low-dec vs mid-dec		-0.039 (0.028)	-1.409 (.159)	0.961 (0.027)	0.910	1.015	-	-	-	-	-
ASD	**0.3**										
Low-dec vs mid-dec		0.099 (0.028)	3.557 (< .001)*	1.104 (0.031)	1.045	1.166	0.084 (0.030)	2.820 (.005)*	1.088 (0.033)	1.026	1.154
Anorexia	**0.01**										
Low-dec vs mid-dec		-0.010 (0.028)	-0.368 (.713)	0.990 (0.027)	0.938	1.045	-	-	-	-	-
ADHD	**0.3**										
Low-dec vs mid-dec		0.085 (0.028)	3.080 (.002)*	1.088 (0.030)	1.031	1.149	0.040 (0.030)	1.317 (.188)	1.041(0.031)	0.981	1.104

Note. N =7,093. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-decreasing' class was used as the reference category. GPS = genome-wide polygenic score (standardised). *f* = fraction of causal markers. *b* = unstandardized regression coefficient. Low-dec = low-decreasing class. Mid-dec = mid-decreasing class. IQ = intelligence. Visited a psychiatrist = ever visited a psychiatrist for nerves, anxiety, tension, or depression. Visited a GP = ever visited a general practitioner for nerves, anxiety, tension, or depression. OCD = obsessive compulsive disorder. MDD = major depressive disorder. ASD = autism spectrum disorder. ADHD = attention deficit hyperactivity disorder. * = significant at $q < .05$ (FDR-adjusted $p < .027$ and $p < .008$ for single- and multiple-predictor regressions, respectively). Bold typeset indicates highest *z* statistic for each GPS.

Table 5.9

Multinomial Logistic Regression Results for Negative Symptoms Latent Trajectory Class Regressed on GPS Variables for Most Predictive f

		Single-predictor regressions					Multiple-predictor regression				
Auxiliary variable (GPS)	***f***	**Beta**		**Odds Ratio**			**Beta**		**Odds Ratio**		
		***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**	***b* (*SE*)**	***z* (*p* value)**	**OR (*SE*)**	**95% CI lower**	**95% CI upper**
Years of education	**1**										
Low-inc vs mid-inc		-0.258 (0.029)	-9.025 (< .001)*	0.772 (0.022)	0.739	0.817	-0.256 (0.032)	-7.943 (< .001)*	0.774 (0.025)	0.727	0.825
IQ	**1**										
Low-inc vs mid-inc		-0.096 (0.028)	-3.437 (.001)*	0.908 (0.025)	0.860	0.960	0.019 (0.031)	0.600 (.548)	1.019 (0.032)	0.959	1.083
Visited a psychiatrist	**0.3**										
Low-inc vs mid-inc		0.068 (0.028)	2.455 (.014)*	1.071 (0.030)	1.014	1.131	0.023 (0.035)	0.646 (.518)	1.023 (0.036)	0.955	1.095
Visited a GP	**1**										
Low-inc vs mid-inc		0.094 (0.028)	3.330 (.001)*	1.099 (0.031)	1.039	1.161	0.035 (0.036)	0.950 (.342)	1.035 (0.038)	0.964	1.112
Schizophrenia	**1**										
Low-inc vs mid-inc		0.021 (0.028)	0.758 (.448)	1.021 (0.029)	0.967	1.079	-	-	-	-	-
OCD	**0.01**										
Low-inc vs mid-inc		0.034 (0.028)	1.195 (.232)	1.034 (0.029)	0.979	1.093	-	-	-	-	-
MDD	**1**										
Low-inc vs mid-inc		0.098 (0.028)	3.461 (.001)*	1.103 (0.031)	1.044	1.167	0.055 (0.031)	1.767 (.077)	1.057 (0.033)	0.994	1.124
Bipolar disorder	**1**										
Low-inc vs mid-inc		-0.058 (0.028)	-2.073 (.038)	0.944 (0.026)	0.894	0.997	-	-	-	-	-
ASD	**0.01**										
Low-inc vs mid-inc		0.047 (0.028)	1.679 (.093)	1.048 (0.029)	0.992	1.107	-	-	-	-	-
Anorexia	**0.3**										
Low-inc vs mid-inc		-0.020 (0.027)	-0.714 (.475)	0.981 (0.027)	0.929	1.035	-	-	-	-	-
ADHD	**0.3**										
Low-inc vs mid-inc		0.067 (0.028)	2.371 (.018)*	1.070 (0.030)	1.012	1.131	0.001 (0.030)	0.028 (.978)	1.001 (0.030)	0.944	1.061

Note. N =7,439. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-increasing' class was used as the reference category. GPS = genome-wide polygenic score (standardised). *f* = fraction of causal markers. *b* = unstandardized regression coefficient. Low-inc = low-increasing class. Mid-inc = mid-increasing class. IQ = intelligence. Visited a psychiatrist = ever visited a psychiatrist for nerves, anxiety, tension, or depression. Visited a GP = ever visited a general practitioner for nerves, anxiety, tension, or depression. OCD = obsessive compulsive disorder. MDD = major depressive disorder. ASD = autism spectrum disorder. ADHD = attention deficit hyperactivity disorder. * = significant at $q < .05$ (FDR-adjusted $p < .027$ and $p < .008$ for single- and multiple-predictor regressions, respectively).

Table 5.10

Characteristics of Latent Trajectory Classes for Paranoia, Hallucinations, and Negative Symptoms

		Paranoia					Hallucinations				Negative symptoms			
Auxiliary variable	Scaling	*N*	Mean (*SE*)			Diff.	*N*	Mean (*SE*)		Diff.	*N*	Mean (*SE*)		Diff.
			Low-dec class (a)	Mid-dec class (b)	High-pers class (c)			Low-dec class (a)	Mid-dec class (b)			Low-inc class (a)	Mid-inc class (b)	
GPS:														
GPS_{EDU}	Std	7,090	-0.186 (0.037)	0.058 (0.021)	0.037 (0.028)	a<b, a<c, b=c	7,093	0.046 (0.019)	-0.027 (0.020)	a>b	7,439	0.157 (0.021)	-0.098 (0.018)	a>b
GPS_{IQ}	Std	7,090	-0.175 (0.037)	0.030 (0.021)	0.087 (0.030)	a<b, a<c, b=c	7,093	-0.012 (0.019)	0.013 (0.020)	a=b	7,439	0.059 (0.021)	-0.038 (0.018)	a>b
GPS_{PSYCH}	Std	7,090	-0.052 (0.038)	-0.041 (0.020)	0.109 (0.029)	a=b, a<c, b<c	7,093	-0.044 (0.019)	0.046 (0.020)	a<b	7,439	-0.046 (0.021)	0.022 (0.018)	a<b
GPS_{GP}	Std	7,090	-0.050 (0.039)	-0.060 (0.021)	0.134 (0.027)	a=b, a<c, b<c	7,093	-0.059 (0.019)	0.057 (0.019)	a<b	7,439	-0.064 (0.021)	0.030 (0.018)	a<b
GPS_{SCZ}	Std	7,090	0.045 (0.038)	-0.024 (0.021)	0.011 (0.029)	a=b, a=c, b=c	7,093	0.004 (0.019)	-0.015 (0.020)	a=b	7,439	-0.008 (0.021)	0.013 (0.018)	a=b
GPS_{OCD}	Std	7,090	-0.041 (0.037)	0.021 (0.021)	-0.031 (0.029)	a=b, a=c, b=c	7,093	-0.018 (0.019)	0.011 (0.020)	a=b	7,439	-0.021 (0.021)	0.012 (0.018)	a=b
GPS_{MDD}	Std	7,090	-0.079 (0.037)	0.008 (0.021)	0.034 (0.029)	a=b, a<c, b=c	7,093	-0.032 (0.019)	0.031 (0.020)	a<b	7,439	-0.056 (0.021)	0.042 (0.018)	a<b
GPS_{BIP}	Std	7,090	0.008 (0.037)	0.004 (0.021)	-0.014 (0.028)	a=b, a=c, b=c	7,093	0.021 (0.019)	-0.019 (0.020)	a=b	7,439	0.034 (0.021)	-0.024 (0.018)	a=b
GPS_{ASD}	Std	7,090	-0.154 (0.036)	0.006 (0.020)	0.098 (0.029)	a<b, a<c, b<c	7,093	-0.043 (0.019)	0.055 (0.020)	a<b	7,439	-0.026 (0.021)	0.021 (0.018)	a=b
GPS_{ANOREX}	Std	7,090	-0.034 (0.038)	-0.018 (0.020)	0.049 (0.029)	a=b, a=c, b=c	7,093	0.004 (0.019)	-0.006 (0.020)	a=b	7,439	0.012 (0.021)	-0.007 (0.018)	a=b
GPS_{ADHD}	Std	7,090	-0.098 (0.037)	-0.015 (0.021)	0.069 (0.029)	a=b, a<c, b=c	7,093	-0.047 (0.019)	0.038 (0.020)	a<b	7,439	-0.040 (0.021)	0.027 (0.018)	a<b
Background:														
Sex (male) [1]	1 = male	12,049	0.479 (0.014)	0.439 (0.008)	0.386 (0.011)	a>b, a>c, b>c	12,054	0.451 (0.007)	0.410 (0.008)	a>b	12,652	0.420 (0.008)	0.484 (0.007)	a<b
SES	Std	11,368	-0.030 (0.030)	0.289 (0.018)	0.191 (0.025)	a<b, a<c, b>c	11,373	0.249 (0.017)	0.157 (0.018)	a>b	11,961	0.351 (0.019)	0.124 (0.016)	a>b
Family SCZ [1]	1 = yes	9,673	0.021 (0.005)	0.038 (0.004)	0.055 (0.007)	a<b, a<c, b<c	9,678	0.035 (0.004)	0.045 (0.004)	a<b	9,737	0.035 (0.004)	0.044 (0.004)	a=b
Family BIP [1]	1 = yes	9,459	0.045 (0.007)	0.055 (0.005)	0.071 (0.007)	a=b, a<c, b=c	9,463	0.050 (0.004)	0.065 (0.005)	a<b	9,523	0.052 (0.005)	0.062 (0.005)	a=b
Age 7:														
Ed attainment	Std	7,662	-0.108 (0.039)	0.193 (0.020)	0.167 (0.028)	a<b, a<c, b=c	7,665	0.185 (0.019)	0.080 (0.019)	a>b	8,172	0.243 (0.020)	0.038 (0.018)	a>b
Life events	0-11	9,605	0.967 (0.043)	0.946 (0.023)	1.095 (0.035)	a=b, a<c, b<c	9,611	0.948 (0.022)	1.037 (0.024)	a<b	10,235	0.944 (0.025)	1.029 (0.022)	a<b
SDQ	0-40	9,601	7.445 (0.154)	7.720 (0.088)	8.998 (0.132)	a=b, a<c, b<c	9,607	7.553 (0.081)	8.538 (0.089)	a<b	10,231	6.611 (0.082)	9.115 (0.083)	a<b
Age 22:														
Ed attainment	Std	8,342	-0.138 (0.040)	0.097 (0.018)	-0.008 (0.026)	a<b, a<c, b>c	8,342	0.096 (0.017)	-0.041 (0.019)	a>b	8,024	0.239 (0.017)	-0.094 (0.018)	a>b
Life events	0-44	8,373	2.170 (0.104)	2.694 (0.062)	5.117 (0.128)	a<b, a<c, b<c	8,372	2.606 (0.053)	4.14 (0.079)	a<b	7,579	2.705 (0.064)	3.562 (0.070)	a<b
MFQ	0-16	8,562	2.215 (0.112)	3.599 (0.070)	7.193 (0.114)	a<b, a<c, b<c	8,562	3.382 (0.062)	5.557 (0.075)	a<b	8,239	3.495 (0.073)	4.963 (0.069)	a<b
SDQ	0-40	8,565	7.075 (0.178)	9.361 (0.099)	14.756 (0.154)	a<b, a<c, b<c	8,565	8.915 (0.091)	12.405 (0.105)	a<b	8,243	8.903 (0.106)	11.634 (0.098)	a<b

Note. N indicates the number of individuals with data contributing to the GMM and not missing on the auxiliary variable. Related and unrelated individuals included, using cluster-robust *SE*. Class-specific means of the auxiliary variable. For binary variables ([1]), the mean represents the proportion. Diff. reflects the chi-square value (*df* 1) of the difference between the means (or proportions), significant at FDR-adjusted $q < .05$ unless indicated by '='. GPS = genome-wide polygenic score. GPS_{EDU} = years of education. GPS_{IQ} = intelligence. GPS_{PSYCH} = ever visited a psychiatrist for nerves, anxiety, tension, or depression. GPS_{GP} = ever visited a general practitioner for nerves, anxiety, tension, or depression. GPS_{OCD} = obsessive compulsive disorder. GPS_{MDD} = major depressive disorder. GPS_{ASD} = autism spectrum disorder. GPS_{ADHD} = attention deficit hyperactivity disorder. SES = socioeconomic status. Family SCZ = family history of schizophrenia. Family BIP = family history of bipolar disorder. Ed attainment = educational attainment. SDQ = Strengths and Difficulties Questionnaire total. MFQ = Short Mood and Feeling Questionnaire. Std = standardised.

5.4 – Discussion

This Chapter investigated the extent to which the latent trajectory classes of paranoia, hallucinations, and NS measured were associated with characteristics previously found to be associated with aggregated PEs, and with polygenic scores for a range of outcomes. Support was found for the hypotheses that the most elevated PENS trajectory class would be associated with less favourable scores on both phenotypic and polygenic measures, with some exceptions. Life events and emotional/behavioural problems (at ages 7 and 22), depressive symptoms (at age 22), and polygenic liability for clinical help-seeking, major depressive disorder, and attention deficit hyperactivity disorder were all associated with membership in the most elevated trajectory class across PENS. Trajectory class associations were not significant for schizophrenia, obsessive compulsive disorder, bipolar disorder, or anorexia GPS.

The phenotypic findings that more life events and emotional/behavioural problems were associated with the most elevated class concur broadly with findings derived from studies that have manually classified individuals into trajectory groups for aggregated PEs (e.g., Rammos et al., 2021), as well as studies that have used GMM to investigate aggregated PEs (e.g., Bourque et al., 2017; Mackie et al., 2011, 2013; Thapar et al., 2012; Wigman, van Winkel, Jacobs, et al., 2011; Wigman, van Winkel, Raaijmakers, et al., 2011). The current results suggested that life events and emotional/behavioural problems reported prospectively in childhood represent markers for suboptimal latent trajectories of paranoia, hallucinations, and NS, separately, measured 10-15 years later.

Of the dimension-wide polygenic score effects that were observed in the current Chapter, the findings of higher GPS for clinical help seeking, major depressive disorder, and attention deficit hyperactivity disorder being associated with the most elevated trajectory classes, showed that latent trajectory class membership for the PENS dimensions is at least in

part associated with measured genetic variants associated with specific clinical outcomes. The association between polygenic liability for clinical help-seeking (for nerves, anxiety, tension, or depression) and for major depressive disorder, can be considered in line with both theory and empirical findings suggesting that affective symptoms exacerbate psychotic symptoms in general, and specifically, contribute to the persistence of paranoia (Bird et al., 2017; Fowler et al., 2012; Freeman et al., 2002, 2012; Freeman & Garety, 2003).

The dimension-wide associations that were observed for the attention deficit hyperactivity disorder GPS add to findings that have shown an association between this GPS and cross-sectional (aggregated) PEs in adolescence (Legge et al., 2019). They are also interesting given that whilst attention deficit hyperactivity disorder GPS was previously found not to predict schizophrenia status in a systematic review (Ronald et al., 2021), the review further highlighted the GPS' association with trajectories of cognitive development within a schizophrenia sample (Dickinson et al., 2020). The current results add to these findings, suggesting that the attention deficit hyperactivity disorder GPS may be important for predicting how PENS and other psychosis-related phenotypes develop over time.

Dimension-*specific* results were also observed in the current Chapter. Male sex was associated with membership in the most elevated trajectory class for NS, as predicted. This finding adds to previously reported cross-sectional associations between male sex and NS in the community (Dominguez et al., 2010; Maric et al., 2003; Ronald et al., 2014), which has also been found in the ultra-high-risk stage of psychosis (Barajas et al., 2015) as well as in schizophrenia (e.g., Roy et al., 2001) – further adding support to a continuum model of NS (Kaiser et al., 2011).

An unexpected result was that the GPS for autism spectrum disorder was associated with the most elevated trajectory for paranoia and hallucinations but not for NS. These results add to previous findings that have shown an association between this GPS and cross-sectional

aggregated PEs in adolescence (Legge et al., 2019). Future research should test whether polygenic propensity for autism spectrum disorder influences only the development of PEs dimensions and not NS in other community samples, and at other ages.

One collective pattern of results to emerge that was not predicted, was that whilst higher educational attainment (at ages 7 and 22), SES, and polygenic liability to years of education (and intelligence, for NS) were associated with decreased odds of being in the most elevated trajectory class for hallucinations and NS, as predicted, the opposite was true for paranoia. These findings for paranoia are hard to interpret in a theoretical context. Replication attempts can test the extent to which the enforced model constraints on the GMM aspect of the model, and the observed classification error (reflected in the entropy), may have influenced the unexpected results.

The finding of a null association for schizophrenia GPS across PENS was unexpected, though it concurs with the finding of a recent study that reported a null association between schizophrenia GPS and persistence of aggregated PEs across adolescence and emerging adulthood (Rammos et al., 2021). To the extent that schizophrenia GPS is associated with PENS measured at single time points (Jones et al., 2016; Pain et al., 2018), the current results suggest that polygenic propensity for schizophrenia may influence the static expression but not the development of PENS.

The current findings of an association between family history of psychosis and bipolar disorder and the most elevated course of paranoia and hallucinations provides support for the proneness-persistence-impairment model of psychosis (van Os et al., 2009). However, the GPS findings further suggest that the association is *not* due to an increased burden of measured polygenic variants for schizophrenia/bipolar disorder, echoing the findings of Rammos et al. (2021). The current findings are in line with previous studies that have found associations between manually-classified persistence of PEs and sibling history of psychosis

(Janssens et al., 2016). However, the same study also found an association between sibling history of psychosis and persistence of NS, which was not found in the current study. The different age of the sample (adults) is noted, and as such, it could be speculated that family history of psychosis manifests as persistent NS in adulthood but not across adolescence/emerging adulthood – though there is no obvious theoretical explanation to support this to my knowledge.

In summary, by studying specific PENS dimensions, dimension-wide as well as dimension-specific behavioural and polygenic associations with the latent trajectory classes were observed. The results provide some evidence towards construct validation of the latent trajectory classes (see Section 5.1). The results further both corroborate previous phenotypic findings and provide novel findings to suggest associations between specific polygenic scores and the developmental course of specific PENS dimensions. Whilst the need for replication is present particularly for the unexpected paranoia results, the findings contribute to a growing body of literature that suggests that a dimension-specific and trajectory-based approach is valuable for delineating the etiological and developmental pathways that underlie PENS dimensions.

5.5 – Appendix

Supplementary Information 5.1

Genotyping of TEDS Participants

This information is reproduced from Havers et al., 2022 (Supplementary Information 2), under a creative commons licence, with minor amendments.

Genotyping of TEDS participants was carried out by other TEDS researchers (Selzam et al., 2018). Full details of the genotyping procedures can be found on the TEDS data dictionary website (https://www.teds.ac.uk/datadictionary/studies/dna.htm).

There have been five phases of genotyping in the TEDS sample since 1998. Data from all phases has contributed towards the 'genotypic sample' in TEDS, for which GPS were calculated. DNA was collected from cheek swabs between 1998 and 2009 for phases 1-4, and from saliva samples between 2014-2015 for phase 5. Twin pairs (or individual twins) who had recently returned data were prioritised for DNA collection. Families were contacted by mail in phase 1. In phase 2, families were contacted by phone before by mail, following initial verbal consent. In the later phases, families were contacted by mail followed by phone for families who had not responded. Cheek swab samples were collected from individuals by their parents and saliva samples were collected by individuals themselves. Collection was carried out at home and samples were returned by post. The Affymetrix platform was used for the cheek swab samples from phases 1-4 (AffymetrixGeneChip 6.0 SNP arrays). The Illumina Human OEE platform was used for the saliva samples from phase 5 (using OmniExpressExome-8v1.2 arrays). The OEE platform was also used for some cheek swab samples from earlier phases (see https://www.teds.ac.uk/datadictionary/studies/dna.htm#oee).

Detailed information regarding exclusions can be found on the TEDS data dictionary website (https://www.teds.ac.uk/datadictionary/studies/dna.htm); broad exclusions were made on the basis that parents self-reported their ethnic origin as 'other' than 'white', and where serious medical conditions and or perinatal complications had been self-reported.

The genotypic sample in TEDS includes data from both the Affymetrix and OEE platforms, which were combined and subjected to quality control procedures (described in detail in S1 Methods, Supplementary Methods, Selzam et al., 2018). From an initial combined sample size of 11869, 1523 samples were removed owing to possible non-European ancestry, heterozygosity anomalies, genotype call rate < 0.98, and genetic relatedness other than dyzygosity. The final genotypic sample is comprised of 10,346 individual twins (3,057 genotyped on Affymetrix, 7,289 genotyped on OEE). Of the 10,346 individuals, there is genotype data from 3,320 twin pairs (all dyzygotic). There are 3,706 twin pairs of any zygosity with only one twin genotyped (2,666 monozygotic, 1,017 dyzygotic and 23 unknown zygosity). There are 7,026 twin pairs with either one or both twin genotyped. Seven million (7),363,646 genotyped and imputed single nucleotide polymorphisms (SNPs) were retained for subsequent analyses.

Supplementary Information 5.2

Calculation of Genome-Wide Polygenic Scores

This information is reproduced from Havers et al., 2022 (Supplementary Information 3), under a creative commons licence, with minor amendments.

GPS were calculated by other TEDS researchers (Selzam et al., 2019).

GPS were calculated for each of the 10,346 individuals in the genotypic sample (Supplementary Information 6.1). GPS for years of education (GPS_{EDU}) were derived using data from the 2018 GWAS with 23andMe samples removed, comprising N = 76,6345 (J. J. Lee et al., 2018). GPS for intelligence (GPS_{IQ}) were derived using data from the 2018 GWAS meta-analysis, comprising N = 26,6453 (Savage et al., 2018). GPS for visited a psychiatrist for nerves, anxiety, tension, or depression (GPS_{PSYCH}), were derived using data from the 2017 GWAS, comprising 64,579 cases and 510,625 controls (Neale Lab, 2017). GPS for visited a general practitioner for nerves, anxiety, tension, or depression (GPS_{GP}), were derived using data from the 2017 GWAS, comprising 192,838 cases and 380,905 controls (Neale Lab, 2017). GPS for schizophrenia (GPS_{SCZ}) were derived using data from the 2018 GWAS, comprising 40,675 cases and 64,643 controls (Pardiñas et al., 2018). GPS for obsessive compulsive disorder (GPS_{OCD}) were derived using data from the 2017 GWAS meta-analysis, comprising 2,688 cases and 7,037 controls (IOCDF-GC and OCGAS, 2018). GPS for major depressive disorder (GPS_{MDD}) were derived using data from the 2018 GWAS meta-analysis (with 23andMe samples removed), comprising 75,607 cases and 231,747 controls (Wray et al., 2018). GPS for bipolar disorder (GPS_{BIP}) were derived using data from the 2011 GWAS, comprising 7,481 cases and 9,250 controls (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011). GPS for autism spectrum disorder (GPS_{ASD}) were derived using data from the 2017 GWAS, comprising 18,381 cases and 27,969 controls (Grove et al., 2019).

GPS for anorexia nervosa (GPS_{ANOREX}) were derived using data from the 2017 GWAS, comprising 3,495 cases and 10,982 controls (Duncan et al., 2017). GPS for attention deficit hyperactivity disorder (GPS_{ADHD}) were derived using data from the 2017 GWAS, comprising 20,183 cases and 35,191 controls (Demontis et al., 2019).

The description of the methods used for the GPS calculation as follows is adapted directly from Selzam et al. (2019, Supplementary Methods), where the methods are fully described. GPS are the sum of single nucleotide polymorphisms (SNPs), individual genetic variants, that are associated with an outcome that are carried by an individual, weighted by the effect sizes of the SNPs. SNP-effect sizes are estimated in a genome-wide association study (GWAS) of an outcome of interest in an independent sample, in which the outcome is regressed on each of the SNPs. LDpred software (Vilhjálmsson et al., 2015) was used to calculate the GPS. LDpred implements Bayesian methods, adjusting for linkage disequilibrium (LD) amongst SNPs rather than removing SNPs that are in high LD (as is the case with the clumping and thresholding approach, see, e.g., Choi et al., 2020). LDpred estimates a posterior effect size for each SNP that is present in the GWAS summary statistics as well as in the target genotyped sample.

The posterior effect size is estimated as the original summary statistic effect size estimate, adjusted by the relative influence of a SNP (taking into account its level of LD with surrounding SNPs in the target sample) and adjusting for a prior on the effect size of each SNP. A radius corresponding to a two megabase window on average around each SNP of interest was set to account for LD. The effect size prior is dependent on the SNP-heritability of the GWAS outcome of interest, and the proportion of SNPs (the fraction of causal markers) believed to influence the outcome. Using the effect size prior, the beta effect sizes are reweighted. Thus, the effects are spread among the SNPs across the genome in proportion to the amount of LD amongst them. The genotype dataset was reduced to SNPs that had

imputation quality information scores of 1 to reduce computational demands, resulting in 515,100 SNPs that could be analysed. Alleles associated with the outcome were counted for each individual (zero, one, or two for each SNP). GPS for each individual were calculated as the sum of the alleles, each weighted by the posterior SNP effect size.

The first 10 principal components (PCs) were calculated using data from the final genotyped sample, and GPS were regressed on these PCs prior to analysis. These PCs reflect and capture population structure within the sample. Regressing the GPSs on the PCs adjusts for any confounding that would otherwise be present due to population structure. GPSs were also regressed on batch and chip type to further remove any potential confounding by these variables.

Supplementary Table 5.1

Multinomial Logistic Regression Results for Paranoia Latent Trajectory Class Regressed on GPSs for all GPS f

	Beta		Odds Ratio		
	b (*SE*)	*z* (*p* value)	OR (*SE*)	95% CI lower	95% CI upper
EA3_1					
Low-dec vs mid-dec	0.244 (0.045)	5.389 (< .001)	1.277 (0.058)	1.168	1.396
Low-dec vs high-persistent	0.223 (0.046)	**4.816 (< .001)**	1.250 (0.058)	1.142	1.369
Mid-dec vs high-persistent	-0.021 (0.038)	-0.550 (.583)	0.979 (0.037)	0.909	1.055
EA3_0.3					
Low-dec vs mid-dec	0.234 (0.046)	5.094 (< .001)	1.264 (0.058)	1.155	1.383
Low-dec vs high-persistent	0.203 (0.046)	4.376 (< .001)	1.225 (0.057)	1.118	1.341
Mid-dec vs high-persistent	-0.031 (0.038)	-0.831 (.406)	0.969 (0.037)	0.900	1.043
EA3_0.01					
Low-dec vs mid-dec	0.060 (0.047)	1.280 (.201)	1.062 (0.050)	0.969	1.164
Low-dec vs high-persistent	0.009 (0.048)	0.181(.856)	1.009 (0.048)	0.919	1.108
Mid-dec vs high-persistent	-0.051 (0.037)	-1.370 (.171)	0.950 (0.036)	0.883	1.022
IQ_1					
Low-dec vs mid-dec	0.200 (0.044)	4.525 (< .001)	1.221(0.054)	1.120	1.331
Low-dec vs high-persistent	0.258 (0.047)	**5.515 (< .001)**	1.295 (0.061)	1.181	1.419
Mid-dec vs high-persistent	0.059 (0.039)	1.491 (.136)	1.060 (0.042)	0.982	1.146
IQ_0.3					
Low-dec vs mid-dec	0.152 (0.044)	3.433 (.001)	1.165 (0.052)	1.068	1.271
Low-dec vs high-persistent	0.218 (0.047)	4.658 (< .001)	1.244 (0.058)	1.135	1.363
Mid-dec vs high-persistent	0.066 (0.039)	1.669 (.095)	1.068 (0.042)	0.989	1.153
IQ_0.01					
Low-dec vs mid-dec	0.060 (0.044)	1.367 (.172)	1.062 (0.047)	0.974	1.158
Low-dec vs high-persistent	0.093 (0.046)	2.014 (.044)	1.098 (0.051)	1.002	1.202
Mid-dec vs high-persistent	0.033 (0.038)	0.861 (.389)	1.034 (0.040)	0.959	1.114
PSYCH_1					
Low-dec vs mid-dec	0.009 (0.046)	0.205 (.837)	1.009 (0.046)	0.923	1.104
Low-dec vs high-persistent	0.160 (0.047)	3.392 (.001)	1.173 (0.055)	1.070	1.287
Mid-dec vs high-persistent	0.150 (0.038)	3.934 (< .001)	1.162 (0.045)	1.078	1.253
PSYCH_0.3					

Low-dec vs mid-dec	0.011 (0.046)	0.234 (.815)	1.011 (0.045)	1.079	1.254
Low-dec vs high-persistent	0.162 (0.047)	**3.426 (.001)**	1.175 (0.055)	1.072	1.289
Mid-dec vs high-persistent	0.151 (0.038)	3.936 (< .001)	1.163 (0.045)	1.079	1.254
PSYCH_0.01					
Low-dec vs mid-dec	0.015 (0.044)	0.343 (.731)	1.015 (0.045)	0.932	1.106
Low-dec vs high-persistent	0.119 (0.045)	2.642 (.008)	1.126 (0.051)	1.031	1.229
Mid-dec vs high-persistent	0.104 (0.038)	2.734 (.006)	1.109 (0.042)	1.030	1.195
GP_1					
Low-dec vs mid-dec	-0.014 (0.049)	-0.284 (.777)	0.986 (0.048)	0.896	1.086
Low-dec vs high-persistent	0.182 (0.049)	3.727 (< .001)	1.200 (0.059)	1.090	1.321
Mid-dec vs high-persistent	0.196 (0.038)	5.232 (< .001)	1.217 (0.046)	1.131	1.310
GP_0.3					
Low-dec vs mid-dec	-0.009 (0.049)	-0.189 (.850)	0.991 (0.049)	0.900	1.091
Low-dec vs high-persistent	0.186 (0.049)	**3.800 (< .001)**	1.205 (0.059)	1.094	1.326
Mid-dec vs high-persistent	0.196 (0.038)	5.203 (< .001)	1.216 (0.046)	1.130	1.309
GP_0.01					
Low-dec vs mid-dec	-0.016 (0.044)	-0.357 (.721)	0.984 (0.043)	0.903	1.073
Low-dec vs high-persistent	0.094 (0.046)	2.060 (.039)	1.099 (0.050)	1.005	1.202
Mid-dec vs high-persistent	0.110 (0.039)	2.831 (.005)	1.116 (0.043)	1.034	1.205
SCZ_1					
Low-dec vs mid-dec	-0.052 (0.047)	-0.119 (.263)	0.949 (0.044)	0.866	1.040
Low-dec vs high-persistent	-0.028 (0.047)	-0.592 (.554)	0.972 (0.046)	0.886	1.067
Mid-dec vs high-persistent	0.024 (0.038)	0.641 (.522)	1.025 (0.039)	0.951	1.104
SCZ_0.3					
Low-dec vs mid-dec	-0.032 (0.045)	-0.696 (.486)	0.969 (0.044)	0.886	1.059
Low-dec vs high-persistent	-0.004 (0.047)	-0.082 (.935)	0.996 (0.047)	0.908	1.093
Mid-dec vs high-persistent	0.028 (0.039)	0.719 (.472)	1.028 (0.040)	0.953	1.109
SCZ_0.01					
Low-dec vs mid-dec	-0.069 (0.046)	-1.491 (.136)	0.933 (0.043)	0.852	1.022
Low-dec vs high-persistent	-0.034 (0.047)	**-0.719 (.472)**	0.967 (0.045)	0.882	1.060
Mid-dec vs high-persistent	0.035 (0.038)	0.934 (.350)	1.036 (0.039)	0.962	1.116
OCD_1					
Low-dec vs mid-dec	0.027 (0.045)	0.600 (.548)	1.027 (0.046)	0.941	1.121
Low-dec vs high-persistent	-0.008 (0.046)	-0.162 (.871)	0.993 (0.046)	0.906	1.087

Mid-dec vs high-persistent	-0.034 (0.038)	-0.897 (.370)	0.966 (0.037)	0.896	1.042
OCD_0.3					
Low-dec vs mid-dec	0.028 (0.045)	0.618 (.537)	1.028 (0.046)	0.942	1.122
Low-dec vs high-persistent	-0.007 (0.046)	-0.157 (.875)	0.993 (0.046)	0.907	1.087
Mid-dec vs high-persistent	-0.035 (0.038)	-0.911 (.362)	0.966 (0.037)	0.896	1.041
OCD_0.01					
Low-dec vs mid-dec	0.062 (0.045)	1.372 (.170)	1.064 (0.048)	0.974	1.162
Low-dec vs high-persistent	0.010 (0.046)	**0.209 (.835)**	1.010 (0.046)	0.923	1.105
Mid-dec vs high-persistent	0.052 (0.038)	1.372 (.170)	0.949 (0.036)	0.881	1.023
MDD_1					
Low-dec vs mid-dec	0.023 (0.044)	0.518 (.604)	1.023 (0.045)	0.938	1.115
Low-dec vs high-persistent	0.202 (0.046)	4.419 (< .001)	1.224 (0.056)	1.119	1.339
Mid-dec vs high-persistent	0.180 (0.039)	4.613 (< .001)	1.197 (0.047)	1.109	1.292
MDD_0.3					
Low-dec vs mid-dec	0.026 (0.044)	0.595 (.552)	1.027 (0.045)	0.942	1.119
Low-dec vs high-persistent	0.205 (0.046)	**4.475 (< .001)**	1.224 (0.056)	1.122	1.343
Mid-dec vs high-persistent	0.179 (0.039)	4.599 (< .001)	1.196 (0.047)	1.108	1.291
MDD_0.01					
Low-dec vs mid-dec	0.077 (0.046)	1.691 (.091)	1.080 (0.049)	0.988	1.181
Low-dec vs high-persistent	0.130 (0.046)	2.811 (.005)	1.139 (0.053)	1.040	1.247
Mid-dec vs high-persistent	0.053 (0.038)	1.406 (.160)	1.055 (0.040)	0.979	1.136
BIP_1					
Low-dec vs mid-dec	-0.005 (0.046)	-0.103 (.918)	0.995 (0.046)	0.909	1.090
Low-dec vs high-persistent	-0.022 (0.047)	**-0.476 (.634)**	0.978 (0.046)	0.892	1.072
Mid-dec vs high-persistent	-0.017 (0.038)	-0.460 (.645)	0.983 (0.037)	0.912	1.059
BIP_0.3					
Low-dec vs mid-dec	-0.005 (0.046)	-0.103 (.918)	0.995 (0.046)	0.909	1.090
Low-dec vs high-persistent	-0.022 (0.047)	-0.464 (.643)	0.979 (0.046)	0.893	1.073
Mid-dec vs high-persistent	-0.017 (0.038)	-0.446 (.656)	0.983 (0.037)	0.913	1.059
BIP_0.01					
Low-dec vs mid-dec	0.000 (0.046)	-0.004 (.997)	1.000 (0.046)	0.913	1.095
Low-dec vs high-persistent	-0.018 (0.047)	-0.388 (.698)	0.982 (0.046)	0.896	1.076
Mid-dec vs high-persistent	-0.018 (0.038)	-0.473 (.636)	0.982 (0.037)	0.912	1.058

ASD_1					
Low-dec vs mid-dec	0.162 (0.044)	3.644 (< .001)	1.176 (0.052)	1.078	1.283
Low-dec vs high-persistent	0.253 (0.046)	5.461 (< .001)	1.287 (0.060)	1.176	1.410
Mid-dec vs high-persistent	0.091 (0.038)	2.361 (.018)	1.095 (0.042)	1.016	1.181
ASD_0.3					
Low-dec vs mid-dec	0.160 (0.044)	3.599 (< .001)	1.173 (0.052)	1.076	1.280
Low-dec vs high-persistent	0.253 (0.046)	**5.464 (< .001)**	1.288 (0.060)	1.176	1.410
Mid-dec vs high-persistent	0.093 (0.038)	2.417 (.016)	1.097 (0.042)	1.018	1.183
ASD_0.01					
Low-dec vs mid-dec	0.097 (0.045)	2.160 (.031)	1.101 (0.049)	1.009	1.202
Low-dec vs high-persistent	0.207 (0.047)	4.441 (< .001)	1.230 (0.057)	1.123	1.348
Mid-dec vs high-persistent	0.111 (0.038)	2.879 (.004)	1.117 (0.043)	1.036	1.204
ANOREX_1					
Low-dec vs mid-dec	0.022 (0.046)	0.478 (.633)	1.022 (0.047)	0.935	1.118
Low-dec vs high-persistent	0.079 (0.047)	1.675 (.094)	1.082 (0.051)	0.987	1.186
Mid-dec vs high-persistent	0.057 (0.038)	1.487 (.137)	1.058 (0.040)	0.982	1.140
ANOREX_0.3					
Low-dec vs mid-dec	0.022 (0.046)	0.484 (.628)	1.022 (0.047)	0.935	1.118
Low-dec vs high-persistent	0.079 (0.047)	1.683 (.092)	1.082 (0.051)	0.987	1.186
Mid-dec vs high-persistent	0.057 (0.038)	1.490 (.136)	1.058 (0.040)	0.982	1.141
ANOREX_0.01					
Low-dec vs mid-dec	0.017 (0.046)	0.366 (.714)	1.017 (0.047)	0.929	1.114
Low-dec vs high-persistent	0.083 (0.047)	**1.778 (.075)**	1.087 (0.051)	0.992	1.191
Mid-dec vs high-persistent	0.066 (0.038)	1.736 (.082)	1.068 (0.041)	0.992	1.151
ADHD_1					
Low-dec vs mid-dec	0.041 (0.044)	0.935 (.350)	1.042 (0.046)	0.956	1.136
Low-dec vs high-persistent	0.148 (0.046)	3.211 (.001)	1.159 (0.053)	1.059	1.269
Mid-dec vs high-persistent	0.107 (0.039)	2.766 (.006)	1.113 (0.043)	1.032	1.200
ADHD_0.3					
Low-dec vs mid-dec	0.044 (0.044)	0.989 (.323)	1.045 (0.046)	0.958	1.139
Low-dec vs high-persistent	0.150 (0.046)	3.259 (.001)	1.162 (0.054)	1.062	1.272
Mid-dec vs high-persistent	0.107 (0.039)	2.763 (.006)	1.112 (0.043)	1.031	1.200
ADHD_0.01					
Low-dec vs mid-dec	0.082 (0.044)	1.842 (.065)	1.085 (0.048)	0.995	1.184

Low-dec vs high-persistent	0.166 (0.046)	**3.602 (< .001)**	1.181 (0.055)	1.079	1.293
Mid-dec vs high-persistent	0.085 (0.039)	2.181 (.029)	1.088 (0.042)	1.009	1.174

Note. N =7,090. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-decreasing' class was used as the reference category. The 'mid-decreasing' class was used as the reference category for mid-dec vs high-persistent comparisons. GPS = genome-wide polygenic score (standardised). f = fraction of causal markers (at 1, 0.3, 0.01). b = unstandardized regression coefficient. Low-dec = low-decreasing class. Mid-dec = mid-decreasing class. High-persistent = high-persistent class. EA3 = years of education. IQ = intelligence. PSYCH = ever visited a psychiatrist for nerves, anxiety, tension, or depression. GP = ever visited a general practitioner for nerves, anxiety, tension, or depression. SCZ = schizophrenia. OCD = obsessive compulsive disorder. MDD = major depressive disorder. BIP = bipolar disorder. ASD = autism spectrum disorder. ANOREX = anorexia. ADHD = attention deficit hyperactivity disorder. Bold typeset indicates highest z statistic for the low-decreasing versus high-persistent comparison for each GPS.

Supplementary Table 5.2

Multinomial Logistic Regression Results for Hallucinations Latent Trajectory Class Regressed on GPSs for all GPS f

	Beta		Odds Ratio		
	b (SE)	*z* (*p* value)	OR (*SE*)	95% CI lower	95% CI upper
EA3_1					
Low-decreasing vs mid-decreasing	-0.074 (0.028)	**-2.648 (.008)**	0.929 (0.026)	0.880	0.981
EA3_0.3					
Low-decreasing vs mid-decreasing	-0.055 (0.028)	-1.999 (.046)	0.946 (0.026)	0.896	0.999
EA3_0.01					
Low-decreasing vs mid-decreasing	-0.018 (0.028)	-0.645 (.519)	0.982 (0.028)	0.982	1.038
IQ_1					
Low-decreasing vs mid-decreasing	-0.013 (0.028)	-0.455 (.649)	0.987 (0.027)	0.935	1.043
IQ_0.3					
Low-decreasing vs mid-decreasing	-0.005 (0.028)	-0.194 (.846)	0.995 (0.028)	0.942	1.050
IQ_0.01					
Low-decreasing vs mid-decreasing	0.025 (0.028)	**0.892 (.373)**	1.025 (0.028)	0.971	1.082
PSYCH_1					
Low-decreasing vs mid-decreasing	0.090 (0.028)	3.245 (.001)	1.094 (0.030)	1.036	1.155
PSYCH_0.3					
Low-decreasing vs mid-decreasing	0.091 (0.028)	**3.288 (.001)**	1.095 (0.030)	1.037	1.156
PSYCH_0.01					
Low-decreasing vs mid-decreasing	0.053 (0.028)	1.915 (.056)	1.054 (0.029)	0.999	1.113
GP_1					
Low-decreasing vs mid-decreasing	0.117 (0.028)	**4.220 (< .001)**	1.124 (0.031)	1.065	1.187
GP_0.3					
Low-decreasing vs mid-decreasing	0.117 (0.028)	4.216 (< .001)	1.124 (0.031)	1.065	1.187
GP_0.01					
Low-decreasing vs mid-decreasing	0.044 (0.028)	1.613 (.107)	1.045 (0.029)	0.990	1.103
SCZ_1					

Low-decreasing vs mid-decreasing	-0.019 (0.028)	**-0.698 (.485)**	0.981 (0.027)	0.929	1.036
SCZ_0.3					
Low-decreasing vs mid-decreasing	-0.013 (0.028)	-0.453 (.650)	0.988 (0.027)	0.935	1.043
SCZ_0.01					
Low-decreasing vs mid-decreasing	-0.004 (0.028)	-0.145 (.884)	0.996 (0.027)	0.944	1.051
OCD_1					
Low-decreasing vs mid-decreasing	0.025 (0.027)	0.927 (.354)	1.026 (0.028)	0.972	1.082
OCD_0.3					
Low-decreasing vs mid-decreasing	0.025 (0.027)	0.929 (.353)	1.026 (0.028)	0.972	1.082
OCD_0.01					
Low-decreasing vs mid-decreasing	0.028 (0.027)	**1.028 (.304)**	1.029 (0.028)	0.975	1.085
MDD_1					
Low-decreasing vs mid-decreasing	0.063 (0.027)	**2.284 (.022)**	1.065 (0.029)	1.009	1.124
MDD_0.3					
Low-decreasing vs mid-decreasing	0.062 (0.027)	2.273 (.023)	1.064 (0.029)	1.009	1.123
MDD_0.01					
Low-decreasing vs mid-decreasing	-0.003 (0.027)	-0.097 (.922)	0.997 (0.027)	0.945	1.052
BIP_1					
Low-decreasing vs mid-decreasing	-0.033 (0.028)	-1.183 (.237)	0.968 (0.027)	0.916	1.022
BIP_0.3					
Low-decreasing vs mid-decreasing	-0.034 (0.028)	-1.204 (.228)	0.967 (0.027)	0.915	1.021
BIP_0.01					
Low-decreasing vs mid-decreasing	-0.039 (0.028)	**-1.409 (.159)**	0.961 (0.027)	0.910	1.015
ASD_1					
Low-decreasing vs mid-decreasing	0.099 (0.028)	3.552 (< .001)	1.104 (0.031)	1.045	1.166
ASD_0.3					
Low-decreasing vs mid-decreasing	0.099 (0.028)	**3.557 (< .001)**	1.104 (0.031)	1.045	1.166
ASD_0.01					

Low-decreasing vs mid-decreasing	0.089 (0.028)	3.222 (.001)	1.093 (0.030)	1.035	1.154
ANOREX_1					
Low-decreasing vs mid-decreasing	-0.005 (0.027)	-0.181 (.856)	0.995 (0.027)	0.943	1.050
ANOREX_0.3					
Low-decreasing vs mid-decreasing	-0.006 (0.027)	-0.204 (.839)	0.994 (0.027)	0.942	1.049
ANOREX_0.01					
Low-decreasing vs mid-decreasing	-0.010 (0.028)	**-0.368 (.713)**	0.990 (0.027)	0.938	1.045
ADHD_1					
Low-decreasing vs mid-decreasing	0.084 (0.028)	3.055 (.002)	1.088 (0.030)	1.031	1.148
ADHD_0.3					
Low-decreasing vs mid-decreasing	0.085 (0.028)	**3.080 (.002)**	1.088 (0.030)	1.031	1.149
ADHD_0.01					
Low-decreasing vs mid-decreasing	0.063 (0.027)	2.303 (.021)	1.065 (0.029)	1.009	1.124

Note. N =7,093. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-decreasing' class was used as the reference category. GPS = genome-wide polygenic score (standardised). *f* = fraction of causal markers (at 1, 0.3, 0.01). *b* = unstandardized regression coefficient. Low-decreasing = low-decreasing class. Mid-decreasing = mid-decreasing class. EA3 = years of education. IQ = intelligence. PSYCH = ever visited a psychiatrist for nerves, anxiety, tension, or depression. GP = ever visited a general practitioner for nerves, anxiety, tension, or depression. SCZ = schizophrenia. OCD = obsessive compulsive disorder. MDD = major depressive disorder. BIP = bipolar disorder. ASD = autism spectrum disorder. ANOREX = anorexia. ADHD = attention deficit hyperactivity disorder. Bold typeset indicates highest *z* statistic for each GPS.

Supplementary Table 5.3

Multinomial Logistic Regression Results for Negative Symptoms Latent Trajectory Class Regressed on GPSs for all GPS f

	Beta		Odds Ratio		
	b (SE)	*z* (*p* value)	OR (*SE*)	95% CI lower	95% CI upper
EA3_1					
Low-increasing vs mid-increasing	-0.258 (0.029)	**-9.025 (< .001)**	0.772 (0.022)	0.739	0.817
EA3_0.3					
Low-increasing vs mid-increasing	-0.205 (0.028)	-7.226 (< .001)	0.815 (0.023)	0.771	0.861
EA3_0.01					
Low-increasing vs mid-increasing	-0.101 (0.028)	-3.648 (< .001)	0.904 (0.025)	0.856	0.954
IQ_1					
Low-increasing vs mid-increasing	-0.096 (0.028)	**-3.437 (.001)**	0.908 (0.025)	0.860	0.960
IQ_0.3					
Low-increasing vs mid-increasing	-0.086 (0.028)	-3.083 (.002)	0.917 (0.026)	0.868	0.969
IQ_0.01					
Low-increasing vs mid-increasing	-0.017 (0.028)	-0.6177 (.537)	0.983 (0.028)	0.930	1.038
PSYCH_1					
Low-increasing vs mid-increasing	0.067 (0.028)	2.425 (.015)	1.070 (0.030)	1.013	1.130
PSYCH_0.3					
Low-increasing vs mid-increasing	0.068 (0.028)	**2.455 (.014)**	1.071 (0.030)	1.014	1.131
PSYCH_0.01					
Low-increasing vs mid-increasing	0.040 (0.028)	1.432 (.152)	1.040 (0.029)	0.985	1.098
GP_1					
Low-increasing vs mid-increasing	0.094 (0.028)	**3.330 (.001)**	1.099 (0.031)	1.039	1.161
GP_0.3					
Low-increasing vs mid-increasing	0.093 (0.028)	3.313 (.001)	1.098 (0.031)	1.039	1.160
GP_0.01					
Low-increasing vs mid-increasing	0.061 (0.028)	2.170 (.030)	1.062 (0.030)	1.006	1.122

SCZ_1					
Low-increasing vs mid-increasing	0.021 (0.028)	**0.758 (.448)**	1.021 (0.029)	0.967	1.079
SCZ_0.3					
Low-increasing vs mid-increasing	0.020 (0.028)	0.707 (.480)	1.020 (0.029)	0.965	1.078
SCZ_0.01					
Low-increasing vs mid-increasing	-0.011 (0.028)	-0.407 (.684)	0.989 (0.027)	0.937	1.044
OCD_1					
Low-increasing vs mid-increasing	0.032 (0.028)	1.144 (.253)	1.033 (0.029)	0.977	1.091
OCD_0.3					
Low-increasing vs mid-increasing	0.032 (0.028)	1.151 (.250)	1.033 (0.029)	0.978	1.091
OCD_0.01					
Low-increasing vs mid-increasing	0.034 (0.028)	**1.195 (.232)**	1.034 (0.029)	0.979	1.093
MDD_1					
Low-increasing vs mid-increasing	0.098 (0.028)	**3.461 (.001)**	1.103 (0.031)	1.044	1.167
MDD_0.3					
Low-increasing vs mid-increasing	0.097 (0.028)	3.418 (.001)	1.102 (0.031)	1.042	1.165
MDD_0.01					
Low-increasing vs mid-increasing	0.038 (0.028)	1.362 (.173)	1.039 (0.029)	0.983	1.098
BIP_1					
Low-increasing vs mid-increasing	-0.058 (0.028)	**-2.073 (.038)**	0.944 (0.026)	0.894	0.997
BIP_0.3					
Low-increasing vs mid-increasing	-0.057 (0.028)	-2.048 (.041)	0.944 (0.046)	0.894	0.998
BIP_0.01					
Low-increasing vs mid-increasing	-0.021 (0.028)	-0.767 (.443)	0.979 (0.027)	0.927	1.034
ASD_1					
Low-increasing vs mid-increasing	0.036 (0.028)	1.270 (.204)	1.036 (0.029)	0.981	1.095
ASD_0.3					
Low-increasing vs mid-increasing	0.036 (0.028)	1.290 (.197)	1.037 (0.029)	0.981	1.096

ASD_0.01					
Low-increasing vs mid-increasing	0.047 (0.028)	**1.679 (.093)**	1.048 (0.029)	0.992	1.107
ANOREX_1					
Low-increasing vs mid-increasing	-0.020 (0.027)	-0.712 (.476)	0.981 (0.027)	0.929	1.035
ANOREX_0.3					
Low-increasing vs mid-increasing	-0.020 (0.027)	**-0.714 (.475)**	0.981 (0.027)	0.929	1.035
ANOREX_0.01					
Low-increasing vs mid-increasing	-0.006 (0.028)	-0.220 (.826)	0.994 (0.027)	0.941	1.049
ADHD_1					
Low-increasing vs mid-increasing	0.067 (0.028)	2.356 (.018)	1.069 (0.030)	1.011	1.130
ADHD_0.3					
Low-increasing vs mid-increasing	0.067 (0.028)	**2.371 (.018)**	1.070 (0.030)	1.012	1.131
ADHD_0.01					
Low-increasing vs mid-increasing	0.050 (0.028)	1.803 (.071)	1.052 (0.029)	0.996	1.111

Note. N =7,439. Related and unrelated individuals included, using cluster-robust *SE*. The 'low-increasing' class was used as the reference category. GPS = genome-wide polygenic score (standardised). f = fraction of causal markers (at 1, 0.3, 0.01). b = unstandardized regression coefficient. Low-increasing = low-increasing class. Mid-increasing = mid-increasing class. EA3 = years of education. IQ = intelligence. PSYCH = ever visited a psychiatrist for nerves, anxiety, tension, or depression. GP = ever visited a general practitioner for nerves, anxiety, tension, or depression. SCZ = schizophrenia. OCD = obsessive compulsive disorder. MDD = major depressive disorder. BIP = bipolar disorder. ASD = autism spectrum disorder. ANOREX = anorexia. ADHD = attention deficit hyperactivity disorder. Bold typeset represents the highest z score for each GPS.

Chapter 6 – The latent structure of negative symptoms in adolescence and emerging adulthood

Published as Havers et al. (2022).

6.1 – Introduction

This Chapter investigates the latent structure of NS in the community in adolescence and emerging adulthood and investigates the extent to which the identified subdomains show associations with GPSs for schizophrenia and major depressive disorder. This Section will outline recent clinical findings, which will provide the rationale for investigating the latent structure of NS in the community in the context of a continuum model of NS.

Section 1.3.3 summarised recent findings suggesting that a 5-factor conceptualisation of NS in schizophrenia may better describe the construct than the 2-factor conceptualisation that is reflected in the DSM-5 (Strauss, Ahmed, et al., 2019). It further discussed the potential gains in terms of treatment development by establishing a more accurate psychometric representation of NS, and the need for further validating the latent subdomains through knowledge of external correlates (for example, genetic, cognitive, neural; Strauss et al., 2018).

As discussed in Section 1.2.4, previous findings suggest that there may be etiological continuity between NS observed in psychotic disorders and non-clinical NS – in support of a continuum model of NS (Kaiser et al., 2011). Continuity between non-clinical and clinical NS can be probed further by testing whether the latent factor measurement models that are hypothesised to underlie NS in schizophrenia also underlie NS in the community. Importantly, through the lens of a continuum model of NS – valuable insights may be

acquired by better understanding the non-clinical presentation of NS in samples that are not subject to the potentially confounding effects of treatment and ascertainment bias that are inherent in clinical samples.

Section 1.4.2 highlighted the relevance of studying psychotic phenomena in adolescence and emerging adulthood, and Section 1.3.3 outlined the findings from the one study (to my knowledge) that has used CFA to investigate the latent structure of NS in the community (Rodríguez-Testal et al., 2019). This study reported the best fit of a 5-factor hierarchical model in an adolescent sample. These results provided evidence to suggest that, like in clinical NS, the latent structure of NS in the community is more fine-grained than either a 1- or 2-factor conceptualisation. However, the 2-factor conceptualisation reflected in the DSM-5 was not tested, precluding a direct test of the extent to which one of the key conceptualisations of NS in schizophrenia is detectable, or not, in the community.

In terms of genetics, there is preliminary evidence in clinical samples to suggest associations between polygenic liability to schizophrenia and a total score of NS (Bigdeli et al., 2017; A. H. Fanous et al., 2012; Xavier et al., 2018), and mixed findings for an association between polygenic liability to schizophrenia and an expressive deficit (Legge et al., 2021). In the community, findings suggest an association between total NS and polygenic liability to schizophrenia, as well as major depressive disorder in the community (Jones et al., 2016; Pain et al., 2018). The extent to which these associations are driven by *specific* NS subdomains is unknown – though theory and empirical findings suggesting that avolition may be a core feature of NS in schizophrenia may indicate that avolition would show elevated associations (e.g., Foussias & Remington, 2010; Strauss et al., 2020, 2021).

In the current study, the latent structure of NS in the community at ages 16, 17, and 22 was investigated; explicitly testing the 2-factor conceptualisation of NS reflected in the DSM-5 and the 5-factor conceptualisation that has been found to underlie NS in clinical

samples (Strauss et al., 2018). Further models that were tested were a 5-factor hierarchical model (encompassing both the 2-factor and 5-factor conceptualisations), a unidimensional model, and a model suggested by EFA in the current sample. Given previous findings that have found associations between schizophrenia and major depressive disorder GPSs and a total score of NS in the community, associations were tested between these GPSs with the subdomains identified in the best fitting factor model. It was hypothesised that, i) a 5-factor model would provide the best fit to the data at ages 16, 17, and 22, ii) the latent structure would be invariant across age, and iii) avolition would be most consistently associated with the two GPSs.

Of note, the analyses in this Chapter partially overlap with those presented in Chapter 2. The NS results are presented in Chapter 2 in the context of longitudinal measurement invariance, which was an essential foundational analytic step before Chapters 3 and 4. Whereas, the analyses presented in the current Chapter are investigating the latent structure of NS in the community and the relevance of the models being tested. The reader is referred to the relevant sections in Chapter 2 where appropriate to avoid repetition, and the methods/results that are novel to the current Chapter are clearly stated as such.

6.2 – Methods

6.2.1 – Participants

The TEDS sample is described in Section 2.2.1.1. For the study conducted in Chapter 6, data from one (randomly selected) twin per pair was used for the main analyses. The cotwin data was used as a pseudo (non-independent) replication sample. Parents completed questions relating to their twins' NS at mean ages 16.32 years (*SD* 0.68; range 14.91-19.45), 17.06 years (*SD* 0.88; range 15.55-19.0), and 22.30 years (*SD* 0.93; range 20.56-25.59).

N for NS in the main subsample at ages 16, 17, and 22 were 4,974, 1,469, and 5,179, respectively.

6.2.2 – Measures

6.2.2.1 – Negative symptoms

NS were assessed using the NS subscale of the SPEQ (Ronald et al., 2014), described in Section 2.2.2. NS items are listed in Supplementary Information 2.3.

6.2.2.2 – GPS

Genotyping of participants is described in Supplementary Information 5.1. As outlined in Section 5.2.2.3, GPSs were calculated by other TEDS collaborators (Selzam et al., 2018, 2019) using LDpred software (Vilhjálmsson et al., 2015). The GPS calculation methods and the GWASs that the individual GPSs were based on are described in Supplementary Information 5.2. GPSs for schizophrenia (GPS_{SCZ}) and major depressive disorder (GPS_{MDD}) were used in the current Chapter. Standardized residuals of the GPS regressed on the first 10 PCs of ancestry, batch, and chip were used. GPS that are available to TEDS researchers correspond to three fractions (*f*) of causal markers (1, 0.3, and 0.01).

6.2.3 – Statistical analyses

6.2.3.1 – Overview of analyses

CFA was used to test five measurement models of NS at each age, in both the main subsample (as in Chapter 2) and in the cotwin subsample (novel to the current Chapter). The focus of the analyses was the main subsample: the CFA were fitted in the cotwin subsample to strengthen any inferences drawn regarding the latent structure findings.

One of the five measurement models that were tested was a model suggested by EFA. The EFA model suggested in the main subsample was respecified as a CFA in the cotwin

subsample (Chapter 2). It was important to pseudo replicate the EFA findings because EFA are overfit to sample variability (discussed in Section 2.2.3.2).

Measurement invariance of the best fitting CFA between the subsamples was tested (novel to the current Chapter). Longitudinal measurement invariance of the best fitting CFA was carried out in the main subsample and in the cotwin subsample (Chapter 2).

The methods of CFA and EFA are described in detail in Section 2.2.3.2.

6.2.3.2 – CFA models

The specifications of the CFA models are described in detail in Section 2.2.3.3.3. The theoretical rationale behind each of the models is provided briefly here, as follows:

Model 1) 1-factor, reflecting the initial conceptualisation of NS that arose from the analysis of NS in combination with other psychotic dimensions.

Model 2) 2-factor model, reflecting an expressive deficit and motivational-pleasure deficit. This model reflects the conceptualisation of NS in schizophrenia in the DSM-5.

Model 3) 4-factor model, reflecting the structure suggested in EFA (Supplementary Table 2.10). Testing this model as a CFA allowed for a test of the extent to which a model that captured the sample-specific variance/covariance provided an adequate, and valid (assessed through pseudo-replication) representation of the NS construct.

Model 4) 5-factor model, reflecting flat affect, alogia, avolition, anhedonia, and asociality. This model reflects the five NS dimensions that were highlighted by expert consensus (Kirkpatrick et al., 2006); also reflecting the model recently found to best represent the NS construct in clinical samples through use of CFA.

Model 5) 5-factor hierarchical model, reflecting the five factors specified in Model 4 as first order factors, and the two factors specified in Model 2 as higher order factors (expressive deficit, motivation-pleasure deficit). This model has been found to provide a good representation of the NS construct in clinical samples.

6.2.3.3 – Model fit

A series of goodness of fit indices were used to assess standalone fit of the CFA models: CFI, RMSEA, and SRMR. Whilst the use of cut off values is debated (Marsh et al., 2004), CFI values > 0.95/0.90, RMSEA values < 0.06, and SRMR values < 0.08 were assumed to indicate generally acceptable fit (Hu & Bentler, 1999; Marsh et al., 2004; van de Schoot et al., 2012).

BIC was primarily used to assess the relative fit between models, with lower values indicative of better fit. A difference between the values in excess of two was considered to reflect 'positive' evidence, and a difference between the values in excess of 10 was considered 'very strong' evidence (Neath & Cavanaugh, 2012). AIC was referred to where the difference in BIC values was less than two, with lower values indicative of better fit. A difference between AIC values in excess of two was considered 'strong' evidence (Burnham & Anderson, 2004).

6.2.3.4 – Measurement invariance

The concept of measurement invariance and the different 'levels' of measurement invariance were described in Section 2.2.3.6. In the current Chapter, an analysis of measurement invariance was conducted to assess, i) the extent to which the measurement model (of the best fitting CFA model) was invariant across the main and cotwin subsamples, and ii) the extent to which the best fitting CFA model was invariant across ages 16, 17, and 22 in each of the subsamples (as in Chapter 2).

For i), it was not necessary to specify family-level clustering (i.e., to adjust the standard errors to account for the relatedness between individuals), because there was only a single family member in each group (Y. Rosseel, personal communication, 2022).

To test for incremental levels of measurement invariance, acceptable standalone fit as well as negligible change in the fit indices between models was required: specifically, CFI < 0.010, RMSEA < 0.015, and SRMR < 0.030 (Chen, 2007).

6.2.3.5 – Data modelling

Any data that was missing was assumed to be missing at random, accommodated using FIML estimation. A robust version of the FIML estimator was used (MLR).

Data was modelled as continuous. As a sensitivity test in response to reviewer comments (Havers et al., 2022), the main CFA models were also rerun with the data modelled as categorical, using diagonally weighted least squares estimation with robust *SE* (WLSMV). This sensitivity test was requested because analysing item-level data measured using less than five scale points using continuous estimation methods may lead to biased estimates and *SE* (Rhemtulla et al., 2012). Of note, this is important in the current context because item-level data is modelled. This differs to the *total* score data that is used for the growth modelling in this Thesis, which allows for a more accurate application of continuous estimation methods (i.e., MLR) (Rhemtulla et al., 2012).

Cross-sectional models were run using lavaan (Rosseel, 2012) in R (version 2.5.2). Mplus (version 8.6) was used to run the longitudinal measurement invariance models and the categorical models.

6.2.3.6 – Association analyses

Associations between the GPSs (schizophrenia and major depressive disorder) and the subdomains suggested by the best fitting CFA model were tested using linear regression. In these analyses, data from both twins per pair was utilised, with family ID specified as the unit of clustering. Mean scores for the subdomains were used as the outcome variables, and the GPSs were used as the predictor variables. For factors with two items, the mean was calculated provided there was data from at least one item.

Single-predictor regressions were first run for each subdomain regressed on each GPS *f* (Supplementary Tables 5.1-5.3). The most predictive GPS *f* (the GPS *f* with the highest *z* value) for each subdomain at each age was selected, and the results were subjected to multiple testing correction.

The FDR method (Benjamini & Hochberg, 1995) was used to correct for multiple testing amongst the 30 tests (i.e., five subdomains, three ages, two GPSs): First, for the single-predictor regressions, the results of the multiple tests were ranked according to their significance levels. The FDR-adjusted *p* value was defined as the highest-ranking test for which the *p* value was less than or equal to the rank number divided by the total number of tests, multiplied by α (.05). The resulting value was the corrected $q < .05$. Equality of the standardised regression coefficients across subdomains at each age was tested (using the lavTestWald function; Klopp, 2019).

For each subdomain at each age, the GPS with the most predictive *f* (i.e., as reported for the single-predictor regressions) were entered into multiple-predictor regressions with schizophrenia GPS_{SCZ} and GPS_{MDD} as the predictors. The FDR method was used to correct for multiple testing amongst the 30 tests (five subdomains, three ages, two GPSs).

6.3 – Results

6.3.1 – Descriptive statistics

Descriptive statistics are shown in Supplementary Table 6.1 for the main and cotwin subsamples. Items showed good internal consistency at each age (coefficient $\alpha = 0.83\text{-}0.88$).

6.3.2 – CFA

6.3.2.1 – Main subsample analyses

The CFA results for the main subsample are shown in Supplementary Table 2.11. The results are discussed briefly in Section 2.3.3.2; described in more detail as follows. The 5-factor model showed the best fit to the data at each age. Standalone fit of the 5-factor model was acceptable at each age (CFI >= 0.99, RMSEA <= 0.06, SRMR <= 0.02). BIC values were lower to a magnitude greater than 100 compared to the next best fitting models (the 4-factor EFA and 5-factor hierarchical models) at ages 16 and 22. At 17 years, the 4- and 5-factor models were indistinguishable in terms of their BIC values (difference ~ 1): the AIC value of the 5-factor model was lower to a magnitude greater than two compared to the 4-factor model, indicating better fit of the 5-factor model.

At each age, the 1-factor and 2-factor models provided a relatively poor fit to the data in terms of RMSEA (0.095-0.179), though model fit was acceptable in terms of SRMR (<= 0.06) and CFI (0.912-0.954) for the 2-factor models. The 4-factor EFA models and the 5-factor hierarchical models provided an acceptable fit to the data at each age across fit indices.

Pseudo replication of the EFA model as a CFA in the cotwin subsample is discussed in Section 2.3.3.3 and the results are shown in Supplementary Table 2.12. Briefly, the models showed good standalone fit in the cotwin subsample at each age.

6.3.2.2 – Sensitivity analyses

A broadly similar pattern of results was observed using WLSMV estimation (Supplementary Table 6.2): the 5-factor model provided the best fit to the data at each age. BIC/AIC are not available for WLSMV estimation, but the 5-factor model showed the best standalone fit across indices. Notably, CFI values were >= 0.99 for the 5-factor as well as the next best fitting models (the 4-factor EFA and 5-factor hierarchical models). Like for the continuous models (Section 6.3.2.1), the 1-factor and 2-factor models provided a relatively

poor fit to the data in terms of RMSEA (0.078-0.145); however, model fit was acceptable in terms of SRMR (<= 0.08) and CFI (0.919-0.986) for the 2-factor models as well as the 1-factor models.

6.3.2.3 – Cotwin subsample analyses

Broadly the same pattern of results was found in the cotwin subsample (Supplementary Table 6.3): the 5-factor model fit the data best at all ages. Standalone fit of the 5-factor model was acceptable at each age in terms of CFI (>= 0.98) and SRMR (<= 0.02); RMSEA was acceptable at ages 16 and 17 (<= 0.04), though was less acceptable at age 22 (0.070). BIC values were lower to a magnitude greater than 10 compared to the next best fitting models (the 4-factor EFA and 5-factor hierarchical models) at each age.

At each age, the 1-factor and 2-factor models provided a relatively poor fit to the data in terms of RMSEA (0.088-0.170), though model fit was acceptable in terms of SRMR (<= 0.05) and CFI (0.921-0.958) for the 2-factor models. The 4-factor EFA models and the 5-factor hierarchical models provided acceptable fit to the data at each age across fit indices, though less so for RMSEA at age 22 (0.075).

6.3.3 – Parameter estimates

Supplementary Tables 6.4-6.6 show the parameter estimates from the 5-factor model at each age in the main subsample. Latent factors were defined as reflecting flat affect, alogia, avolition, anhedonia, and asociality. Inter-factor correlations were moderate to high (.33-.82). The highest inter-factor correlations were between flat affect and alogia at each age. Standardised factor loadings were .61-.89 (i.e., for factors with more than one indicator), reflecting that the factors explained between 37.21% and 79.21% of the variance in the items. Across items, the factors explained 62.50% of the total variance at age 16, 67.16% at age 17,

and 56% at age 22 (Supplementary Table 6.7). Figure 6.1 shows the 5-factor model at each age.

6.3.4 – Measurement invariance

6.3.4.1 – Measurement invariance between the subsamples

Full strict measurement invariance of the 5-factor model was found at each age between the main and cotwin subsamples (Tables 6.1-6.3).

6.3.4.2 – Longitudinal measurement invariance

The results for the main subsample are shown in Table 2.3 and are discussed in Section 2.3.3.2: The same pattern of results was observed for the cotwin subsample (Supplementary Table 6.12), discussed as follows: the configural, metric and scalar invariance models showed acceptable fit and negligible change in fit indices. Further constraining the residual variances in the strict model resulted in a model with non-negligible change in CFI value (> 0.010). Consultation of the modification indices led to a revision of the model, and a partial-strict model was specified with the item 2 parameters *("My child seems emotionally 'flat'"*) freely estimated. This modification resulted in an acceptable CFI change (from the scalar to partial-strict model), and acceptable overall fit of the partial-strict model (CFI = 0.976, RMSEA = 0.022, 90% CI 0.020, 0.023, SRMR = 0.025). Partial strict invariance was concluded.

6.3.5 – Associations between GPSs and subdomains

Table 6.4 shows the results for the most predictive GPS *f* for each subdomain at each age, for GPS_{SCZ} and GPS_{MDD} separately. Results for all GPS *f* are shown in Supplementary Tables 6.13 and 6.14 for GPS_{SCZ} and $GPS_{MDD,}$ respectively. The subdomain with the greatest

number of significant associations was avolition, which showed four associations at $q < 0.05$ (with GPS_{SCZ} at age 17, and GPS_{MDD} at each age).

GPS_{SCZ} showed significant associations with flat affect at age 16 ($ß = 0.037$), and with avolition at age 17 ($ß = 0.058$). When standardised regression coefficients were compared (Supplementary Table 6.15), the association for flat affect at age 16 was significantly stronger than the association with asociality at ages 16 and 17 ($p = .035$-$.042$), and the association for avolition at age 17 was stronger than the association with asociality at 17 ($p = .018$). For the multiple-predictor models, the GPS_{SCZ} associations that were significant in the single-predictor models did not remain significant (Supplementary Table 6.16).

GPS_{MDD} showed significant associations with flat affect at ages 16 and 22 ($ß = 0.041$-0.050), with avolition ($ß = 0.045$-0.084) and anhedonia ($ß = 0.043$-0.065) at each age, and with asociality at ages 16 and 22 ($ß = 0.049$-0.056). Alogia was not associated with GPS_{MDD} at any age. When standardised regression coefficients were compared (Supplementary Table 6.15), all associations were significantly stronger for avolition than for alogia at each age ($p = .008$-$.031$) and were significantly stronger for anhedonia and asociality than alogia at ages 16 and 22 ($p = .021$-$.029$). The association for avolition was also significantly stronger than for flat affect at age 17 ($p = .013$). All GPS_{MDD} associations that were significant in the single-predictor models remained significant in the multiple-predictor models, except for anhedonia at age 17 (Supplementary Table 6.16).

Table 6.1

Measurement Invariance Analysis of 5-Factor Structure of Negative Symptoms at Age 16 Between Main and Cotwin Subsamples

	Parameters	Fit indices			Comparison of fit indices between nested models		
		CFI	RMSEA [90% CI]	SRMR	Δ CFI	Δ RMSEA	Δ SRMR
Configural invariance model (no constraints)	64	0.996	0.031 [0.024, 0.040]	0.011	-	-	-
Metric invariance model (factor loadings constrained)	58	0.996	0.026 [0.018, 0.035]	0.014	0.000	0.005	-0.003
Scalar invariance model (factor loadings and intercepts constrained)	55	0.996	0.025 [0.017, 0.033]	0.014	0.000	0.001	0.000
Strict invariance model (factor loadings, intercepts and residual variances constrained)	49	0.997	0.022 [0.013, 0.029]	0.015	-0.001	0.003	-0.001

Note. N = 9,951 (main subsample N = 4,974, cotwin subsample N = 4,977). CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Δ denotes change value.

Table 6.2

Measurement Invariance Analysis of 5-Factor Structure of Negative Symptoms at Age 17 Between Main and Cotwin Subsamples

	Parameters	Fit indices			Comparison of fit indices between nested models		
		CFI	RMSEA [90% CI]	SRMR	Δ CFI	Δ RMSEA	Δ SRMR
Configural invariance model (no constraints)	64	1.000	0.010 [0.000, 0.031]	0.010	-	-	-
Metric invariance model (factor loadings constrained)	58	1.000	0.000 [0.000, 0.025]	0.030	0.000	0.010	0.020
Scalar invariance model (factor loadings and intercepts constrained)	55	1.000	0.000 [0.000, 0.023]	0.030	0.000	0.000	0.000
Strict invariance model (factor loadings, intercepts and residual variances constrained)	49	1.000	0.000 [0.000, 0.020]	0.033	0.000	0.000	-0.003

Note. N = 2,942 (main subsample N = 1,469, cotwin subsample N = 1,473). CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Δ denotes change value.

Table 6.3

Measurement Invariance Analysis of 5-Factor Structure of Negative Symptoms at Age 22 Between Main and Cotwin Subsamples

	Parameters	Fit indices			Comparison of fit indices between nested models		
		CFI	RMSEA [90% CI]	SRMR	Δ CFI	Δ RMSEA	Δ SRMR
Configural invariance model (no constraints)	64	0.982	0.064 [0.057, 0.071]	0.021	-	-	-
Metric invariance model (factor loadings constrained)	58	0.982	0.056 [0.050, 0.063]	0.021	0.000	0.008	0.000
Scalar invariance model (factor loadings and intercepts constrained)	55	0.982	0.053 [0.048, 0.060]	0.021	0.000	0.003	0.000
Strict invariance model (factor loadings, intercepts and residual variances constrained)	49	0.983	0.048 [0.043, 0.054]	0.022	-0.001	0.005	-0.001

Note. N = 10,149 (main subsample N = 5,179, cotwin subsample N = 5,181). CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Δ denotes change value.

Table 6.4

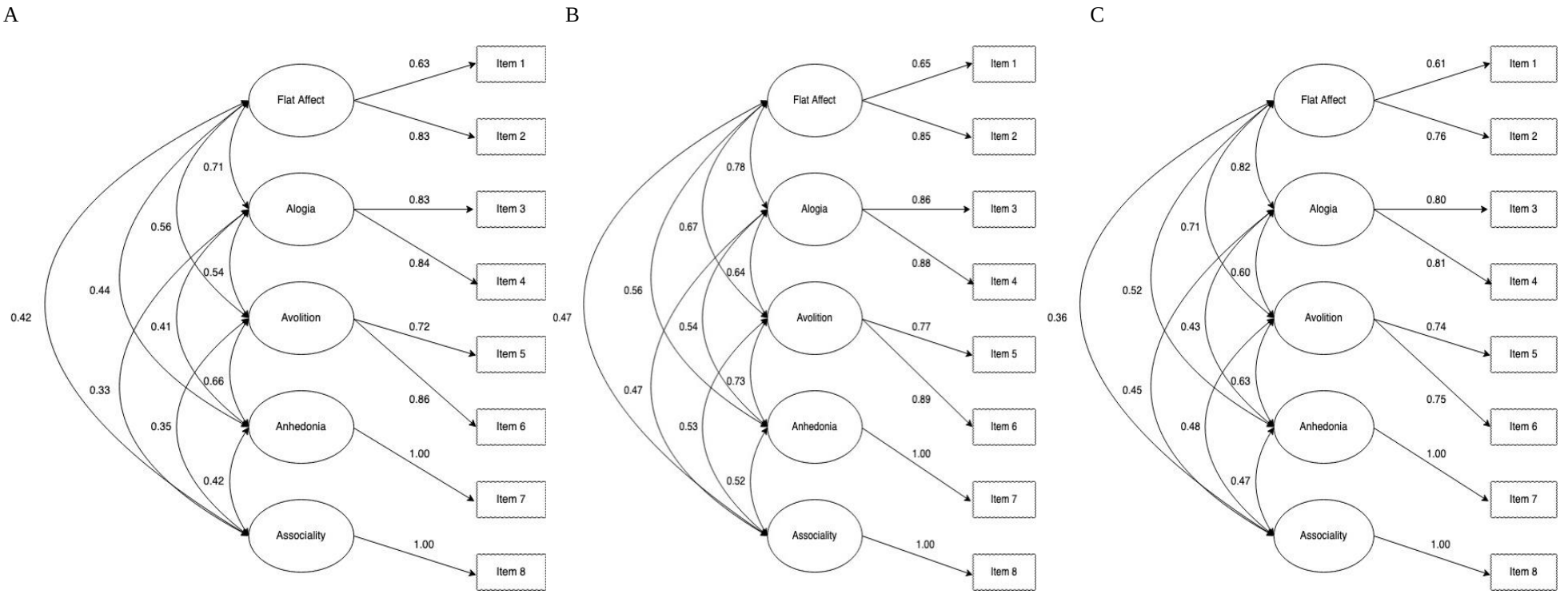
Single-Predictor Linear Regressions of Subdomain Mean Scores on Schizophrenia GPS and Major Depressive Disorder GPS for Most Predictive GPS f

	MDD GPS					Schizophrenia GPS			
	N	*f*	*b* (SE)	*z (P)*	ß	*f*	*b* (SE)	*z (P)*	ß
Age 16									
Flat affect	6,005	**0.3**	**0.019 (0.005)**	**3.504 (< .001)**	**0.050**	**1**	**0.014 (0.005)**	**2.659 (.008)**	**0.037**
Alogia	6,006	1	0.010 (0.008)	1.289 (.197)	0.017	0.3	0.007 (0.008)	0.893 (.372)	0.012
Avolition	5,995	**0.3**	**0.030 (0.007)**	**3.986 (< .001)**	**0.054**	0.01	-0.004 (0.008)	-0.496 (.620)	-0.007
Anhedonia	5,971	**1**	**0.029 (0.009)**	**3.359 (.001)**	**0.046**	0.3	0.008 (0.009)	0.922 (.356)	0.012
Asociality	5,971	**1**	**0.028 (0.006)**	**4.321 (< .001)**	**0.056**	0.01	-0.007 (0.008)	-0.858 (.391)	-0.013
Age 17									
Flat affect	1,818	0.3	0.016 (0.012)	1.410 (.159)	0.035	1	0.027 (0.012)	2.162 (.031)	0.057
Alogia	1,815	1	0.019 (0.015)	1.253 (.210)	0.030	1	0.006 (0.016)	0.387 (.699)	0.010
Avolition	1,816	**1**	**0.054 (0.016)**	**3.367 (.001)**	**0.084**	**1**	**0.038 (0.016)**	**2.404 (.016)**	**0.058**
Anhedonia	1,807	**1**	**0.046 (0.019)**	**2.433 (.015)**	**0.065**	0.3	0.017 (0.017)	0.967 (.334)	0.023
Asociality	1,794	1	0.025 (0.016)	1.539 (.124)	0.040	0.01	-0.019 (0.016)	-1.153 (.249)	-0.030
Age 22									
Flat affect	6,274	**0.3**	**0.018 (0.006)**	**3.195 (.001)**	**0.041**	0.01	-0.004 (0.006)	-0.737 (.461)	-0.009
Alogia	6,278	1	0.009 (0.008)	1.072 (.284)	0.014	0.01	0.002 (0.008)	0.225 (.822)	0.003
Avolition	6,276	**1**	**0.028 (0.008)**	**3.487 (< .001)**	**0.045**	0.01	-0.006 (0.008)	-0.738 (.460)	-0.010
Anhedonia	6,251	**1**	**0.030 (0.009)**	**3.233 (.001)**	**0.043**	0.3	-0.007 (0.009)	-0.729 (.466)	-0.010
Asociality	6,259	**0.3**	**0.029 (0.008)**	**3.702 (< .001)**	**0.049**	1	0.007 (0.008)	0.893 (.372)	0.011

Note. Subdomain mean scores at each age regressed on MDD and schizophrenia GPS separately. Related and unrelated individuals included, using cluster-robust *SE*. Results shown for the most predictive GPS *f*. GPS = genome-wide polygenic score. MDD = major depressive disorder. *f* = fraction of causal markers. *b* = unstandardized regression coefficient. ß = standardized regression coefficient. Bold typeset represents significance under corrected *q* <.05 threshold.

Figure 6.1

Five-Factor Model of Negative Symptoms at Ages 16, 17, and 22 in Main Subsample



Note. A. Model at age 16. B. Model at age 17. C. Model at age 22. Standardized estimates from best fitting confirmatory factor analysis models. Rectangles represent measured variables. Circles represent latent variables. Double headed arrows represent correlations. Single headed arrows represent factor loadings.

6.4 – Discussion

This Chapter investigated the latent structure of NS in the community in adolescence and emerging adulthood and tested the extent to which the identified subdomains showed associations with GPSs for schizophrenia and major depressive disorder. A 5-factor model was found to best describe NS at ages 16, 17, and 22, and the latent structure was invariant across these ages. Specific GPS-subdomain associations were found – most notably, these were most numerous for avolition and were null for alogia.

The results reported in this Chapter suggested that the underlying structure of NS that appears to be consistent across different stages of psychotic illness (Ahmed et al., 2019; Chang et al., 2020; Strauss et al., 2018) also extends to the current non-clinical population. The current findings of less acceptable fit for the 2-factor model and good fit of the 5-factor hierarchical model are further in-line with the findings from these studies (Ahmed et al., 2019; Chang et al., 2020; Strauss et al., 2018).

Pseudo replication of the 5-factor structure and the measurement invariance that was found across the subsamples suggests that the 5-factor structure that was found is not solely attributable to sample variability. Further, as discussed in Section 2.4, longitudinal measurement invariance of the 5-factor structure suggests that the factor structure is not specific to a developmental age, nor solely the result of occasion-specific properties of the measurement instrument that was used (Grimm et al., 2017). Collectively, these results further corroborate findings from the clinical literature suggesting that a 5-factor conceptualisation of NS appears to be an empirically robust representation of the construct.

Previous work that has found measurement invariance of the 5-factor structure between high-risk and first-episode psychosis samples (Chang et al., 2020) has demonstrated that a 5-factor conceptualisation is consistent across the early stages of psychotic illness. Future work will undoubtedly seek to merge data from samples at early and chronic stages of

illness (Strauss et al., 2018), and the current results could lend initial support to further include community samples in such analyses. This can be considered an important endeavour because identifying aspects of continuity or discontinuity between nonclinical, prodromal, and clinical NS may contribute to delineating the pathways involved in the development of NS. Large community samples are essential to understand the early manifestation of NS prior to illness onset and without ascertainment biases and treatment confounds inherent in clinical samples.

The results are the first to show associations between polygenic liability to schizophrenia in adulthood, and avolition and flat affect in adolescence, and between polygenic liability to major depressive disorder in adulthood, and avolition, flat affect, anhedonia and asociality in adolescence and emerging adulthood. One recent clinical study reported suggestive evidence for an association between GPS_{SCZ} and diminished expressivity (broadly), though no association was observed for motivation and pleasure (Legge et al., 2021): Whilst these and the current results are not entirely aligned, the current findings showing subdomain-*specific* associations may, broadly, highlight the value in disaggregating the expressivity and motivation-pleasure domains to detect polygenic associations.

The finding that avolition showed the greatest number of associations with the GPSs compared to the other subdomains may suggest that genetic predisposition for schizophrenia and major depressive disorder could manifest particularly as avolition during adolescence/emerging adulthood. This may contribute to discussion based on clinical findings and theory suggesting that avolition is a core feature of NS (e.g., Foussias & Remington, 2010; Strauss et al., 2020, 2021): Notwithstanding, associations were also observed with some consistency between anhedonia and GPS_{MDD} in this Chapter. Replication in independent samples is therefore needed to probe the interpretation of the current avolition results further.

Of note, some of the subdomains of NS (avolition, anhedonia, asociality) are also core symptoms of major depressive disorder, and there is known genetic overlap between major depressive disorder and schizophrenia (S. H. Lee et al., 2013). The findings that, i) there were more numerous associations between the NS subdomains and GPS_{MDD} than GPS_{SCZ}, and, ii) the GPS_{MDD} associations remained significant in the multiple-predictor models (but the GPS_{SCZ} associations did not), may add to empirical findings and theoretical models suggesting that a transdiagnostic approach to analysing narrowly-defined (NS and depression) symptoms may be necessary in order to better understand both the broad and specific factors contributing to their manifestation and maintenance (Cowan & Mittal, 2021; Cuthbert, 2014; Krynicki et al., 2018; Strauss et al., 2021).

The observed absence of association between GPS_{MDD} and alogia may provide support to suggestions that alogia may be a distinguishing feature of NS that is separable from depressive symptoms (Krynicki et al., 2018; Strauss & Cohen, 2017). However, the lack of association between GPS_{SCZ} and alogia warrants further investigation.

Of note, the 5-factor model in the current Chapter included anhedonia and asociality as single-item indicators. The use of single-item indicators in structural equation models continues to be debated (e.g., Hayduk & Littvay, 2012; Petrescu, 2013), however, there is considerable support for their use (e.g., Benet-Martínez et al., 2002; Gosling et al., 2003; Postmes et al., 2013), and evidence for a 5-factor structure has been found in models of NS both with and without single-item indicators in clinical samples (Strauss, Ahmed, et al., 2019).

The 5-factor structure of NS that has been found in clinical samples also appears to be present in young people in the community. These findings suggest that research into NS at the subdomain-level in the community may have the potential to inform endeavours to delineate NS beyond community samples, both within and across diagnostic boundaries.

6.5 – Appendix

Supplementary Table 6.1

Descriptive Statistics for Negative Symptoms Items, Subdomains, and Totals at Ages 16, 17, and 22 in Main and Cotwin Subsamples

	Main sample						Co-twin sample					
	16 years		17 years		22 years		16 years		17 years		22 years	
	Mean (*SD*)	Skewness	Mean (*SD*)	Skewness	Mean (*SD*)	Skewness	Mean (*SD*)	Skewness	Mean (*SD*)	Skewness	Mean (*SD*)	Skewness
Item 1	0.14 (0.44)	3.85	0.26 (0.59)	2.66	0.15 (0.46)	3.81	0.14 (0.44)	3.86	0.24 (0.57)	2.75	0.14 (0.56)	3.85
Item 2	0.16 (0.46)	3.33	0.25 (0.57)	2.63	0.26 (0.60)	2.72	0.16 (0.47)	3.47	0.23 (0.54)	2.71	0.25 (0.58)	2.73
Item 3	0.34 (0.65)	2.18	0.44 (0.72)	1.79	0.36 (0.70)	2.19	0.34 (0.67)	2.22	0.41 (0.70)	1.88	0.36 (0.70)	2.16
Item 4	0.35 (0.65)	2.07	0.42 (0.71)	1.81	0.39 (0.70)	1.96	0.35 (0.67)	2.15	0.37 (0.68)	1.95	0.39 (0.70)	1.96
Item 5	0.34 (0.65)	2.18	0.44 (0.74)	1.84	0.41 (0.71)	1.99	0.33 (0.65)	2.26	0.42 (0.70)	1.79	0.40 (0.71)	1.98
Item 6	0.35 (0.64)	2.04	0.43 (0.71)	1.76	0.42 (0.69)	1.82	0.33 (0.62)	2.11	0.43 (0.69)	1.70	0.41 (0.68)	1.86
Item 7	0.34 (0.65)	2.06	0.47 (0.76)	1.67	0.43 (0.73)	1.82	0.34 (0.65)	2.12	0.44 (0.72)	1.73	0.42 (0.70)	1.83
Item 8	0.19 (0.53)	3.31	0.29 (0.68)	2.61	0.25 (0.63)	2.86	0.18 (0.52)	3.37	0.27 (0.63)	2.63	0.24 (0.62)	2.91
Flat affect	0.15 (0.39)	3.65	0.26 (0.52)	2.67	0.20 (0.46)	3.10	0.15 (0.39)	3.57	0.24 (0.49)	2.66	0.20 (0.45)	3.04
Alogia	0.34 (0.60)	2.15	0.43 (0.67)	1.82	0.37 (0.63)	2.07	0.35 (0.62)	2.23	0.39 (0.64)	1.92	0.38 (0.63)	2.05
Avolition	0.34 (0.58)	2.20	0.44 (0.67)	1.87	0.41 (0.62)	1.90	0.33 (0.57)	2.21	0.43 (0.63)	1.77	0.41 (0.62)	1.87
Anhedonia	0.34 (0.65)	2.06	0.47 (0.76)	1.67	0.43 (0.73)	1.82	0.34 (0.65)	2.12	0.44 (0.72)	1.73	0.42 (0.70)	1.83
Asociality	0.19 (0.53)	3.31	0.29 (0.68)	2.61	0.25 (0.63)	2.86	0.18 (0.52)	3.37	0.27 (0.63)	2.63	0.24 (0.62)	2.91
Total NS	2.21 (3.21)	2.40	3.01 (4.07)	2.11	2.66 (3.64)	2.27	2.17 (3.18)	2.41	2.82 (3.81)	2.05	2.61 (3.57)	2.23
Coefficient α	0.83		0.88		0.83		0.83		0.87		0.83	

Note. *N* at age 16 in main sample = 4,942-4,971; *N* at age 17 in main sample = 1,451-1,469; *N* at age 22 in main sample = 5,147-5,177. *N* at age 16 in co-twin sample = 4,945-4,973; *N* at age 17 in co-twin sample = 1,450-1,473; *N* at age 22 in co-twin sample = 5,154-5,178. NS = negative symptoms. Flat affect is a mean composite of items 1 and 2, alogia is a mean composite of items 3 and 4, avolition is a mean composite of items 5 and 6, anhedonia is item 7 and asociality is item 8. Coefficient alpha (α) for items 1-8.

Supplementary Table 6.2

Confirmatory Factor Analysis of Negative Symptoms in Main Subsample using Diagonally Weighted Least Squares Estimation: Model Fit Results

	Parameters	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
16 years					
1-factor model	32	1,962.143 (20), $p < .001$	0.919	0.140 [0.135, 0.145]	0.080
2-factor model	33	587.791 (19), $p < .001$	0.976	0.078 [0.072, 0.083]	0.048
4-factor (EFA) model	38	177.280 (14), $p < .001$	0.993	0.048 [0.042, 0.055]	0.026
5-factor model	**40**	**39.476 (12), $p < .001$**	**0.999**	**0.021 [0.014, 0.029]**	**0.011**
5H-factor model	35	231.643 (17), $p < .001$	0.991	0.050 [0.045, 0.056]	0.033
17 years					
1-factor model	32	640.255 (20), $p < .001$	0.949	0.145 [0.136, 0.155]	0.067
2-factor model	33	194.541 (19), $p < .001$	0.986	0.079 [0.069, 0.090]	0.035
4-factor (EFA) model	38	40.857 (14), $p < .001$	0.998	0.036 [0.024, 0.049]	0.016
5-factor model	**40**	**17.656 (12), $p = .127$**	**1.000**	**0.018 [0.00, 0.035]**	**0.009**
5H-factor model	35	67.184 (17), $p < .001$	0.996	0.045 [0.034, 0.056]	0.022
22 years					
1-factor model	32	1,515.325 (20), $p < .001$	0.932	0.120 [0.115, 0.125]	0.060
2-factor model	33	643.384 (19), $p < .001$	0.972	0.080 [0.074, 0.085]	0.042
4-factor (EFA) model	38	251.789 (14), $p < .001$	0.989	0.057 [0.051, 0.064]	0.025
5-factor model	**40**	**145.939 (12), $p < .001$**	**0.994**	**0.046 [0.040, 0.053]**	**0.018**
5H-factor model	35	220.843 (17), $p < .001$	0.991	0.048 [0.043, 0.054]	0.027

Note. *N* at age 16 = 4,974; *N* at age 17 = 1,469; *N* at age 22 = 5,179. Diagonally weighted least squares estimation with robust standard errors (WLSMV), using pair-wise present data. EFA = exploratory factor analysis. 5H-factor model = 5-factor hierarchical model. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Bold typeset represents best fitting model at each age.

Supplementary Table 6.3

Confirmatory Factor Analysis of Negative Symptoms in Cotwin Subsample: Model Fit Results

	Parameters	Log-likelihood	AIC	BIC	χ^2 value (*df*)	CFI	RMSEA [90% CI]	SRMR
16 years								
1-factor model	24	-29,108.553	58,265.106	58,421.408	1,219.008 (20), $p < .001$	0.785	0.170 [0.162, 0.178]	0.073
2-factor model	25	-28,159.432	56,368.864	56,531.679	404.879 (19), $p < .001$	0.927	0.102 [0.093, 0.111]	0.050
4-factor (EFA) model	30	-27,736.599	55,533.198	55,728.575	76.584 (14), $p < .001$	0.987	0.047 [0.037, 0.057]	0.024
5-factor model	**32**	**-27,694.953**	**55,453.905**	**55,662.308**	**42.989 (12), $p < .001$**	**0.994**	**0.035 [0.024, 0.047]**	**0.013**
5H-factor model	28	-27,766.264	55,588.528	55,770.880	99.747 (16), $p < .001$	0.983	0.051 [0.042, 0.061]	0.024
17 years								
1-factor model	24	-9,373.984	18,795.969	18,923.050	393.060 (20), $p < .001$	0.851	0.161 [0.147, 0.175]	0.061
2-factor model	25	-9,099.306	18,248.612	18,380.989	126.873 (19), $p < .001$	0.958	0.088 [0.074, 0.103]	0.036
4-factor (EFA) model	30	-9,000.982	18,061.964	18,220.816	30.802 (14), $p = .006$	0.994	0.039 [0.020, 0.058]	0.019
5-factor model	**32**	**-8,988.129**	**18,040.258**	**18,209.699**	**17.693 (12), $p = .125$**	**0.998**	**0.024 [0.000, 0.047]**	**0.011**
5H-factor model	28	-9,008.632	18,073.264	18,221.526	37.317 (16), $p = .002$	0.992	0.042 [0.025, 0.060]	0.020
22 years								
1-factor model	24	-34,116.997	68,281.955	68,439.261	927.699 (20), $p < .001$	0.856	0.138 [0.131, 0.146]	0.057
2-factor model	25	-33,667.269	67,384.539	67,548.358	519.302 (19), $p < .001$	0.921	0.105 [0.097, 0.113]	0.047
4-factor (EFA) model	29	-33,398.283	66,854.567	67,044.596	285.644 (15), $p < .001$	0.960	0.084 [0.076, 0.093]	0.030
5-factor model	**32**	**-33,271.475**	**66,606.950**	**66,816.638**	**161.114 (12), $p < .001$**	**0.978**	**0.070 [0.061, 0.080]**	**0.022**
5H-factor model	28	-33,358.651	66,773.302	66,956.781	242.011 (16), $p < .001$	0.966	0.075 [0.067, 0.084]	0.029

Note. *N* at age 16 = 4,977; *N* at age 17 = 1,473; *N* at age 22 = 5,181. EFA = exploratory factor analysis. 5H-factor model = 5-factor hierarchical model. AIC = Akaike's Information Criterion. BIC = Bayesian Information Criterion. χ^2 = chi-square value. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. Bold typeset represents best fitting model at each age.

Supplementary Table 6.4

Parameter Estimates from 5-Factor Model of Negative Symptoms at Age 16 in Main Subsample

	Estimate	*SE*	*z*	*p*	Fully standardized path coefficient
Factor loadings					
Flat affect					
Item 1	0.28	0.02	17.19	<.001	0.63
Item 2	0.39	0.02	23.77	<.001	0.83
Alogia					
Item 3	0.55	0.02	35.18	<.001	0.83
Item 4	0.55	0.02	36.16	<.001	0.84
Avolition					
Item 5	0.47	0.02	29.87	<.001	0.72
Item 6	0.55	0.02	36.06	<.001	0.86
Anhedonia					
Item 7	1.00 [a]	-	-	-	1.00
Asociality					
Item 8	1.00 [a]	-	-	-	1.00
Covariances					
Flat affect					
Alogia	0.71	0.02	29.87	<.001	0.71
Avolition	0.56	0.03	21.57	<.001	0.56
Anhedonia	0.28	0.02	15.71	<.001	0.44
Asociality	0.23	0.02	12.34	<.001	0.42
Alogia					
Avolition	0.54	0.02	25.61	<.001	0.54
Anhedonia	0.27	0.02	17.33	<.001	0.41
Asociality	0.18	0.02	12.12	<.001	0.33
Avolition					
Anhedonia	0.43	0.02	27.20	<.001	0.66
Asociality	0.19	0.01	12.93	<.001	0.35
Anhedonia					
Asociality	0.15	0.01	13.69	<.001	0.42
Intercepts					
Item 1	0.14	0.01	22.18	<.001	0.31
Item 2	0.16	0.01	24.82	<.001	0.35
Item 3	0.34	0.01	36.58	<.001	0.52
Item 4	0.35	0.01	37.85	<.001	0.54
Item 5	0.34	0.01	36.43	<.001	0.52
Item 6	0.35	0.01	39.12	<.001	0.56
Item 7	0.35	0.01	37.45	<.001	0.53
Item 8	0.19	0.01	24.86	<.001	0.35
Variances					
Item 1	0.12	0.01	16.72	<.001	0.60
Item 2	0.07	0.01	10.51	<.001	0.31
Item 3	0.13	0.01	13.34	<.001	0.30
Item 4	0.13	0.01	13.74	<.001	0.29
Item 5	0.20	0.01	21.82	<.001	0.48
Item 6	0.10	0.01	11.44	<.001	0.26
Item 7	0.00 [a]	-	-	-	0.00
Item 8	0.00 [a]	-	-	-	0.00
Flat affect	1.00 [b]	-	-	-	1.00
Alogia	1.00 [b]	-	-	-	1.00
Avolition	1.00 [b]	-	-	-	1.00
Anhedonia	0.42	0.02	28.17	<.001	1.00
Asociality	0.29	0.02	19.03	<.001	1.00

Note. N = 4,974. Estimate = unstandardized factor loading. [a] = Factor loadings fixed to 1 and residual variances fixed to 0 for factors with single indicators. Anhedonia and asociality have freely estimated variances due to the fixed factor loadings. [b] = Factor variances fixed to 1 for factor scaling.

Supplementary Table 6.5

Parameter Estimates from 5-Factor Model of Negative Symptoms at Age 17 in Main Subsample

	Estimate	*SE*	*z*	*p*	Fully standardized path coefficient
Factor loadings					
Flat affect					
Item 1	0.39	0.03	14.04	<.001	0.65
Item 2	0.49	0.03	17.07	<.001	0.85
Alogia					
Item 3	0.61	0.03	24.95	<.001	0.86
Item 4	0.63	0.03	25.09	<.001	0.88
Avolition					
Item 5	0.57	0.03	19.94	<.001	0.77
Item 6	0.63	0.03	25.49	<.001	0.89
Anhedonia					
Item 7	1.00 [a]	-	-	-	1.00
Asociality					
Item 8	1.00 [a]	-	-	-	1.00
Covariances					
Flat affect					
Alogia	0.78	0.03	23.29	<.001	0.78
Avolition	0.67	0.04	19.16	<.001	0.67
Anhedonia	0.42	0.03	13.82	<.001	0.56
Asociality	0.32	0.03	9.83	<.001	0.47
Alogia					
Avolition	0.64	0.03	21.25	<.001	0.64
Anhedonia	0.41	0.03	14.61	<.001	0.54
Asociality	0.32	0.03	10.21	<.001	0.47
Avolition					
Anhedonia	0.55	0.03	20.43	<.001	0.73
Asociality	0.36	0.03	11.47	<.001	0.53
Anhedonia					
Asociality	0.27	0.03	10.58	<.001	0.52
Intercepts					
Item 1	0.26	0.02	16.75	<.001	0.44
Item 2	0.25	0.02	16.82	<.001	0.44
Item 3	0.44	0.02	23.32	<.001	0.61
Item 4	0.42	0.02	22.42	<.001	0.59
Item 5	0.44	0.02	22.64	<.001	0.59
Item 6	0.43	0.02	23.35	<.001	0.61
Item 7	0.47	0.02	23.80	<.001	0.62
Item 8	0.29	0.02	16.49	<.001	0.43
Variances					
Item 1	0.21	0.02	10.22	<.001	0.58
Item 2	0.09	0.01	6.94	<.001	0.27
Item 3	0.14	0.02	8.64	<.001	0.26
Item 4	0.12	0.01	8.44	<.001	0.23
Item 5	0.23	0.02	12.56	<.001	0.41
Item 6	0.11	0.01	7.50	<.001	0.22
Item 7	0.00 [a]	-	-	-	0.00
Item 8	0.00 [a]	-	-	-	0.00
Flat affect	1.00 [b]	-	-	-	1.00
Alogia	1.00 [b]	-	-	-	1.00
Avolition	1.00 [b]	-	-	-	1.00
Anhedonia	0.58	0.03	18.49	<.001	1.00
Asociality	0.46	0.04	13.02	<.001	1.00

Note. *N* = 1,469. Estimate = unstandardized factor loading. [a] = Factor loadings fixed to 1 and residual variances fixed to 0 for factors with single indicators. Anhedonia and asociality have freely estimated variances due to the fixed factor loadings. [b] = Factor variances fixed to 1 for factor scaling.

Supplementary Table 6.6

Parameter Estimates from 5-Factor Model of Negative Symptoms at Age 22 in Main Subsample

	Estimate	*SE*	*z*	*p*	Fully standardized path coefficient
Factor loadings					
Flat affect					
Item 1	0.28	0.02	17.96	<.001	0.61
Item 2	0.46	0.02	26.86	<.001	0.76
Alogia					
Item 3	0.56	0.02	36.05	<.001	0.80
Item 4	0.57	0.02	37.67	<.001	0.81
Avolition					
Item 5	0.53	0.02	33.31	<.001	0.74
Item 6	0.52	0.02	35.14	<.001	0.75
Anhedonia					
Item 7	1.00 [a]	-	-	-	1.00
Asociality					
Item 8	1.00 [a]	-	-	-	1.00
Covariances					
Flat affect					
Alogia	0.82	0.02	40.22	<.001	0.82
Avolition	0.71	0.02	29.26	<.001	0.71
Anhedonia	0.38	0.02	19.95	<.001	0.52
Asociality	0.36	0.02	17.52	<.001	0.57
Alogia					
Avolition	0.60	0.02	28.22	<.001	0.60
Anhedonia	0.32	0.02	19.49	<.001	0.43
Asociality	0.28	0.02	17.21	<.001	0.45
Avolition					
Anhedonia	0.46	0.02	28.51	<.001	0.63
Asociality	0.30	0.02	18.03	<.001	0.48
Anhedonia					
Asociality	0.21	0.01	16.46	<.001	0.47
Intercepts					
Item 1	0.15	0.01	22.65	<.001	0.32
Item 2	0.26	0.01	30.82	<.001	0.43
Item 3	0.36	0.01	36.92	<.001	0.51
Item 4	0.39	0.01	40.15	<.001	0.56
Item 5	0.41	0.01	40.98	<.001	0.57
Item 6	0.42	0.01	43.28	<.001	0.60
Item 7	0.43	0.01	42.88	<.001	0.60
Item 8	0.25	0.01	28.99	<.001	0.40
Variances					
Item 1	0.14	0.01	17.18	<.001	0.63
Item 2	0.15	0.01	15.16	<.001	0.42
Item 3	0.18	0.01	15.45	<.001	0.36
Item 4	0.17	0.01	15.82	<.001	0.34
Item 5	0.23	0.01	20.08	<.001	0.45
Item 6	0.21	0.01	18.86	<.001	0.43
Item 7	0.00 [a]	-	-	-	0.00
Item 8	0.00 [a]	-	-	-	0.00
Flat affect	1.00 [b]	-	-	-	1.00
Alogia	1.00 [b]	-	-	-	1.00
Avolition	1.00 [b]	-	-	-	1.00
Anhedonia	0.53	0.02	31.98	<.001	1.00
Asociality	0.39	0.02	22.45	<.001	1.00

Note. N = 5,179. Estimate = unstandardized factor loading. [a] = Factor loadings fixed to 1 and residual variances fixed to 0 for factors with single indicators. Anhedonia and asociality have freely estimated variances due to the fixed factor loadings. [b] = Factor variances fixed to 1 for factor scaling.

Supplementary Table 6.7

Communality and Uniqueness Estimates from 5-Factor Model of Negative Symptoms at Ages 16, 17, and 22 in Main Subsample

	Factor	Pattern coefficient	Communality	Uniqueness
16 years				
Item 1	Flat affect	0.63	0.40	0.60
Item 2	Flat affect	0.83	0.69	0.31
Item 3	Alogia	0.83	0.69	0.31
Item 4	Alogia	0.84	0.71	0.29
Item 5	Avolition	0.72	0.52	0.48
Item 6	Avolition	0.86	0.74	0.26
Item 7	Anhedonia	1.00	1.00	0.00
Item 8	Asociality	1.00	1.00	0.00
17 years				
Item 1	Flat affect	0.65	0.42	0.58
Item 2	Flat affect	0.85	0.72	0.27
Item 3	Alogia	0.86	0.74	0.26
Item 4	Alogia	0.88	0.77	0.23
Item 5	Avolition	0.77	0.59	0.41
Item 6	Avolition	0.89	0.79	0.22
Item 7	Anhedonia	1.00	1.00	0.00
Item 8	Asociality	1.00	1.00	0.00
22 years				
Item 1	Flat affect	0.61	0.37	0.63
Item 2	Flat affect	0.76	0.58	0.42
Item 3	Alogia	0.80	0.64	0.36
Item 4	Alogia	0.81	0.66	0.34
Item 5	Avolition	0.74	0.55	0.45
Item 6	Avolition	0.75	0.56	0.44
Item 7	Anhedonia	1.00	1.00	0.00
Item 8	Asociality	1.00	1.00	0.00

Note. Pattern coefficient = correlation between factor and item (fully standardized path coefficient). Communality = squared pattern coefficient (i.e., a^2), percentage of variance in item explained by the factor. Uniqueness = residual variance (i.e., 1 - a^2), percentage of variance not explained by the factor. Item 7 and item 8 directional paths fixed to 1 and residual variances fixed to 0. Total variance in the items explained by the factors is the sum of the estimated squared pattern coefficients divided by the number of items. Total variance explained at 16 = 3.75/6, 62.50%; at 17 = 4.03/6, 67.16.%; at 22 = 3.36/6, 56%.

Supplementary Table 6.8

Longitudinal Measurement Invariance of 5-Factor Structure of Negative Symptoms Between Ages 16, 17, and 22 in Cotwin Subsample

	Parameters	Fit indices			Comparison of fit indices between nested models		
		CFI	RMSEA [90% CI]	SRMR	Δ CFI	Δ RMSEA	Δ SRMR
Configural invariance model (no constraints)	189	0.986	0.017 [0.015, 0.019]	0.018	-	-	-
Metric invariance model (factor loadings constrained)	183	0.984	0.018 [0.016, 0.020]	0.021	0.002	-0.001	-0.003
Scalar invariance model (factor loadings and intercepts constrained)	177	0.981	0.019 [0.017, 0.021]	0.022	0.003	-0.001	-0.001
Strict invariance model (factor loadings, intercepts and residual variances constrained)	165	0.967	0.025 [0.023, 0.027]	0.030	0.014	-0.006	-0.008
Partial strict invariance model (factor loadings, intercepts and residual variances constrained, excluding item 2) [a]	171	0.976	0.022 [0.020, 0.023]	0.025	0.005 [b]	-0.003 [b]	-0.003 [b]

Note. *N* = 6,336. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = standardized root mean square residual. CI = confidence intervals. Δ denotes change value. [a] The change in CFI value from the scalar model to the strict model exceeded the acceptable limit (of 0.010). Consultation of the modification indices and subsequent free estimation of the item 2 parameters provided acceptable deterioration in model fit. [b] Change values compared to scalar invariance model.

Supplementary Table 6.9

Single-predictor Linear Regressions of Subdomain Mean Scores on Schizophrenia GPS for All GPS f

	Age 16		Age 17		Age 22	
	b (*SE*)	*z* (*p*)	*b* (*SE*)	*z* (*p*)	*b* (*SE*)	*z* (*p*)
Flat affect						
GPS *f*						
1	0.014 (0.005)	2.659 (.008)	0.027 (0.012)	2.162 (.031)	0.001 (0.006)	0.147 (.883)
0.3	0.013 (0.005)	2.467 (.014)	0.023 (0.012)	1.848 (.065)	0.003 (0.006)	0.488 (.626)
0.01	-0.003 (0.006)	-0.525 (.600)	0.002 (0.0212)	0.192 (.848)	-0.004 (0.006)	-0.737 (.461)
Alogia						
GPS *f*						
1	0.002 (0.007)	0.307 (.759)	0.006 (0.016)	0.387 (.699)	-0.001 (0.008)	-0.032 (.974)
0.3	0.007 (0.008)	0.893 (.372)	0.003 (0.015)	0.182 (.855)	-0.000 (0.008)	-0.004 (.997)
0.01	-0.002 (0.008)	-0.304 (.761)	-0.001 (0.015)	-0.069 (.945)	0.002 (0.008)	0.225 (.822)
Avolition						
GPS *f*						
1	0.001 (0.008)	0.108 (.914)	0.038 (0.016)	2.405 (.016)	0.003 (0.008)	0.345 (.730)
0.3	0.001 (0.008)	0.135 (.892)	0.031 (0.016)	2.021 (.043)	-0.001 (0.008)	-0.090 (.928)
0.01	-0.004 (0.008)	-0.496 (.620)	0.008 (0.016)	0.478 (.632)	-0.006 (0.008)	-0.738 (.460)
Anhedonia						
GPS *f*						
1	0.005 (0.009)	0.534 (.593)	0.014 (0.018)	0.777 (.437)	-0.006 (0.010)	-0.639 (.523)
0.3	0.008 (0.009)	0.922 (.356)	0.017 (0.017)	0.967 (.334)	-0.007 (0.009)	-0.729 (.466)
0.01	-0.002 (0.009)	-0.268 (.789)	-0.007 (0.018)	-0.366 (.714)	-0.003 (0.009)	-0.310 (.757)
Asociality						
GPS *f*						
1	0.004 (0.007)	0.511 (.609)	0.005 (0.016)	0.312 (.755)	0.007 (0.008)	0.893 (.372)
0.3	0.001 (0.007)	0.133 (.894)	0.001 (0.015)	0.043 (.966)	0.005 (0.007)	0.652 (.515)
0.01	-0.007 (0.008)	-0.858 (.391)	-0.019 (0.016)	-1.154 (.249)	-0.004 (0.008)	-0.532 (.595)

Note. *N* age 16 = 5,971-6,006. *N* age 17 = 1,791-1,818. *N* age 22 = 6,259-6,278. Related and unrelated individuals included, using cluster-robust *SE*. Subdomain mean scores regressed on schizophrenia GPS. GPS = genome-wide polygenic score. *f* = fraction of causal markers. *b* = unstandardized regression coefficient.

Supplementary Table 6.10

Single-Predictor Linear Regressions of Subdomain Mean Scores on Major Depressive Disorder GPS for All GPS f

	Age 16		Age 17		Age 22	
	b (*SE*)	*z* (*p*)	*b* (*SE*)	*z* (*p*)	*b* (*SE*)	*z* (*p*)
Flat affect						
GPS *f*						
1	0.019 (0.005)	3.465 (.001)	0.016 (0.012)	1.387 (.165)	0.018 (0.006)	3.191 (.001)
0.3	0.019 (0.005)	3.504 (< .001)	0.016 (0.012)	1.410 (.159)	0.018 (0.006)	3.195 (.001)
0.01	0.011 (0.005)	1.981 (.048)	0.002 (0.012)	0.148 (.882)	0.006 (0.006)	0.978 (.328)
Alogia						
GPS *f*						
1	0.010 (0.008)	1.289 (.197)	0.019 (0.015)	1.253 (.210)	0.009 (0.008)	1.072 (.284)
0.3	0.010 (0.008)	1.252 (.211)	0.019 (0.015)	1.244 (.213)	0.009 (0.008)	1.062 (.288)
0.01	-0.002 (0.008)	-0.304 (.761)	0.010 (0.015)	0.688 (.492)	0.004 (0.008)	0.516 (.606)
Avolition						
GPS *f*						
1	0.030 (0.007)	3.978 (< .001)	0.054 (0.016)	3.368 (.001)	0.028 (0.008)	3.487 (< .001)
0.3	0.030 (0.007)	3.986 (< .001)	0.053 (0.016)	3.351 (.001)	0.028 (0.008)	3.461 (.001)
0.01	0.021 (0.008)	2.612 (.009)	0.029 (0.017)	1.736 (.082)	0.007 (0.008)	0.893 (.372)
Anhedonia						
GPS *f*						
1	0.029 (0.009)	3.359 (.001)	0.046 (0.019)	2.434 (.015)	0.030 (0.009)	3.233 (.001)
0.3	0.029 (0.009)	3.348 (.001)	0.046 (0.019)	2.399 (.016)	0.030 (0.009)	3.200 (.001)
0.01	0.024 (0.009)	2.671 (.008)	0.010 (0.019)	0.538 (.591)	0.019 (0.009)	1.986 (.047)
Asociality						
GPS *f*						
1	0.028 (0.006)	4.321 (< .001)	0.025 (0.016)	1.539 (.124)	0.029 (0.008)	3.693 (< .001)
0.3	0.028 (0.006)	4.270 (< .001)	0.024 (0.016)	1.462 (.144)	0.029 (0.008)	3.702 (< .001)
0.01	0.010 (0.007)	1.326 (.185)	-0.008 (0.018)	-0.440 (.660)	0.014 (0.008)	1.702 (.089)

Note. *N* age 16 = 5,971-6,006. *N* age 17 = 1,791-1,818. *N* age 22 = 6,259-6,278. Related and unrelated individuals included, using cluster-robust *SE*. Subdomain mean scores regressed on schizophrenia GPS. GPS = genome-wide polygenic score. *f* = fraction of causal markers. *b* = unstandardized regression coefficient.

Supplementary Table 6.11

Pairwise Wald Test Results for Subdomain Mean Scores Regressed on Schizophrenia GPS And Major Depressive Disorder GPS

	MDD GPS				Schizophrenia GPS			
	Flat affect	Alogia	Avolition	Anhedonia	Flat affect	Alogia	Avolition	Anhedonia
Age 16								
Alogia	1.937 (.164)				1.648 (.199)			
Avolition	2.612 (.106)	**7.141 (.008)**			3.764 (.052)	0.770 (.380)		
Anhedonia	1.721 (.190)	**4.752 (.029)**	0.004 (.950)		0.504 (.478)	0.057 (.811)	0.834 (.361)	
Asociality	1.719 (.190)	**5.189 (.023)**	0.060 (.322)	0.024 (.876)	**4.124 (.042)**	1.492 (.222)	0.116 (.733)	1.818 (.178)
Age 17								
Alogia	0.046 (.830)				2.365 (.124)			
Avolition	**6.231 (.013)**	**4.627 (.031)**			0.550 (.458)	4.708 (.030)		
Anhedonia	2.871 (.090)	1.179 (.181)	0.223 (.637)		0.405 (.524)	0.300 (.583)	1.097 (.295)	
Asociality	0.179 (.672)	0.016 (.900)	3.574 (.059)	2.036 (.154)	**4.420 (.035)**	1.235 (.267)	**5.554 (.018)**	1.450 (.229)
Age 22								
Alogia	1.868 (.172)				0.719 (.396)			
Avolition	1.727 (.189)	**5.356 (.021)**			0.076 (.782)	0.960 (.327)		
Anhedonia	1.913 (.167)	**5.190 (.023)**	0.135 (.714)		0.304 (.582)	0.551 (.458)	0.004 (.950)	
Asociality	2.280 (.131)	**5.287 (.021)**	0.106 (.745)	0.002 (.964)	1.126 (.289)	0.103 (.789)	0.980 (.322)	2.265 (.132)

Note. *N* at age 16 = 5,971-6,006. *N* at age 17 = 1,791-1,818. *N* at age 22 = 6,259-6,278. Related and unrelated individuals included, using cluster-robust *SE*. Subdomains regressed on MDD GPS and schizophrenia GPS separately. Wald tests conducted for the most predictive GPS *f* (Table 6.4). Wald tests (*df* = 1) conducted for the difference between the standardized regression coefficients. *P* values shown in parentheses, indicating significance of difference. GPS = genome-wide polygenic score. MDD = major depressive disorder. *f* = fraction of causal markers. Bold typeset represents significance at $p < .05$.

Supplementary Table 6.12

Multiple-Predictor Linear Regressions of Subdomain Mean Scores on Schizophrenia GPS and Major Depressive Disorder GPS

	MDD GPS					Schizophrenia GPS			
	N	*f*	*b* (SE)	*z (p)*	ß	*f*	*b* (SE)	*z (p)*	ß
Age 16									
Flat affect	6,005	**0.3**	**0.017 (0.005)**	**3.169 (.002)**	**0.044**	1	0.011 (0.005)	2.089 (.037)	0.029
Alogia	6,006	1	0.009 (0.008)	1.154 (.249)	0.015	0.3	0.005 (0.008)	0.678 (.498)	0.009
Avolition	5,995	**0.3**	**0.031 (0.008)**	**4.075 (< .001)**	**0.055**	0.01	-0.007 (0.008)	-0.898 (.369)	-0.013
Anhedonia	5,971	**1**	**0.029 (0.009)**	**3.254 (.001)**	**0.045**	0.3	0.003 (0.009)	0.307 (.758)	0.004
Asociality	5,971	**1**	**0.029 (0.007)**	**4.436 (< .001)**	**0.057**	0.01	-0.010 (0.008)	-1.229 (.219)	-0.019
Age 17									
Flat affect	1,818	0.3	0.013 (0.012)	1.084 (.278)	0.027	1	0.025 (0.012)	2.009 (.045)	0.052
Alogia	1,815	1	0.019 (0.015)	1.225 (.220)	0.029	1	0.003 (0.016)	0.202 (.840)	0.005
Avolition	1,816	**1**	**0.049 (0.016)**	**3.036 (.002)**	**0.077**	1	0.030 (0.016)	1.885 (.059)	0.046
Anhedonia	1,807	1	0.045 (0.019)	2.327 (.020)	0.062	0.3	0.010 (0.017)	0.578 (.563)	0.014
Asociality	1,794	1	0.027 (0.016)	1.651 (.099)	0.043	0.01	-0.021 (0.016)	-1.299 (.194)	-0.033
Age 22									
Flat affect	6,274	**0.3**	**0.019 (0.006)**	**3.275 (.001)**	**0.042**	0.01	-0.006 (0.006)	-1.043 (.297)	-0.013
Alogia	6,278	1	0.009 (0.008)	1.062 (.288)	0.014	0.01	0.001 (0.008)	0.133 (.894)	0.002
Avolition	6,276	**1**	**0.029 (0.008)**	**3.565 (< .001)**	**0.046**	0.01	-0.009 (0.008)	-1.033 (.302)	-0.014
Anhedonia	6,251	**1**	**0.032 (0.009)**	**3.424 (.001)**	**0.046**	0.3	-0.012 (0.009)	-1.314 (.189)	-0.018
Asociality	6,259	**0.3**	**0.029 (0.008)**	**3.628 (< .001)**	**0.048**	1	0.001 (0.008)	0.179 (.858)	0.002

Note. Subdomains regressed on MDD and schizophrenia GPS jointly for the most predictive GPS *f* (as shown in Table 6.4). Related and unrelated individuals included, using cluster-robust *SE*. GPS = genome-wide polygenic score. MDD = major depressive disorder. *f* = fraction of causal markers. *b* = unstandardized regression coefficient. ß = standardized regression coefficient. Bold typeset represents significance under corrected *q* <.05 threshold.

Chapter 7 – Discussion

This Discussion will review the aims and findings of each of the empirical Chapters in the Thesis. Key findings from across the Chapters will then be discussed in terms of broader themes. Limitations relevant to the findings in this Thesis will be outlined and will provide a platform for discussion of future research recommendations in this field. The Chapter will conclude by summarising the implications emerging from the findings of this Thesis.

7.1 – Aims and findings of each Chapter

This Section will outline the aims and the findings from each of the empirical Chapters in the Thesis.

Chapter 2 aimed to assess the extent to which measurement of the PENS dimensions across adolescence and emerging adulthood could be considered invariant over time, which has not previously been assessed. The results showed that the best fitting measurement models for paranoia, hallucinations, and NS, established through CFA, were longitudinally invariant (with one noninvariant item for each of the measures). Invariance was at the scalar level for paranoia and hallucinations, and at the strict level for NS.

The aims of **Chapter 3** were to establish the optimal growth form for the PENS dimensions and to report the characteristics of latent growth in PENS across adolescence and emerging adulthood for the sample as a whole. A supplementary aim was to establish the adequacy of accounting for the relatedness between the TEDS participants using a clustering method. Chapter 3 built on existing findings because previous latent trajectory studies, which have investigated development in aggregated PEs (e.g., Thapar et al., 2012; Wigman, van Winkel, Jacobs, et al., 2011; Wigman, van Winkel, Raaijmakers, et al., 2011), have not tested

different forms of growth, nor reported on any variability around the sample-wide averages of growth. A linear growth form was judged to adequately represent growth in the three PENS dimensions. At the sample-wide level, paranoia and hallucinations showed a general pattern of decrease from ages 16 to 22, with variability in terms of both baseline scores and systematic change over time. For NS, a general pattern of increase was found, with variability evident for baseline scores but not for systematic change in these scores. In relation to the secondary aim, the cluster method was found to be comparable to the other methods that were tested in accounting for the nonindependence between individuals.

Chapter 4 aimed to identify latent heterogeneity in terms of the growth trajectories underlying the separate PENS dimensions. This builds on previous latent trajectory studies that have reported multiple latent trajectory classes including a persistent/increasing class for aggregated PEs. Three classes emerged for paranoia (including a persistent class and two decreasing classes), two decreasing classes emerged for hallucinations, and two increasing classes emerged for NS. The latent classes were mainly differentiated by differences in baseline scores, but also by differences in systematic levels of change over time.

Building on the findings from Chapter 4, the aim of **Chapter 5** was to investigate the extent to which the emergent trajectory classes showed associations with precursors and correlates previously found to be associated with persistence of aggregated PEs, and with a range of polygenic scores that had not previously been investigated. Across PENS dimensions, the most elevated trajectory classes were associated with prospectively reported adversities and emotional/behavioural difficulties in childhood (and in emerging adulthood), and polygenic liability for major depressive disorder, clinical help-seeking, and attention deficit hyperactivity disorder. A dimension-specific pattern of correlates was observed for persistent paranoia; specifically for higher educational and socioeconomic factors.

Chapter 6 aimed to investigate the latent structure of NS in the community and to test associations between the subdomains suggested by the best fitting model and polygenic scores. This would reveal the extent to which the latent structure found in samples ascertained for psychosis in the past literature extends into the community. A 5-factor structure, previously found to best represent clinical NS, was found to best fit the data. Significant associations between mean scores of the five subdomains and polygenic scores for schizophrenia and major depressive disorder were most numerous for avolition and were null for alogia.

7.2 – Key findings and emerging themes across Chapters

This Section will highlight the key findings from across the Chapters and will discuss the broader themes to emerge from the results. These findings and themes will be contextualised amidst previous findings in this area, and the importance of the key findings will be highlighted.

7.2.1 – The measurement of paranoia, hallucinations, and negative symptoms shows (partial) invariance across adolescence and emerging adulthood

This Thesis presented novel evidence showing that the measurement of paranoia, hallucinations, and NS in this community sample is at least partially invariant across adolescence and emerging adulthood. The partial nature of the invariance reflects that the factors indicated by the non-invariant items, were associated with a different *level* of the items at different ages (for scalar partial invariance) – which may suggest a novel avenue for future research (Section 7.4.1). The current findings are important: Prior studies that have reported an age-related decrease/increase for the reporting of PEs/NS, respectively (e.g., De Loore et al., 2011; Dominguez et al., 2010; Rössler et al., 2007; Smeets et al., 2012) did not

provide evidence for age-related change at the *construct* level, because none of these prior studies tested for measurement invariance. The findings reported in Chapter 2 suggested that any inferences of change over time in the PENS dimensions in the current Thesis can be considered at least in part to reflect true, construct-level change, rather than change solely at the level of the measurement instrument.

7.2.2 – Similar patterns of average latent change over time for paranoia and hallucinations, and an overall difference to negative symptoms

The importance of investigating PENS as *separate dimensions* and the advantages of estimating growth as a *latent* process were highlighted throughout this Thesis. Whilst at the sample-wide level (Chapter 3), paranoia and hallucinations showed broadly the same characteristics of latent growth – dimension-specific characteristics were at least free to emerge. The current results are important, because they suggest that previously reported findings of a decrease in aggregated PEs with increasing age is not contingent on combining scores from across dimensions. At the latent level, the positive dimensions of paranoia and hallucinations appeared broadly similar in terms of the *average* trajectories of growth: notably however, higher levels of variability were observed for paranoia than for hallucinations, for both baseline scores and change over time. Variability in latent growth for paranoia and hallucinations in the community has not previously been reported. The current findings show an average decrease in each of the dimensions at the latent level, above and beyond any time-specific effects and stochastic measurement error.

The contrasting results for NS appear to highlight a distinction in the latent development of positive and negative psychotic phenomena: The results are the first to show that the latent growth process for NS is characterised by an average *increase* across adolescence and emerging adulthood. Further, this development over time does not

systematically vary between individuals. The current findings build on those of a previous study that were suggestive of an increase in NS across adolescence/emerging adulthood but were limited because of the inconsistency of measurement across ages (Dominguez et al., 2010). They further show an average increase at the latent level, separate to time-specific effects and measurement error, as detailed above.

7.2.3 – Different patterns of latent heterogeneity underlie the trajectories of paranoia, hallucinations, and negative symptoms

This Thesis was the first study to investigate *latent heterogeneity* in the trajectories of *separate* PEs dimensions, and of NS in the community. Whilst the sample-wide averages for the latent development of paranoia and hallucinations were similar (Chapter 3; Section 7.2.2), a clear difference was seen when multiple latent classes were allowed to emerge (Chapter 4). A high-persistent latent trajectory class was observed for paranoia, but unexpectedly, not for hallucinations: for hallucinations, even when heterogeneity was modelled, the best representation of the data was one which included two latent classes characterised by a decrease over time.

The current results are important because, whilst there is within-class variability and some classification error, they suggest that paranoia scores that are high in adolescence may be likely to persist into emerging adulthood, unlike hallucinations. The current results are further at least suggestive that previous latent trajectory studies that have consistently identified persistent/increasing trajectory classes for aggregated PEs may have been conditional on the inclusion of paranoia scores. Interestingly, in a recent study of individuals meeting criteria for first episode of psychosis, an age-related increase in the prevalence of delusions and an age-related decrease in the prevalence of hallucinations was found (Bridgwater et al., 2020).

For NS, when latent heterogeneity was modelled, the best representation of the data was one which included two latent classes both characterised by an increase over time. The current results suggest that regardless of the baseline level of NS reported in adolescence, these behaviours are likely to increase into emerging adulthood. This is an important finding: on the one hand, it could suggest that the reporting of NS at any level indicates that a suboptimal (increasing) trajectory is likely. On the other, because the rate of increase was higher in the latent class characterised by elevated baseline scores, it could highlight that *elevated* NS scores reported in adolescence are an indicator of suboptimal developmental course (addressed in the following Section, 7.2.4).

7.2.4 – The most elevated trajectory classes show associations with suboptimal phenotypic and polygenic correlates

Contributing towards construct validation of the identified latent trajectory classes, the most elevated trajectory classes across PENS dimensions were associated with a number of the hypothesised phenotypic and polygenic correlates (Chapter 5). For all PENS, these included adversities and emotional/behavioural difficulties in childhood and emerging adulthood, and polygenic liability for major depressive disorder, clinical help-seeking, and attention deficit hyperactivity disorder. The current results corroborate previous findings that have reported similar phenotypic associations for aggregated PEs: suggesting that these correlates have dimension-wide relevance for PENS and are not contingent on the aggregation of PEs.

Beyond a contribution towards construct validation of the latent trajectory classes, the current results add to only a handful of other prospective reports (Rammos et a., 2021; Thapar et al., 2012) to show that specific characteristics reported in early childhood appear to be an indicator of the manner in which PENS are likely to develop in adolescence/emerging

adulthood. They further add novel findings to suggest that specific polygenic scores (available at birth) may also be an indicator of this development. SES, phenotypic educational achievement, and educational attainment GPS appear also to be indicators of PENS trajectories, though with some degree of dimension-specificity (Section, 7.2.5).

However, importantly, some hypothesised correlates, which were all polygenic score variables, did not show associations with the most elevated trajectory classes for any PENS dimension: specifically, these were GPSs for schizophrenia, obsessive compulsive disorder, bipolar disorder, and anorexia. The hypothesis for an association between the most elevated (persistent) class across the *range* of polygenic scores was based on phenotypic findings and theory suggesting that PEs represent an indicator of vulnerability to psychiatric outcomes broadly (Healy et al., 2019; Kaiser et al., 2011; McGrath et al., 2016; van Os & Reininghaus, 2016; Yung et al., 2009).

To the extent that the most elevated trajectory classes showed associations with polygenic scores for affective phenotypes including major depressive disorder and clinical help seeking for nerves, anxiety, tension, or depression, but not with bipolar disorder, may highlight a distinction between the polygenic influences of bipolar disorder compared to the polygenic influences of other affective phenotypes.

The current results further suggest that, whilst polygenic propensity for schizophrenia has previously been found to be associated with PENS at single time points (Jones et al., 2016; Pain et al., 2018), and with *specific* NS subdomains at specific time points (Chapter 6), it appears not to influence the *development* of PENS in this study: This is discussed in terms of a future research direction in Section 7.4.5.

7.2.5 – Dimension-specific correlates, and the distinct pattern of correlates for persistent paranoia

The rationale for investigating the latent development of separate PENS dimensions was discussed in the Introduction to this Thesis: the empirical value of doing so was illustrated by the dimension-specific characteristics of latent growth and heterogeneity that were identified in Chapters 3 and 4. These findings provided the platform for allowing *dimension-specific correlates* of the latent developmental trajectories to be tested (Chapter 5).

The distinct pattern of results to emerge for paranoia was that *higher* educational attainment, SES, and polygenic liability to years of education and intelligence were associated with increased odds of being in the high-persistent trajectory class. Previous findings are limited in terms of reporting associations between education/intelligence and paranoia specifically, though findings from two studies reported no association between education/intelligence and persistence of PEs (Rammos et al., 2021: Thapar et al., 2012). Of potential contextual interest, one further cross-sectional study reported that whilst higher phenotypic intelligence was associated with lower levels of paranoia in adulthood (compared to lower intelligence), lower levels of education were associated with lower levels of paranoia (Freeman et al., 2011). The current results appear to suggest that high educational attainment – both at the phenotypic and polygenic level, may be associated with a suboptimal trajectory of paranoia in adolescence/emerging adulthood. This is discussed in terms of a future research direction in Section 7.4.2.

7.2.6 – The latent structure of negative symptoms in this community sample mirrors the latent structure of negative symptoms in clinical samples – and the potential role of polygenic influences

The current findings suggest that the 5-factor structure that has been found in clinical NS (Ahmed et al., 2019; Chang et al., 2021; Strauss et al., 2012) also best represents NS in adolescence and in emerging adulthood in the current community sample (Chapter 6). The

extent to which this structure appears similar in non-clinical NS to clinical NS is important for three related reasons. First, cumulative findings from across high-risk, clinical, and now, non-clinical domains, converge to suggest that a bifurcated conceptualization of the NS construct, as reflected in the current DSM, does not adequately capture its granularity (Strauss, Ahmed, et al., 2019). Both the psychometric and genetic results reported in Chapter 6 offered evidence to support this assertion (discussed further, below). Second, it provides evidence to suggest that the latent structure of NS is not solely an artefact of treatment effects, ascertainment bias, or any of the other potentially confounding effects inherent in clinical samples – further substantiating the empirical robustness of the hypothesised 5-factor structure. Third, it provides evidence in further support of a continuum model of NS (Kaiser et al., 2011), because of the similarities that are suggested in terms of the psychometric structure between clinical and non-clinical NS.

The observed associations between polygenic scores for schizophrenia and major depressive order with the subdomains provided evidence to support the construct validation of the five subdomains; building on findings that have observed associations between *total* NS and these polygenic scores in the community (Jones et al., 2016; Pain et al., 2018) and in clinical samples (Bigdeli et al., 2017; A. H. Fanous et al., 2012; Xavier et al., 2018). Importantly however, the GPSs did not associate with *all* the subdomains, nor were the associations consistent across all ages for both GPSs. Most notably, alogia did not associate with the GPSs at any age. Whilst the *GPS* was not for alogia specifically, the findings could be understood in terms of evidence *against* construct validation of alogia in this sample. On the other hand, it could highlight a novel avenue for future research (addressed in Section 7.4.5).

Similarly, the age-specific associations that were observed (e.g., schizophrenia GPS was associated with flat affect at age 16 but not at the other ages) could be considered as

weak evidence for construct validation of some of the subdomains. Alternatively, they could suggest that the GPSs have age-specific resonance, even across a relatively short developmental period. The latter explanation is supported by previous findings from a twin study in the TEDS sample that showed that 18% of the variance in NS at age 17 was due to novel genetic influences not shared with age 16 (Havers et al., 2019).

Two further findings are discussed together here: First, major depressive disorder GPS showed more associations with the NS subdomains compared to the schizophrenia GPS (furthermore, GPS_{MDD} remained significant above and beyond the effects GPS_{SCZ} but not vice-versa). Second, avolition was most consistently associated with the GPSs, and associations were more numerous for the motivation and pleasure subdomains (avolition, anhedonia, asociality) than for the expressive subdomains (flat affect, alogia). It is important to consider that the motivation and pleasure subdomains are also symptoms of depression. Therefore, the current findings could be interpreted such that GPS_{MDD} simply manifests as the symptoms that it would be expected to manifest as. Notwithstanding, the results should not be interpreted such that avolition, anhedonia, asociality are not valid components of the NS construct: previous work has shown a clear psychometric distinction between depression and NS, despite the shared variance between them (e.g., Cowan & Mittal, 2021; Ronald et al., 2014; Stefanis et al., 2002). The current results may highlight that the polygenic effects of major depressive disorder more clearly manifest as identifiable behaviours in adolescence/emerging adulthood than those of schizophrenia.

7.3 – Limitations

This Section will address some of the broad limitations relevant to the studies from this Thesis.

7.3.1 – Sample/cohort effects

Four specific limitations pertaining to the current sample are highlighted. First, the repeated measures may have led to practise/familiarisation effects, leading to biased reports of PENS at time points subsequent to the first. As such, it is an advantage of the current Thesis that the development of PENS was modelled as a latent process, which is inherently *less* biased by any potential practise/familiarisation effects than would be the case if relying on static, observed measurements to infer change over time (Willett & Sayer, 1994).

Second, there are two instances of attrition that should be considered: one, across the ~ 20-year period from when TEDS was established up to the current study period, and two, across the study period itself. Recent analysis by TEDS researchers showed that 63%/61% of families who returned data at first contact returned data in adolescence/emerging adulthood, respectively (Rimfeld et al., 2019): In the study, this attrition was found to be associated with several indicators of SES (including lower parental education and employment status), though differences between the initial sample and the non-attritted families were no greater than half a standard deviation, on average. Attrition across the study period itself is addressed in the following paragraph.

Due to a smaller amount of funding available for the age 17 data collection, the sample at age 17 was smaller than at ages 16 and 22. Because this was part of the design of the study, the 'missing' data at age 17 can be considered to a large degree to be 'missing by design' (Rhemtulla & Hancock, 2016) (Section 2.2.1.1). Even so, only approximately 50%-60% of the cross-age sample had either complete or complete with missing by design data, and these individuals had higher SES and were more likely to be female than individuals without PENS data at age 22 (Supplementary Tables 4.1-4.3). In addition to the main analyses that included data from all individuals, therefore, it was important to conduct the GMM using complete data only. Though the differences were slight in terms of the latent

trajectories of individuals with complete data compared to individuals with *any* data (Chapter 4), they were substantively meaningful. The results suggested that missing data across the study period (including missing by design) was associated with a more elevated course, particularly for paranoia and NS. These results highlight the importance of having utilised data from all individuals in this Thesis, using full information maximum likelihood estimation. Excluding individuals with missing data would otherwise have obscured these ostensibly important developmental trajectories.

Third, it is possible that cohort effects influenced the current results. Nonetheless, the results that were found were broadly as predicted and were broadly in line with findings from other cohorts, which lessens the likelihood that the findings are cohort dependent.

Fourth, it is an advantage that the current Thesis investigated the development of PENS dimensions across adolescence/emerging adulthood, because this is a common period of onset for a range of mental health problems, including psychosis (Kessler et al., 2007; Kim-Cohen et al., 2003; Maibing et al., 2015) (Section 1.4.2). Nonetheless, it is possible that had the PENS dimensions been assessed at other (earlier, or later) ages – different trajectory findings would have emerged. For example, recent findings have shown *nonconstant* age-related change in the prevalence of hallucinations: this topic is discussed in Section 7.4.3 in terms of future research.

7.3.2 – Measures

There are many benefits to using self-report and parent-report questionnaires, including the inherent ability to gather data from large numbers of individuals without the high labour demands that would be associated with gathering data by in-person interview or observation. Evidence to support the validity of using self-report questionnaires to study PENS was discussed in Section 1.1.2. Whilst it was not feasible to collect an interview-based

assessment of the PENS measures in the TEDS sample, it is acknowledged that this method of assessment may have given rise to different results than the current results that were based on self-report/parent-report.

From a continuum perspective, it is a strength of the current Thesis that paranoia and hallucinations were studied, because these experiences mirror two out of the three "key features" of schizophrenia (Section 1.1.1). It is a further strength that NS were investigated given the paucity of research into NS in the community (Section 1.2.2) and considering the poor outcomes associated with their presence (Sections 1.2.1 and 1.2.5). Nonetheless, alongside delusions and hallucinations, the other key feature of schizophrenia according to the DSM-5 is disorganised thinking (speech) (defined as the behavioural manifestation of 'thought disorder'; American Psychiatric Association, 2013). It would be therefore of interest to chart the longitudinal course of this phenotype in the community. However, whilst the SPEQ subscale of 'cognitive disorganisation' was assessed at ages 16 and 17, it was not assessed at age 22, thus precluding longitudinal analysis of cognitive disorganisation beyond two time points (e.g., Havers et al., 2019). Furthermore, whilst the cognitive disorganisation subscale measures several aspects of thought disorder (e.g., problems relating to concentration/attention/decision-making; Mason et al., 1997), it includes only one item pertaining to disorganised speech *("Do you ever feel that your speech is difficult to understand because the words are all mixed up and don't make sense?"*). Therefore, the cognitive disorganisation subscale may or may not be an adequate index of disorganised speech in the community. Other more specific measures of thought and language that have been shown to detect speech aberrations in the general population as well as in individuals diagnosed with schizophrenia, may be better placed to assess the development of disorganised speech in community settings (e.g., Liddle et al., 2002).

7.3.3 – Specifications of latent growth

The decision to select a linear growth form for the GMM (Chapter 4) was informed by the results of models in which slope factor loadings were fixed across individuals (Chapter 3). It is possible that accommodating variability in time scores by allowing for individual slope factor loadings (as was done in Chapter 4) would have given rise to different conclusions regarding the optimal functional form of growth. However, because the nonlinear LGC models were highly constrained to aid both identification and convergence, it is probable that the linear growth form would have been selected even in the event of better fit of the nonlinear models (i.e., as was the case for hallucinations, Section 3.3.1.2).

7.3.4 – Generalisability of the findings

There are four main points to consider in terms of generalisability of the current findings. First, as was highlighted in Chapters 4 and 5 – the empirical identification of multiple classes should be considered as suggestive evidence for the latent classes that were ostensibly identified (Bauer, 2007; Bauer & Curran, 2003, 2004; Lubke & Neale, 2008). Evidence towards construct validation of the latent classes was suggested through the observed associations with the hypothesised correlates (Chapter 5). Notwithstanding, considering the empirical constraints that were placed on the GMM and some of the unexpected results, the need for replication of the current findings is highlighted.

Second, whilst pseudo replication of the 5-factor structure of NS was demonstrated (Chapter 6), and whilst the findings were in line with previous clinical findings – replication in *independent* community samples is suggested as a future goal owing to the relatedness of the subsamples.

Third, the association results were framed in terms of 'the most elevated trajectory class', to aid communication of the findings: This description could be considered intuitive

for paranoia (i.e., a high-persistent class) and for NS (i.e., a mid-increasing class), though it was less intuitive for hallucinations – since the trajectory was characterised by a *reduction* of hallucinations reported over time (i.e., a mid-decreasing class). Supporting the current approach, however, whilst the mid-decreasing class showed a significantly greater rate of decrease over time compared to the low-decreasing class, average hallucinations scores were nonetheless still higher at the end of the study period in the mid-decreasing class compared to the low-decreasing class. Further, many of the hypothesised correlates were associated with increased odds of membership in the mid-decreasing class compared to the low-decreasing class.

Fourth, it is noted that only individuals whose parents self-identified as 'white' were included in the genotypic sample (Supplementary Information 5.1). Whilst this makes intuitive sense from the standpoint that most current GWAS are, regrettably, not accurate for individuals of 'non-white' ethnic background (Wang et al., 2022) – the GPS findings (Chapters 5 and 6) should nonetheless be considered generalisable only to 'white' individuals. Beyond the genotypic sample (which comprised approximately 60% of the current cross-age sample; Supplementary Tables 4.1-4.3), it is noted that recent analysis has shown the TEDS sample to be representative of the population in England/Wales in terms of ethnic and socioeconomic characteristics (Rimfeld et al., 2019).

7.3.5 – GPS selection

One potential limitation pertaining to the GPS variables is highlighted. The GPS levels (reflecting different fractions of causal markers, estimated under a Bayesian framework; Vilhjálmsson et al., 2015) were selected based on their significance with each outcome, and multiple testing was corrected for amongst the selected tests. Whilst this approach is commonplace in the field, it is noted that more optimal methods are available,

such as *p*-value permutation and pseudo validation (Allegrini et al., 2022). The significant GPS results were broadly in line with theoretical predictions, which adds strength to the conclusions drawn using the current approach. Notwithstanding, replication of the results using other correction methods will be informative for strengthening the interpretations of the current association findings.

Further, it is possible that other GPS variables that were not included in this Thesis would show associations with the latent trajectory classes (Chapter 5) and the NS subdomain mean scores (Chapter 6). Selection of polygenic scores was constrained by the availability of specific GPSs in the TEDS dataset. From those available, the GPS variables were selected to reflect a range of outcomes, based on theory suggesting that PENS represent a marker for broad vulnerability to poor outcomes (Healy et al., 2019; Kaiser et al., 2011; McGrath et al., 2016; van Os & Reininghaus, 2016; Yung et al., 2009). It is possible that testing other GPSs could be informative for identifying other polygenic influences on the expression of PENS phenotypes. Also, incorporating multiple GPSs could be used to strengthen prediction of the PENS phenotypes (Krapohl et al., 2018).

It would be of further interest to investigate associations between polygenic scores for specific, transdiagnostic symptoms or behaviours (i.e., rather than outcomes at the 'disorder' level), with both the latent trajectory classes (Chapter 5) and the NS subdomain mean scores (Chapter 6).

It is possible that the differential GPS associations that were observed in Chapters 5 and 6 of this Thesis could reflect differences in the power of the GWASs that the GPSs were based on (Dudbridge, 2013; Wray et al., 2014). *A priori* power calculations for the predictive power of the GPSs were not performed, because i) the GPSs were calculated using Bayesian methods that preclude the assessment of the predictive power of the GPSs using GWAS summary statistics (So & Sham, 2017), and ii) SNP heritabilities of the phenotypes (i.e., the

latent trajectory classes, NS subdomains) were unknown, precluding accurate use of popular GPS power calculation tools (e.g., Dudbridge, 2013).

7.4 – Future research directions

This Section will discuss some of the future research directions that are prompted by the findings in this Thesis.

7.4.1 – Embracing longitudinal noninvariance

It has been stated that "noninvariance can be informative and may lead researchers to important conclusions about how different groups interpret the same construct" (p.19, Putnick & Bornstein, 2016). Considering the longitudinal partial noninvariance that was observed for the PENS dimensions in this Thesis (Chapter 2), one application of the previous statement could be to guide future qualitative or mixed method studies that explore *themes* surrounding the experience of the specific noninvariant items at different life stages. This may be particularly important during the transition from adolescence to emerging adulthood (Chapter 2). The importance of this endeavour can be considered such that novel insights into age-related experience of PENS could emerge that would be not accessible solely through quantitative data analysis, which may guide subsequent theory development and testing. Such an approach is exemplified by a recent study into the lived experience of paranoia, which identified themes of paranoia specific to female individuals through the application of interpretative phenomenological analysis (Bird et al., 2022; Smith & Shinebourne, 2012).

7.4.2 – Paranoia-specific effects

The unexpected, dimension-specific findings for paranoia (Chapter 5) are worthy of further exploration. On the surface, the current findings could suggest that higher educational

attainment – both at the phenotypic and polygenic level, as well as SES and intelligence GPS, are associated with a more severe developmental trajectory of paranoia in adolescence and emerging adulthood. In line with the findings from a recent qualitative study (Bird et al., 2022, also discussed in Section 7.4.1), it could be speculated that higher levels of education/intelligence/SES could be associated with greater exposure to threat-provoking situations and or situations of perceived vulnerability, which in turn could lead to the maintenance of paranoid experiences. Whilst there is some (broad) concurrence of the current results with previous cross-sectional findings in an adult sample, which found that lower levels of education were associated with lower levels of paranoia (Freeman et al., 2011) – a first step in exploring the proposed suggestion further would be to see a replication of the current paranoia findings in other developmental samples. Longitudinal associations could then further be explored, for example, by investigating the extent to which and the manner in which affective factors may or may not be implicated in this association, in line with existing theoretical models (Freeman, 2007; Freeman et al., 2002, 2012).

7.4.3 – Gathering more data to infer change more accurately across the lifespan

The repeated PENS measures across the finite period studied in this Thesis should be considered to provide a "snapshot" of a larger developmental PENS landscape. It stands to reason therefore that a greater number of repeated measures over a greater period of time would widen the developmental picture on view. In terms of latent trajectory modelling specifically – the current Thesis with its three time points of data was limited in its ability to infer the extent to which nonlinear forms of growth underlie the PENS repeated measures (Chapter 3). Collecting further repeated measures data on the PENS dimensions in the TEDS sample would allow for a fuller investigation of *nonlinearity*, which would allow for finer-grained theories regarding the age-related development of PENS to be tested. This may be

important, for example, considering recent findings that suggest that the prevalence of hallucinations across the lifespan (assessed using consistent measurement) declines at a *nonconstant* rate (Yates et al., 2021). Whilst the inference of change across age through the study of prevalence rates differs to the current approach of studying trajectories of change, results such as these are important from a developmental perspective: they may suggest, at the group-level, that age-specific factors may in part underlie the reporting of PENS. Testing nonlinear latent growth models that specify a nonconstant rate of change between time points (e.g., quadratic, exponential, latent basis models) and expanding these models further to include predictors of nonlinearity (Curran & Hussong, 2003), may contribute to theory building regarding mechanisms that underlie the development of PENS dimensions (Bridgwater et al., 2020; Yates et al., 2021).

7.4.4 – Co-developmental processes of latent growth

Future studies should build on the current findings by investigating the extent to which, and the ways in which, trajectories of PENS dimensions impact each other across development. Previous findings support the rationale for this approach: For example, one study found that persistent NS predicted persistent PEs, which together predicted psychotic impairment (Dominguez et al., 2010), further showing that PEs did not predict NS. Other findings suggest that it may also be informative to consider trajectories of affective symptoms alongside trajectories of multiple PENS dimensions. For example, two studies reported that affective symptoms predicted persistent paranoia (Freeman et al., 2012; van Rossum et al., 2011), and another study reported that persistent hallucinations predicted delusions as well as affective symptoms (De Loore et al., 2011). Utilising latent trajectory modelling to investigate the co-development of these phenotypes may reveal novel aspects of change over time that would be inherently obscured outside of a latent variable framework. Such findings

would have the potential to contribute to existing dimensional theories (e.g., Freeman, 2007; Freeman et al., 2002, 2012; Garety et al., 2001) and potentially offer new insights regarding the processes involved in the development and maintenance of specific PENS dimensions.

7.4.5 – Developmental associations for polygenic liability to schizophrenia

Motivated by recent clinical findings that showed an association specifically between schizophrenia GPS and the development of avolition in first episode of psychosis (Jonas et al., 2019), future research should test the extent to which schizophrenia GPS is associated with the development of *specific* NS dimensions in the community. Such an investigation would augment the findings reported in Chapters 5 and 6 of this Thesis in two ways: first, because an association was not observed between schizophrenia GPS and the development of total NS scores (Chapter 5), it would allow for a test of the extent to which schizophrenia GPS manifests *dimensionally* in terms of development. Second, it would allow for further probing of the null findings between schizophrenia GPS and alogia at single time points (Chapter 6), by testing whether schizophrenia GPS associates with the *development* of alogia.

Further in the context of alogia, which has been purported to be a distinguishing feature of NS in schizophrenia (Krynicki et al., 2018; Strauss & Cohen, 2017), future work should ascertain whether associations between schizophrenia GPS and alogia are found at other ages across the lifespan in the community, or, building on recent findings (Legge et al., 2021), whether polygenic risk for schizophrenia manifests specifically as alogia only in clinical populations, if at all.

7.4.6 – Genetic influences on environmental effects

Identifying markers in childhood that appear to signal risk for an elevated developmental course of PENS in adolescence/emerging adulthood is important (Chapter 5).

It suggests that *identifying* children with high levels of these markers (i.e., life events, emotional/behavioural problems) may allow for theory-guided intervention at an early stage, which in turn has the potential to alter the developmental course of PENS. Importantly however, future work should investigate the extent to which genetic influences may explain these associations. For example, previous findings in the TEDS sample have shown, not only that variation in bullying-victimisation was itself influenced by genetic factors, but that most of the observed association between bullying-victimisation reported at age 12 and paranoia reported at age 16 was explained by genetic factors (Shakoor, McGuire, et al., 2015b). Findings from genetically informed studies such as these may have implications for the theoretical models that can ultimately inform any interventions. For example, rather than assuming that the outcome is amenable to change via the earlier phenotype, behaviours and characteristics that underlie the propensity to both the phenotype and the outcome may be more consequential targets for intervention.

7.5 – Conclusions

In conclusion, this Thesis aimed to investigate the development of psychotic experiences and negative symptoms in the community across adolescence and into emerging adulthood, using a dimensional approach. It further aimed to investigate the latent structure of NS in the community.

The Thesis provided several novel findings: First, it provided evidence showing that the measurement of paranoia, hallucinations, and NS was adequately invariant over time to facilitate the inference of age-related change over time at the *construct*-level in this sample. Second, it showed that the sample-wide, average latent trajectories of paranoia and hallucinations systematically decreased across the study period, and that the average latent trajectory of NS systematically increased. The results were also the first to report on the

variability around the averages, which differed across the PENS dimensions. Third, latent heterogeneity in the trajectories of the separate PENS dimensions was identified, and dimension-specific latent classes emerged: a persistent latent class emerged for paranoia but not for hallucinations, and the emergent latent classes for NS both followed an increasing course. Fourth, it was shown that polygenic influences for a range of outcomes were associated with the most elevated course across PENS dimensions, with notable null findings for schizophrenia, and notable dimension-specific findings for paranoia with educational/socioeconomic factors. Fifth, the latent structure of NS that has been reported in clinical samples was also found in this community sample, and the 5-factor structure was superior compared to the DSM-5 conceptualisation of NS in schizophrenia. Significant associations at the polygenic level were most numerous for avolition and were null for alogia.

Results in this Thesis show that a more elevated course of paranoia, hallucinations, and NS in adolescence/emerging adulthood is more likely to occur in individuals who experience adverse life events in childhood (and, for paranoia and hallucinations, in individuals with a family history of schizophrenia/bipolar disorder) – and in those with an increased polygenic risk for a specific range of poor outcomes. The current findings are *broadly* aligned with expectations of the proneness-persistence-impairment model (Linscott & van Os, 2013; van Os et al., 2009), and further make a novel contribution of potential relevance to the model: They show that for hallucinations, increased polygenic risk and adverse life events in childhood are associated with an elevated trajectory class, but that this trajectory is represented by an average *decline* in these experiences: Future work can assess the extent to which the elevated hallucinations trajectory across adolescence/emerging adulthood forms part of a nonlinear trajectory of growth, with persistence becoming evident, or not, at a later age or life stage (Section 7.4.3).

At a broad level, further research and development of theory is needed to ascertain the mechanisms that connect adverse life events as well as emotional/behavioural difficulties in childhood to elevated trajectories of paranoia, hallucinations, and NS in adolescence/emerging adulthood (and SES and educational attainment, at a dimension-specific level): Multiple GPSs could be used to strengthen prediction of the PENS phenotypes (Section 7.3.5), subsequently allowing for mechanisms to be investigated in individuals stratified by broad polygenic risk.

One potentially relevant implication for clinical practice relates to the dimension-specific findings for paranoia (Section 7.2.5). That is, individuals who demonstrate higher educational attainment in childhood could be vulnerable to a later persistent course of paranoia. Similarly, higher educational attainment in emerging adulthood could indicate a concurrent trajectory of persistent paranoia. Notwithstanding the need for replication of the current findings, the extent to which the association between early educational attainment and later development of paranoia is moderated and or mediated by for example, affective factors (Sections 7.4.2 and 7.4.4), genetic factors (Section 7.4.6), and or other as yet unknown factors (Section 7.4.1), may guide theory towards a specific, practical framework for intervention.

Studying the development of PENS at both a dimensional level and at a latent level in this Thesis revealed substantive differences between the separate dimensions. These differences would have otherwise been obscured by analysing PEs and PENS at an aggregate level, by using only complete data, and or by manually grouping individuals in terms of their PENS trajectories. As was set out in the Introduction (Section 1.5.5), the latent variable modelling findings to emerge from this Thesis appear at the very least to have offered a broad triangulation of evidence from existing, manual classification studies: They further appear to offer additional insights into the development of separate PENS dimensions. Whilst requiring

replication – the findings of this Thesis should be used as a platform for future research that aims to test theories relating to the development and maintenance of PENS dimensions, with the overarching goal of identifying and helping individuals at risk both for concurrent psychopathology and for later poor clinical and functional outcomes.

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